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Original Article

Maternal and neonatal risk factors of asthma in children: Nationwide population based study

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KEYWORDS
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Abstract *Background:* Small population group-based cohorts have found that perinatal factors may contribute to the development of asthma in children. We aimed to investigate maternal and neonatal risk factors for the asthma phenotypes using two databases from the Taiwan's Maternal and Child Health Database (TMCHD) and the National Health Insurance Research Database (NHIRD).
Methods: Perinatal data was obtained from 2004 to 2008 in the TMCHD and linked the NHIRD to obtain relevant medical information regarding maternal and neonatal risk factors of three asthma phenotypes which were identified as transient early asthma, persistent asthma, and late-onset asthma. A multivariate logistic regression analysis was conducted to adjust for covariates.

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Results: The percentage of non-asthmatic patients was 77.02% and asthmatic (transient early asthma, late onset asthma, and persistent asthma) patients were 8.96%, 11.64%, and 2.42%, respectively. Maternal risk factors—including Cesarean section, maternal asthma, maternal allergic rhinitis (AR), and premature rupture of membranes—and neonatal risk factors, such as male gender, gestational age 29—37 weeks, ventilator use, antibiotics use, AR, and atopic dermatitis, were associated with the development of these three asthma phenotypes. Twins and a gestational age of 28 weeks or less premature were associated with the development of transient early asthma and persistent asthma, but not late onset asthma. Triplets and above were associated with the development of transient early asthma, but not late onset or persistent asthma.

Conclusion: Various asthma phenotypes have different risk factors; therefore, their distinct risk factors should be identified in order to early diagnosis and treatment.

Introduction

The prevalence of asthma in children has been increasing in most industrialized countries.[1,2] The development of childhood asthma is related to numerous genetic and environmental factors.[3]

The Tucson Children's Respiratory Study (TCRS) team determined distinct types of early childhood wheezing based on clinical observations. The study proposed four wheezing phenotypes [never wheeze, transient early wheeze, late-onset wheeze, and persistent wheeze].[4] Another two cohort studies identified five to six wheezing phenotypes in childhood.[5,6] The above three studies revealed that these phenotypes varied in allergen sensitization and levels of lung function. Associations of wheezing phenotypes with asthma, atopy, and lung function were remarkably similar in the three cohorts.

Herrenhausen Conference proposed the concept of a "neonatal window of opportunity" that maternal, fetal, and neonatal interaction affects lifelong host-microbial and immune homeostasis.[7] The influence of environmental factors appears to be present during the maternal and neonatal period.[8] Some studies revealed that maternal and neonatal factors, including maternal smoking, maternal atopic disease, number of older siblings, prematurity, antibiotics exposure, and mode of delivery, may contribute to the development of childhood asthma.[4,5,9—11] Childhood asthma does not indicate a single disease, but encompasses a variety of different wheezing phenotypes, each of which may have distinct risk factors.

Some birth- or small population-group-based cohorts have found that prenatal factors, including maternal and neonatal factors, may contribute to the development of wheezing in children.[4—6,12] These birth cohorts contained small numbers of the study population and subjective questionnaires. But the evidence was limited to the impact of perinatal factors on childhood asthma, especially in population-based birth cohorts.

We accorded two nationwide, population-based databases of Taiwan's Maternal and Child Health Database (TMCHD) and the National Health Insurance Research Database (NHIRD) to identify "early transient," "persistent," and "late-onset" physician-diagnosed asthma phenotypes. Based on these three phenotypes, we investigated maternal and neonatal risk factors for these asthma phenotypes. If these asthma phenotypes have distinct risk factors, then we can implement effective primary prevention and early treatment of asthma.

Methods

Data sources

The current study consists of two databases on population-based claims that contain the TMCHD database and the NHIRD. The NHIRD includes details of beneficiaries enrolled in Taiwan's National Health Insurance (NHI) program launched in 1995. Up to 99.8% of Taiwan's residents are enrolled under this program. The information of the NHIRD include the registry for beneficiaries, detailed clinical records in ambulatory care claims, hospitalizations, diagnostic codes, and prescription records.[13] The TMCHD is a specific dataset designed to examine the family study by further integration of information about newborn information (i.e., parental identity, child identity, and year of childbirth) since 2004 in Taiwan, which contains records on 99.78% of all births nationwide, and can further linked birth certificate.[14] In this study, we used perinatal data between 2004 and 2008 in the TMCHD database, and linked the NHIRD to obtain relevant medical information regarding maternal and neonatal risk factors of asthma.

Ethical statements

This study was approved by the Institutional Review Board of the Taichung Jen-Ai Hospital, Taiwan (Institutional Review Board No. 108-83). Informed consent was not required given that the databases used in the present study contain only de-identified data.

