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Association between preterm birth and asthma and atopic dermatitis in preschool children: a nationwide population-based study

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Abstract

Asthma and atopic dermatitis (AD) are representative chronic diseases in childhood. This study aimed to investigate the impact of preterm birth on the incidence and severity of asthma and AD in children, as well as to identify neonatal risk factors for asthma and AD. We used health claims data recorded between 2007 and 2014 in the Korean National Health Insurance Service database. We recruited 2,224,476 infants born between 2007 and 2014 and divided them into three groups: 3518 of extremely preterm (EP) infants (< 28 weeks of gestational age (GA)), 82,579 of other preterm (OP) infants (28–36 weeks of GA), and 2,138,379 of full-term (FT) infants (> 37 weeks of GA). We defined asthma as > 3 episodes of clinical visits in a year before 6 years of age, early asthma as onset at < 2 years of age, and severe asthma as > 1 event of status asthmaticus or admission to a hospital via an emergency room. AD was defined as ≥ 3 diagnoses in a year before 6 years of age, early AD as onset at < 2 years of age, and severe AD as prescription of high-potency topical steroids or immunosuppressants. An association of preterm birth with asthma and AD was assessed using inverse probability of treatment-weighted multivariable Cox regression analysis. Cardiorespiratory conditions, such as respiratory distress syndrome, bronchopulmonary dysplasia, patent ductus arteriosus, and pulmonary hypertension, significantly increased the risk of asthma. Specifically, bronchopulmonary dysplasia emerged as a significant risk factor for both severe and early-onset asthma (odds ratio (OR) 1.36, 95% CI 1.21–1.37 for severe asthma; OR 1.55, 95% CI 1.30–1.85 for early asthma), while it was associated with a decreased risk of AD (OR 0.86, 95% CI 0.80–0.92). Neonatal sepsis, jaundice, and retinopathy of prematurity were also identified as significant risk factors for later asthma. A stepwise increase in the risk of asthma with an increasing degree of prematurity was observed, with the OP group showing an adjusted hazard ratio (aHR) of 1.24 (95% CI: 1.22–1.26) and the EP group showing an aHR of 1.51 (95% CI: 1.41–1.63). Conversely, preterm birth was inversely associated with the risk of AD, with aHRs of 0.73 (95% CI: 0.67–0.79) for the OP group and 0.88 (95% CI: 0.87–0.89) for the EP group. *Conclusion* Preterm children have a significantly higher risk of asthma and lower risk of AD, with cardiorespiratory conditions significantly increasing the risk of asthma. Thus, we highlight the need for targeted respiratory management strategies for this high-risk population.

What is Known:
• *Asthma and atopic dermatitis are prevalent chronic diseases in childhood, reducing the quality of life of children.*
• *Preterm birth was associated with an increased risk of asthma, but few large nationwide studies.*
• *Research on the relationship between preterm birth and pediatric atopic dermatitis is controversial, with few large nationwide studies.*

What is New:
• *Preterm children, especially born before 28 weeks of gestational age, had a significantly higher risk of asthma and lower risk of atopic dermatitis.*
• *Cardiorespiratory comorbidities such as RDS, BPD, PDA, and pulmonary hypertension in neonatal period are prominent risk factors for asthma.*
• *Preterm children are vulnerable to both early-onset and severe asthma.*

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Abbreviations

AD	Atopic dermatitis
ASD	Absolute standardized difference
BPD	Bronchopulmonary dysplasia
CI	Confidence interval
EP	Extremely preterm infants
FT	Full-term infants
GA	Gestational age
GDM	Gestational diabetes mellitus
HR	Hazard ratio
ICD-10	International Classification of Diseases-Tenth Revision
IUGR	Intrauterine growth restriction
IPTW	Inverse probability of treatment-weighted
NHSPIC	The National Health Screening Program for Infants and Children
NHIS	The Korean National Health Insurance Service
OP	Other preterm infants
OR	Odds ratio
PIH	Pregnancy-induced hypertension
PS	Propensity score
RDS	Respiratory distress syndrome
SES	Socioeconomic status

Introduction

The incidence of preterm birth, defined as delivery before 37 weeks of gestational age (GA), has been on a steady incline in Korea [1]. It is attributed to such factors as advanced maternal age, smoking during pregnancy, and increased multiple births resulting from assisted reproductive technologies [2]. Concurrently, advancements in neonatology have significantly improved the survival rates of preterm infants [3], sparking a heightened interest in the long-term health outcomes of these children.