Study population

The present study was a population-based cohort study designed to identify neonatal and maternal risk factors for

certain asthma phenotypes in children. The study investigated subjects who enrolled live births from 2004 to 2008. The diagnoses of asthma were consistent with the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD*-9-CM*)* code 493.X and *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD*-10-CM*)* code J45. A new diagnosis of asthma was defined as having at least three ambulatory visits within any 90-day period or one hospital admission with a diagnosis of asthma. We monitored subjects until the age of 9 years between 2004 and 2017. Three phenotypes of childhood asthma were identified: transient early asthma (newly-diagnosed asthma before three years old and remittance before age six), persistent asthma (newly-diagnosed asthma before three years old and persistence until age six to nine years), and late-onset asthma [newly-diagnosed asthma after three years-old].[4] We excluded infants with congenital anomalies (ICD-9-CM: 740—759) and death (ICD-9-CM: 798.x) during the study observation period. The flow chart is shown in Fig. 1.

Covariates (risk factors)

Allergic rhinitis (AR) (ICD-9-CM: 477.X) and atopic dermatitis (AD) (ICD-9-CM: 691.8) are among the conditions that commonly co-occur with asthma. In this study, a given subject had to have a diagnosis of AR and AD registered on at least three ambulatory visits within any 90-day period. We followed subjects who had a diagnosis of AR and AD until the age of 9 years. The maternal data, including maternal age at delivery (years), gestational age (weeks), multiple birth (twins, triplets and above). and mode of delivery were obtained from TMCHD. The maternal allergic diseases (asthma, AR and AD) were determined by the same ICD-9-CM code registered either 3 times in ambulatory visits or once in admission during any one-year period prior to delivery. We also included maternal systemic lupus erythematosus (SLE) (ICD-9-CM: 710.0), other autoimmune diseases (ICD-9-CM: 279.4), premature rupture of membranes (PROM) (ICD-9-CM: 658.10-13), and chorioamnionitis (ICD-9-CM: 658.40-43) as covariates that could potentially be linked to asthma in children. The neonatal data comprised gestation age (28 weeks or less, 29—32 weeks, 33—37 weeks and 38 weeks or above) were obtained from TMCHD. Ventilator use (procedure code: 57001B) and antibiotics use (ATC code J01), being associated with asthma, were also surveyed. Neonatal risk factors, including perinatal asphyxia (ICD-9-CM: 768.0, 768.1, 768.5, 768.6, 768.9), respiratory distress syndrome (RDS) (ICD-9-CM: 769), meconium aspiration syndrome (MAS) (ICD-9-CM: 770.1), chronic lung disease/bronchopulmonary (CLD/BPD) (ICD-9-CM: 770.7), and perinatal infection (ICD-9-CM: 771.8) determined by diagnosis code occurred once in admission within one month of birth, could be related to childhood asthma.

Statistical analysis

SAS software version 9.4 (SAS Institute, Cary, NC, USA) was used to perform the statistical analysis. Statistical

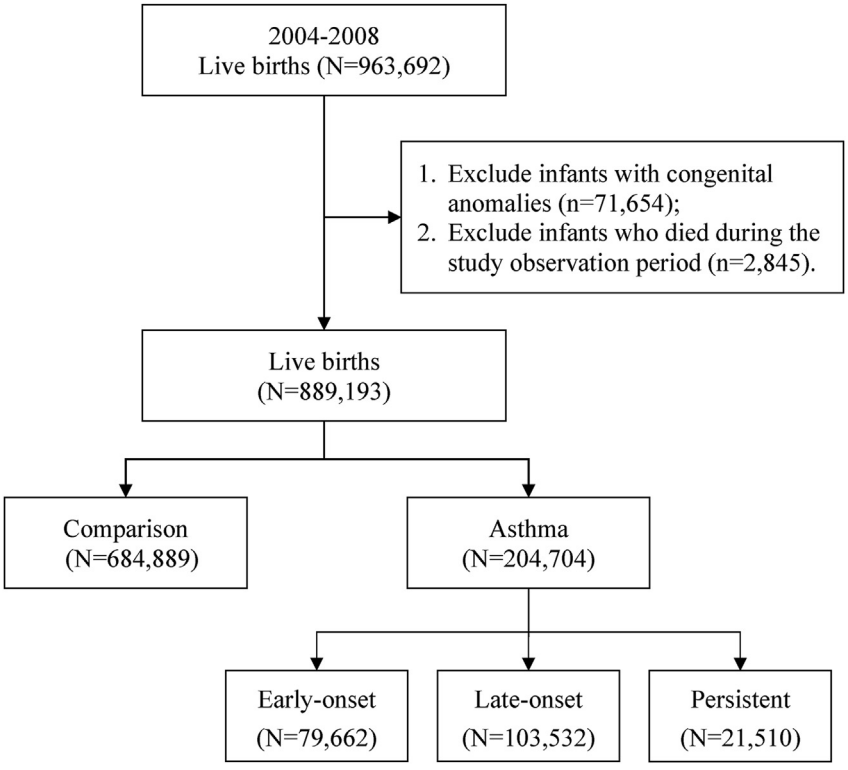

Figure 1. Flow chart of subjects' enrollment.

significance was indicated if p-value < 0.05. Descriptive statistics were first used to show distributions and incident rate (IR) of different asthma phenotype characteristics, including maternal and neonatal factors. Besides, we investigated the risk factors of different asthma phenotypes using multiple logistic regression analysis after adjusting all control variables. The adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated and the forest plots were drawn for each model.

Results

Demographic characteristics

In this study cohort, three asthma phenotypes, including transient early asthma, late onset asthma and persistent asthma, were investigated. A total of 963,692 newborns were initially included in the observation period from 2004 to 2008, infants with congenital anomalies (n = 71,654) and those who died during the study observation period (n = 2845) were excluded, leaving a remainder of 889,193 infants in this cohort (Fig. 1). Table 1 lists the basic demographic characteristics of the asthma patients in the three asthma phenotypes. The number of non-asthmatic patients was 684,889 (77.02%) and that of asthmatic patients (transient early asthma, late onset asthma and persistent asthma) was 79,762 (8.96%), 103,532 (11.64%), and 21,510 (2.42%), respectively (Fig. 1 and Table 1). Among asthmatic children, the most prevalent phenotype was late onset asthma (11.64%), with persistent asthma being the least prevalent phenotype (2.42%). The prevalence of AR and AD is 28.03% and 6.2%, respectively, prior to age 9 years in Taiwan. Table 2 shows the incident rate (IR) of asthma phenotype in each maternal and neonatal risk factor.

Adjusted odds ratio of maternal risk factors for asthma phenotypes in multivariate logistical regression

Multivariate logistical regression (Table 3) shows the aOR of maternal risk factors for all asthma phenotypes compared with non-asthma. Maternal age of <23 years and >35 years had a significantly lower risk in transient early, late onset, and persistent asthma phenotypes compared to a maternal age of 23–35 years. Cesarean section relative to vaginal delivery significantly increased the risk of transient early, late, and persistent transient asthma phenotypes. Twin gestation presented a higher risk of transient early onset asthma and persistent asthma compared to singleton gestation, but not late onset asthma. Higher order gestation increased the risk of transient early onset asthma compared to singleton gestation, but not late onset or persistent asthma. Maternal asthma and AR were associated with a higher risk of transient early, late onset, and persistent asthma. PROM had a higher risk of transient early onset asthma and persistent asthma, but no effect on later onset asthma. Maternal AD, SLE, autoimmune disease, and chorioamnionitis did not differ significantly affect the risk in all asthma phenotypes.

Adjusted odds ratio of neonatal risk factors for asthma phenotypes in multivariate logistical regression

Table 4 reveals the adjusted odds ratio of neonatal risk factors for all asthma phenotypes compared with non-asthma in multivariate logistical regression. The risk of each of the three phenotypes of asthma in male patients was higher than in female patients. A gestational age of 28 weeks or less had a higher risk of development of transient early asthma and persistent asthma than a gestational age

Table 1 Baseline characteristics of the study subjects (N = 889,193).

Variables	N	%
Maternal factors		
Age, mean (SD)	29.33 (4.66)	
<23	85,625	9.63
23–35	696,048	78.28
>35	107,520	12.09
Delivery		
Vaginal Delivery	583,303	65.60
Cesarean section	305,890	34.40
Multiple births		
Singleton	867,737	97.59
Twins	21,039	2.37
Triplets and above	417	0.05
Comorbidities		
Asthma	8879	1.00
Allergic rhinitis	30,920	3.48
Atopic dermatitis	5068	0.57
SLE	871	0.10
Autoimmune disease	6532	0.73
PROM	32,843	3.69
Chorioamnionitis	2420	0.27
Neonatal factors		
Gender		
Female	426,559	47.97
Male	462,634	52.03
Gestational age		
≤28 weeks	996	0.11
29–32 weeks	4771	0.54
33–37 weeks	183,520	20.64
≥38 weeks	699,906	78.71
Health status at birth		
Ventilator use	3992	0.45
Antibiotics use	14,369	1.62
Perinatal asphyxia	257	0.03
RDS	2053	0.23
Meconium aspiration syndrome	437	0.05
CLD/BPD	126	0.01
Perinatal infection	2984	0.34
Allergic rhinitis	249,255	28.03
Atopic dermatitis	55,142	6.20

Abbreviation: SLE, Systemic lupus erythematosus; PROM, Premature rupture of membranes; RDS, Respiratory distress syndrome; CLD, Chronic lung disease; BPD, Bronchopulmonary dysplasia.

Table 2 The incident rate of asthma phenotype in each maternal and neonatal risk factor.

Variables	Early-onset asthma		Late-onset asthma		Persistent asthma	
	Events	IR (%)	Events	IR (%)	Events	IR (%)
Over all	79,662	8.96	103,532	11.64	21,510	2.42
Maternal factors						
Age, mean (SD)	29.46 (4.54)		29.39 (4.68)		29.70 (4.55)	
<23	6325	7.39	9006	10.52	1551	1.81
23-35	64,483	9.26	82,351	11.83	17,298	2.49
>35	8854	8.23	12,175	11.32	2661	2.47
Delivery						
Vaginal Delivery	50,629	8.68	66,873	11.46	13,469	2.31
Cesarean section	29,033	9.49	36,659	11.98	8041	2.63
Multiple births						
Singleton	77,293	8.91	100,903	11.63	20,836	2.40
Twins	2300	10.93	2592	12.32	662	3.15
Triplets and above	69	16.55	37	8.87	12	2.88
Asthma						
No	78,405	8.91	102,052	11.59	20,983	2.38
Yes	1257	14.16	1480	16.67	527	5.94
Allergic rhinitis						
No	76,062	8.86	98,982	11.53	20,242	2.36
Yes	3600	11.64	4550	14.72	1268	4.10
Atopic dermatitis						
No	79,136	8.95	102,887	11.64	21,350	2.41
Yes	526	10.38	645	12.73	160	3.16
SLE						
No	79,569	8.96	103,416	11.64	21,482	2.42
Yes	93	10.68	116	13.32	28	3.21
Autoimmune disease						
No	79,015	8.95	102,685	11.63	21,318	2.42
Yes	647	9.91	847	12.97	192	2.94
PROM						
No	76,062	8.88	99,573	11.63	20,480	2.39
Yes	3600	10.96	3959	12.05	1030	3.14
Chorioamnionitis						
No	79,409	8.95	103,246	11.64	21,426	2.42
Yes	253	10.45	286	11.82	84	3.47
Neonatal factors						
Gender						
Female	32,428	7.60	46,004	10.78	7501	1.76
Male	47,234	10.21	57,528	12.43	14,009	3.03
Gestational age						
≤28 weeks	199	19.98	120	12.05	46	4.62
29—32 weeks	661	13.85	654	13.71	189	3.96
33—37 weeks	18,291	9.97	21,787	11.87	5130	2.80
≥38 weeks	60,511	8.65	80,971	11.57	16,145	2.31
Ventilator use						
No	79,092	8.93	102,992	11.63	21,341	2.41
Yes	570	14.28	540	13.53	169	4.23
Antibiotics use						
No	77,899	8.90	101,660	11.62	21,007	2.40
Yes	1763	12.27	1872	13.03	503	3.50
Perinatal asphyxia						
No	79,643	8.96	103,496	11.64	21,498	2.42
Yes	19	7.39	36	14.01	12	4.67
RDS						
No	79,356	8.95	103,263	11.64	21,426	2.42
Yes	306	14.91	269	13.10	84	4.09
Meconium aspiration syndrome						

Table 2 (*continued*)

Variables	Early-onset asthma		Late-onset asthma		Persistent asthma	
	Events	IR (%)	Events	IR (%)	Events	IR (%)
No	79,612	8.96	103,473	11.64	21,496	2.42
Yes	50	11.44	59	13.50	14	3.20
CLD/BPD						
No	79,633	8.96	103,517	11.64	21,505	2.42
Yes	29	23.02	15	11.90	5	3.97
Perinatal infection						
No	79,313	8.95	103,152	11.64	21,416	2.42
Yes	349	11.70	380	12.73	94	3.15
Allergic rhinitis						
No	36,061	5.64	42,367	6.62	4733	0.74
Yes	43,601	17.49	61,165	24.54	16,777	6.73
Atopic dermatitis						
No	69,516	8.33	92,081	11.04	16,776	2.01
Yes	10,146	18.40	11,451	20.77	4734	8.59

Abbreviation: IR, Incidence rate; SLE, Systemic lupus erythematosus; PROM, Premature rupture of membranes; RDS, Respiratory distress syndrome; CLD, Chronic lung disease; BPD, Bronchopulmonary dysplasia.

of 38 weeks or above. Late onset asthma was not significantly different at a gestational age of 28 weeks or less. Gestational ages of 29—32 and 33—37 weeks were associated with a higher risk of all three asthma phenotypes compared to a gestational age of 38 weeks or above. Antibiotic use at one week after birth, and ventilator use in the neonatal period had elevated risks in all three asthma phenotypes. Perinatal asphyxia had a protective effect in transient early asthma, but there was no significant difference in the late onset and persistent asthma phenotypes. AR and AD have been linked to an increased risk for all asthma phenotypes. RDS, CLD/BPD, meconium aspiration syndrome, and perinatal infection were not significant risk factors in all asthma phenotypes.

Discussion

In this population-based study, we investigated maternal and neonatal factors that impact development of various asthma phenotypes using the TMCHD and NHIRD population-based databases. We found that maternal risk factors, including Cesarean section, maternal asthma, maternal AR and PROM (Fig. 2 a), and neonatal risk factors—including

Table 3 Adjusted odds ratio with 95% confidence interval of maternal risk factors for asthma phenotype.

Variables	Early-onset asthma			Late-onset asthma			Persistent asthma		
	aOR	95% CI	p-value[a]	aOR	95% CI	p-value[a]	aOR	95% CI	p-value[a]
Maternal factors									
Age (vs 23—35)									
<23	0.89	0.87—0.92	<0.001	0.98	0.96—1.00	0.033	0.89	0.84—0.93	<0.001
>35	0.85	0.83—0.87	<0.001	0.92	0.90—0.94	<0.001	0.92	0.88—0.95	<0.001
Delivery (Cesarean section vs vaginal delivery)	1.05	1.03—1.06	<0.001	1.02	1.01—1.04	0.002	1.05	1.02—1.08	0.001
Multiple births (vs singleton)									
Twins	1.07	1.03—1.12	0.002	1.04	1.00—1.09	0.054	1.11	1.03—1.21	0.011
Triplets and above	1.33	1.05—1.70	0.018	0.77	0.56—1.06	0.112	0.98	0.55—1.73	0.941
Asthma (yes vs no)	1.52	1.43—1.61	<0.001	1.39	1.31—1.46	<0.001	1.99	1.82—2.18	<0.001
Allergic rhinitis (yes vs no)	1.11	1.08—1.15	<0.001	1.09	1.05—1.12	<0.001	1.25	1.18—1.32	<0.001
Atopic dermatitis (yes vs no)	1.04	0.96—1.13	0.363	1.01	0.93—1.09	0.894	1.08	0.92—1.26	0.338
SLE (yes vs no)	1.18	0.95—1.47	0.128	1.15	0.95—1.39	0.165	1.28	0.86—1.89	0.224
Autoimmune disease (yes vs no)	0.98	0.90—1.07	0.647	1.02	0.95—1.09	0.638	0.99	0.85—1.15	0.895
PROM (yes vs no)	1.17	1.13—1.21	<0.001	1.03	1.00—1.06	0.074	1.21	1.14—1.29	<0.001
Chorioamnionitis (yes vs no)	1.05	0.93—1.19	0.463	0.99	0.88—1.11	0.878	1.23	0.99—1.53	0.058

Abbreviation: aOR, adjusted odds ratio; CI, confidence interval; SLE, Systemic lupus erythematosus; PROM, Premature rupture of membranes.

[a] Multiple logistic regression. Neonatal factors were adjusted in this model.

Table 4 Adjusted odds ratio with 95% confidence interval of neonatal risk factors for asthma phenotype.

Variables	Early-onset asthma			Late-onset asthma			Persistent asthma		
	aOR	95% CI	p-value[a]	aOR	95% CI	p-value[a]	aOR	95% CI	p-value[a]
Neonatal factors									
Gender (male vs female)	1.28	1.27–1.30	<0.001	1.10	1.09–1.12	<0.001	1.53	1.49–1.58	<0.001
Gestational age (vs ≥ 38 weeks)									
≤28 weeks	1.84	1.56–2.15	<0.001	1.09	0.90–1.32	0.397	1.54	1.12–2.13	0.009
29–32 weeks	1.46	1.34–1.59	<0.001	1.22	1.12–1.33	<0.001	1.51	1.29–1.78	<0.001
33–37 weeks	1.13	1.11–1.15	<0.001	1.04	1.02–1.05	<0.001	1.18	1.14–1.22	<0.001
Ventilator use (yes vs no)	1.30	1.19–1.43	<0.001	1.14	1.04–1.25	0.006	1.36	1.14––1.61	0.001
Antibiotics use (yes vs no)	1.15	1.09–1.22	<0.001	1.07	1.01–1.13	0.020	1.16	1.04–1.29	0.008
Perinatal asphyxia (yes vs no)	0.57	0.36–0.89	0.014	1.05	0.75–1.46	0.792	1.16	0.65–2.07	0.609
RDS (yes vs no)	0.98	0.86–1.13	0.817	0.99	0.86–1.13	0.843	1.01	0.78–1.30	0.947
Meconium aspiration syndrome (yes vs no)	1.03	0.78–1.37	0.815	1.06	0.82–1.37	0.665	1.02	0.60–1.74	0.953
CLD/BPD (yes vs no)	1.21	0.83–1.78	0.322	0.94	0.55–1.58	0.806	0.85	0.34–2.12	0.733
Perinatal infection (yes vs no)	0.91	0.81–1.02	0.113	0.94	0.84–1.05	0.258	0.84	0.67–1.04	0.112
Allergic rhinitis (yes vs no)	4.11	4.05–4.17	<0.001	4.83	4.77–4.89	<0.001	12.01	11.63–12.41	<0.001
Atopic dermatitis (yes vs no)	1.91	1.87–1.95	<0.001	1.59	1.56–1.62	<0.001	3.02	2.92–3.12	<0.001

Abbreviation: aOR, adjusted odds ratio; CI, confidence interval; RDS, Respiratory distress syndrome; CLD, Chronic lung disease; BPD, Bronchopulmonary dysplasia.

[a] Multiple logistic regression. Maternal factors were adjusted in this model.

gestation age of 29–37 weeks prematurity, ventilator use, antibiotics use, AR and AD (Fig. 2 b)—were associated with higher risk for development of various asthma phenotypes. The risk factors of maternal SLE, maternal AD, maternal autoimmune disease, chorioamnionitis, RDS, meconium aspiration syndrome, and perinatal infection were not found to have a significant difference in all asthma phenotypes. However, twin gestation had a higher risk for transient early asthma and persistent asthma, while triplet and higher order gestation also had increased risk of transient early asthma (Fig. 2 a). Regarding neonatal factors, this study showed that a gestation age of 28 weeks or less presented an elevated risk for transient early asthma and persistent asthma, but not for late onset asthma (Fig. 2 b). We identified a different contribution of risk factors for specific childhood wheezing phenotypes.

Our study found that maternal asthma and AR, and childhood AR and atopic dermatitis were associated with the development of all asthma phenotypes. Transient early wheezes were associated with diminished lung function at birth. However, transient early wheezes do not increase the risk of allergies, but are associated with persistent and late wheezes within the Tucson cohort.[4] Nevertheless, an allergy family history has been linked to all wheezing phenotypes in other research.[5,15,16] Follow-up of the Tucson cohort revealed a lower pulmonary function into adulthood in transient early wheezes.[17] The follow-up study also showed that the prevalence of atopy before the age of 16 was similar for transient wheezers, persistent, and late-onset wheezers.[17] Tucson cohort initially supposed that allergies were not at risk of transient early asthma; nonetheless, subsequent follow-up studies showed that allergies increased the risk of all three phenotypes. Consequently, we speculated that allergies may be at risk of transient early asthma. Previous literature revealed that males were more likely than females to have transient early wheezing,[5] late onset, and persistent wheeze.[4] Boys tend to have a higher incidence of allergy diseases than girls before puberty.[18] Our study also found that boys were at greater risk of developing all asthma phenotypes.

Chronic lesions of AD reveal immune responses from Th2 to Th1/Th17. The skin immunity of AD adult patients is characterized by decreased Th2/Th22 and increased Th1/Th17 immune responses.[19] Lin et al. also reported childhood AD (aOR 1.31, 95% CI 1.22–1.40) was independent risk factor for childhood asthma, but maternal AD (aOR 1.06, 95% CI 0.99–1.14, p = 0.09) was not significant to be associated with childhood asthma.[11] Therefore, this study could not illustrate the correlation between maternal AD and childhood asthma, which may be related to the immunity of maternal AD skewing Th2 to Th1/Th17 immune activation.

We demonstrated that antibiotic therapy during the first month of life reduces microorganisms in infants, and raises the risk of all asthma phenotypes. Some investigations indicate that microbial exposure protects against allergies. Reduced exposure to microorganisms is associated with increased allergic effects in humans.[20] A recent systematic review has identified a relationship between antibiotic use and the development of an allergy in children during the first 6–12 months of life.[21] There is a constant dose-dependent relationship between prescribing antibiotics during infancy and the further development of asthma in children.[22] Antibiotic treatment in the first week of life raises the risk of atopic asthma at 12 years old.[23] We though that antibiotic treatment alters microbial equilibrium and thus may raise the risk of asthma. PROM has the potential to increase antibiotic treatment. PROM also presented a greater risk to all asthma phenotypes in our study which may be as result of antibiotic treatment.

The study also discovered that cesarean section is a hazard factor for all asthma phenotypes. A meta-analysis

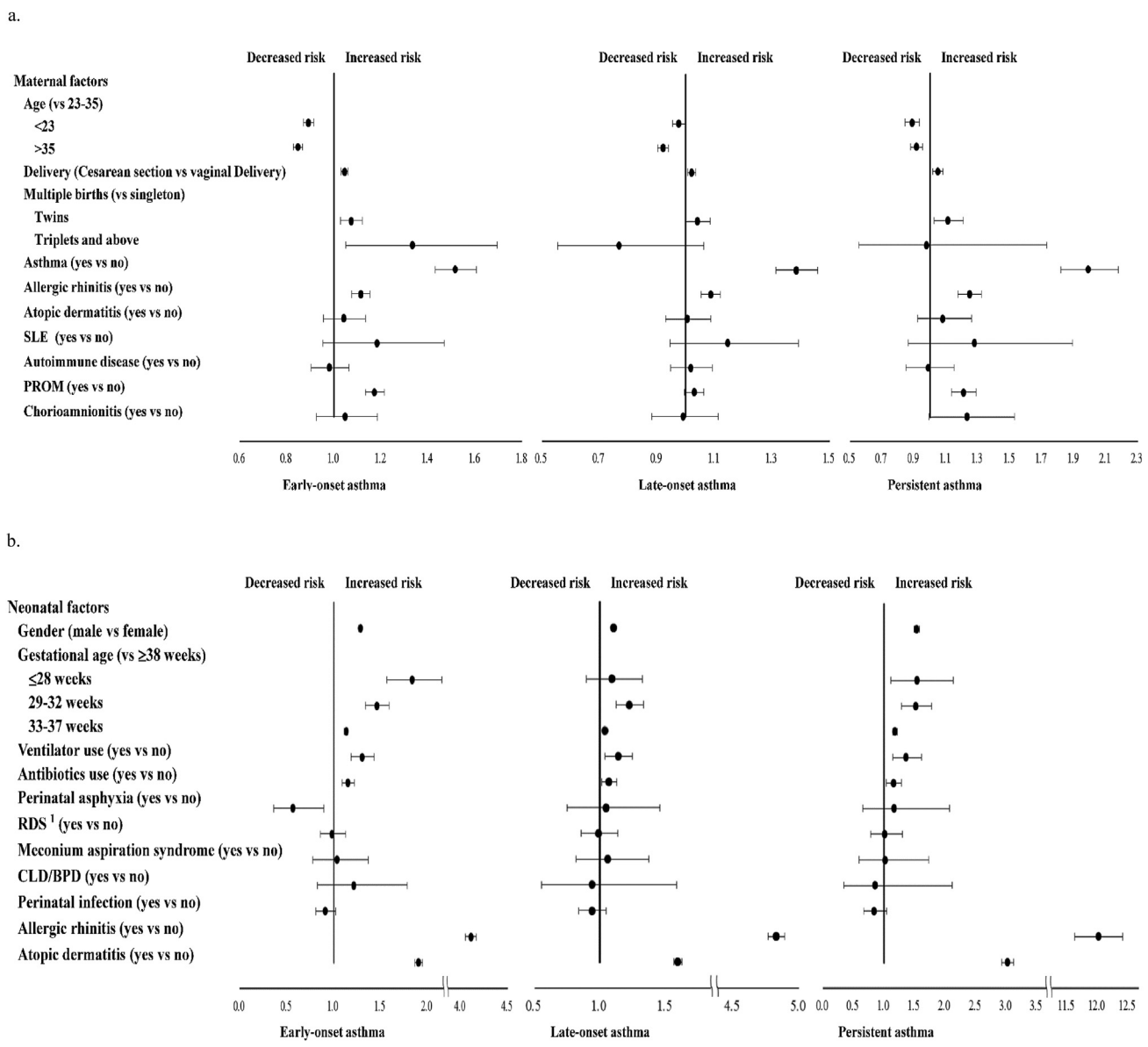

Figure 2. a. Odds ratios of maternal risk factors after multivariable adjustment, b. Odds ratios of neonatal risk factors after multivariable adjustment.

indicates a 20% increase in the subsequent risk of asthma in children delivered via cesarean sections.[24] Cesarean section is accompanied by significant changes in the composition of the intestinal microbiota at one week and one month old, and an increased risk of developing asthma at age 6 years.[25] Research illustrates that there are significant differences in the microbiome profile of infants born vaginally compared with those born via caesarean section.[26] Intestinal microbiota dysbiosis is linked to an allergy and only particular bacterial taxa of the intestinal microbiota protect against an allergic phenotype in mice.[27] Furthermore, caesarean section is associated with transient tachypnea in neonates, which increases the risk of asthma.[28,29] Caesarean section may affect gut microbiota and lung function, resulting in an increased risk of asthma.

In this study, twins and triplets were found to have an increased risk of early transient asthma and persistent asthma; however, twin, triplet, and higher order gestation did not constitute a risk factor for late asthma. One study showed that the presence of older siblings and being a member of a multiple birth seemingly protect against developing asthma after the age of 2 years, but having older siblings increases the prevalence of early asthma.[30] A longitudinal study reported that the presence of older siblings results in an increased risk of wheezing in the first few years of life. In contrast, exposure to older siblings protects against developing asthma later in childhood.[31] This significant protective effect may reflect the hygienic hypothesis. Older siblings modify the microbiome by sharing protecting bacteria with their infant sibling. The higher the number of family members, the higher the exposure to infections in early life. Early respiratory infections appear to raise the risk of asthma at the age of four years.[32] An increased risk of transient early asthma in twins and triplets may be caused by early respiratory infections. Twin or triplet siblings may share protective bacteria to reduce late onset

asthma. Interestingly, our study noted that a high maternal age had a decreased risk for all asthma phenotypes. Another study also showed that a high maternal age at delivery was a protective factor for asthma.[11] The effect of siblings on asthma may also partly interpret the protective effect between high maternal age and childhood asthma.

We showed that a gestational age of 29—37 weeks and ventilator use presented a higher risk for the development of all asthma phenotypes, but a gestational age of 28 weeks or less had a higher risk of transient early and persistent onset asthma. In a systematic review and meta-analysis, prematurity increased the risk of asthma.[9] Late-preterm birth may be a significant risk factor for developing asthma.[33] A large proportion of school-aged children who were born very preterm exhibits persistent obstruction of the peripheral airway.[34] Maternal stress is associated with prematurity and asthma through disturbance of the hypothalamic-pituitary-adrenal (HPA) axis and immune responses.[35] Chronic lung diseases, the need for mechanical ventilation, and the use of corticosteroids were correlated with development of asthma. Prematurity was also associated with the development of asthma.[36] Preterm birth has also shown a reduction in asthma after school age.[37] The Tucson cohort found that transient early wheezing was associated with a reduction in lung function at birth and no increased risk of allergy later in life.[4] The use of a ventilator may be a risk factor for pulmonary function reduction. A previous study suggested that asthma caused by prematurity requires both structural changes in the lungs and abnormal immune responses in later childhood.[38] We found that the risk of transient early asthma and persistent asthma were greater than that of late onset asthma in preterm and ventilator use infants. This may be caused by impaired pulmonary function at birth.

The incident rate (IR) of RDS and CLD/BPD have higher IR among all asthma phenotype, particularly in early-onset asthma (Table 2). A systematic review demonstrated that BPD may be not as an independent factor of prematurity to increase the risk of asthma in school children and adolescents.[39] The feature of BPD inflammation tend to Th1-mediated responses, but childhood asthma is associated with atopy through Th2-mediated responses.[40] Exhaled NO levels were significantly lower in BPD patients than in asthma patients.[41] Some studies have shown the prevalence of atopy, doctor-diagnosed asthma, and allergies is not more frequently in patients with a history of BPD.[42,43] Though RDS and CLD/BPD have a higher in this study, but they were not related to the risk of all asthma phenotype after adjustment due to other variables, e.g. prematurity, in this study.

This study contains a number of strengths. In this article, both population-based application databases were used, including TMCHD and the NHIRD. Two databases of population-based applications deal with possible mother—child associations between different phenotypes of infant asthma. This study is a large and real-world sample of patients and nationwide prescription data. Most earlier studies on the relationship between asthma in children and risk factors have focused on small cohorts of population groups. However, this research has several limitations. For example, the validation of asthma may be problematic because the study population was extracted from the NHIRD using arbitrary encoding by physicians, while the NHIRD does not have lung function or laboratory data to support the correct diagnosis of asthma. Furthermore, the known risk factors associated with asthma, including breastfeeding,[44] air pollution, maternal smoking, passive smoking, maternal educational levels, and socioeconomic factors,[45] could not be evaluated on the application databases from this study. Finally, the study may have the ascertain bias that only used the ICD code to define disease without any medical procedure or drug codes. It may have biased diagnoses, although the study identified the incident disease as having at least three outpatient or one inpatient diagnoses in a given period of time. For instance, the diagnoses of MAS and perinatal infection didn't include antibiotics code.

Genetics and environmental factors may influence maternal and neonatal factors regarding the development of asthma in children. Microbiota in early life, reduced lung function in newborns, maternal allergy, and maternal stress have been associated with the development of asthma. We identified a variety of maternal and neonatal risk factors for specific wheezing phenotypes in children. A decrease in cesarean sections and use of antibiotics early in life may be an important goal of prevention programs. Various asthma phenotypes have different risk factors; therefore, it would be useful to identify distinct risk factors for the various asthma phenotypes in order to diagnose and treat earlier.

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