Asthma and atopic dermatitis (AD) are representative chronic respiratory and skin diseases, respectively, occurring in children due to various causes. Asthma represents the most common chronic respiratory disease in children, characterized by reversible airway obstructions [4]. The prevalence of asthma has been shown to vary among studies in Korea. Studies in other countries show a decreasing trend in the prevalence of asthma [5]; however, Korean studies show that the recent asthma incidence is stagnant or increasing without significant change. Some studies demonstrate that asthma incidence has not changed in all ages since 2008, except for the 20 s, which showed a steady increase [6]. The Korea Community Health Survey database shows that the overall prevalence of asthma increased. The National Health Insurance Service-National Sample Cohort indicated a gradual increase in annual asthma prevalence from 4.5 to 6.2% [7]. Nationally, children aged < 18 years exhibit the highest rates of asthma medication prescriptions, with the annual incidence of pediatric asthma on an upward trajectory [8, 9]. Research indicates that the etiology of asthma is multifactorial, encompassing genetic predisposition, environmental influences (such as air pollution), and perinatal factors, including low birth weight [10–12].

AD, a prevalent inflammatory skin condition during childhood, is marked by chronic, pruritic lesions in a characteristic distribution. The general prevalence of AD ranges from approximately 10 to 20%, affecting a significant portion (14.7%) of school-aged children in Korea, the number that has notably increased over the last 2–3 decades [13, 14]. Factors contributing to AD include skin barrier dysfunction, a feature prominently observed in preterm infants. Existing literature on the relationship between preterm birth and AD yielded conflicting results. Some European studies report that preterm birth is associated with a decreased risk of AD [15–18]. Conversely, research by Kvenshagen et al. [19] involving 512 children monitored from birth to 2 years found no significant association between AD and preterm birth.

As preterm birth is increasing, managing their quality of life is important. Asthma and AD become important factors in the health-related quality of life of such patients. Therefore, we aimed to determine whether premature infants and their accompanying medical conditions influence the incidence and severity of asthma and AD. Various past studies have analyzed the correlation between premature infants and both diseases. However, controversial results were shown regarding atopic dermatitis. To our knowledge, comprehensive studies examining the impact of preterm birth on asthma and AD while utilizing nationwide data are scarce in Korea. Furthermore, the incidence of these diseases segmented by gestational age (GA) remains unexplored. Therefore, we aimed to confirm a more accurate correlation through large-scale analysis using national data, and also investigate the difference in incidence rates according to GA. Our study seeks to the overall incidence of asthma and AD in preschool-aged children in Korea, utilizing medical claims data for newborns born between 2008 and 2014. We would classify them by GA to determine differences in incidence and severity depending on GA. Additionally, we aim to identify neonatal risk factors for asthma and AD.

Materials and methods

Data source

The data for this study were obtained from the Korean National Health Insurance Service (NHIS), the entity

responsible for administering the health insurance coverage mandated by the Korean government. In Korea, each individual is assigned a unique identification number, ensuring that over 98% of the population is covered by a single-payer healthcare system. Medical claims data were collected from all people who visited the hospital (all 1st, 2nd, and 3rd medical institutions).

The NHIS compiles medical claims data, demographic details, and outcomes from the National Health Screening Program for Infants and Children (NHSPIC). The NHSPIC provides annual health screening tests for children of preschool age. Collected medical claims data were cataloged using the ICD-10 codes. This study was performed according to the principles of the Declaration of Helsinki and received an exemption from review by the Institutional Review Board of Hanyang University Guri Hospital (approval no. GURI 2022–04-017). Additionally, this study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Online Resource 1).

Study population

Figure 1 depicts the flow diagram of the study population. We identified newborns born between 2008 and 2014 and classified them according to the ICD-10 codes for preterm birth (P07) and full-term birth (Z38), finding a total of 2,330,289 individuals. These individuals were monitored up to the age of 6 years. The cohort was divided into three groups based on gestational age (GA): (1) extremely preterm (EP) infants born at < 28 weeks of GA; (2) other preterm (OP) infants born between 28 and 36 weeks of GA; and (3) full-term (FT) infants born at ≥ 37 weeks of GA. Given the strong correlation between birth weight (BW) and GA, both indicate the level of prematurity in preterm infants.

Individuals who (1) died during the follow-up after birth ($n = 5971$), (2) were diagnosed with chromosomal anomalies ($n = 5080$), (3) had any malignancies ($n = 5475$), or (4) possessed incomplete medical records ($n = 106,056$) were excluded. Finally, a total of 2,224,476 children were included in the final analysis.

Definition of asthma and atopic dermatitis

Asthma and AD were the primary outcomes of interest. Asthma was defined as having > 3 outpatient or inpatient visits coded as J45 or J46 according to the ICD-10 codes within a year, with at least 6 months separating the first and last visits. Early-onset asthma was categorized as a clinical diagnosis made before the child reached 2 years of age. Severe asthma was determined by at least 1 hospital visit of status asthmaticus (coded as J46 in ICD-10) or > 1 emergency department visit primarily for asthma.

AD was characterized by > 3 hospital visits for AD coded as J20.8 and J20.9 within a year, using the ICD-10 codes. An early AD diagnosis was defined as that made before the child reached 2 years of age. Severe AD was identified in patients
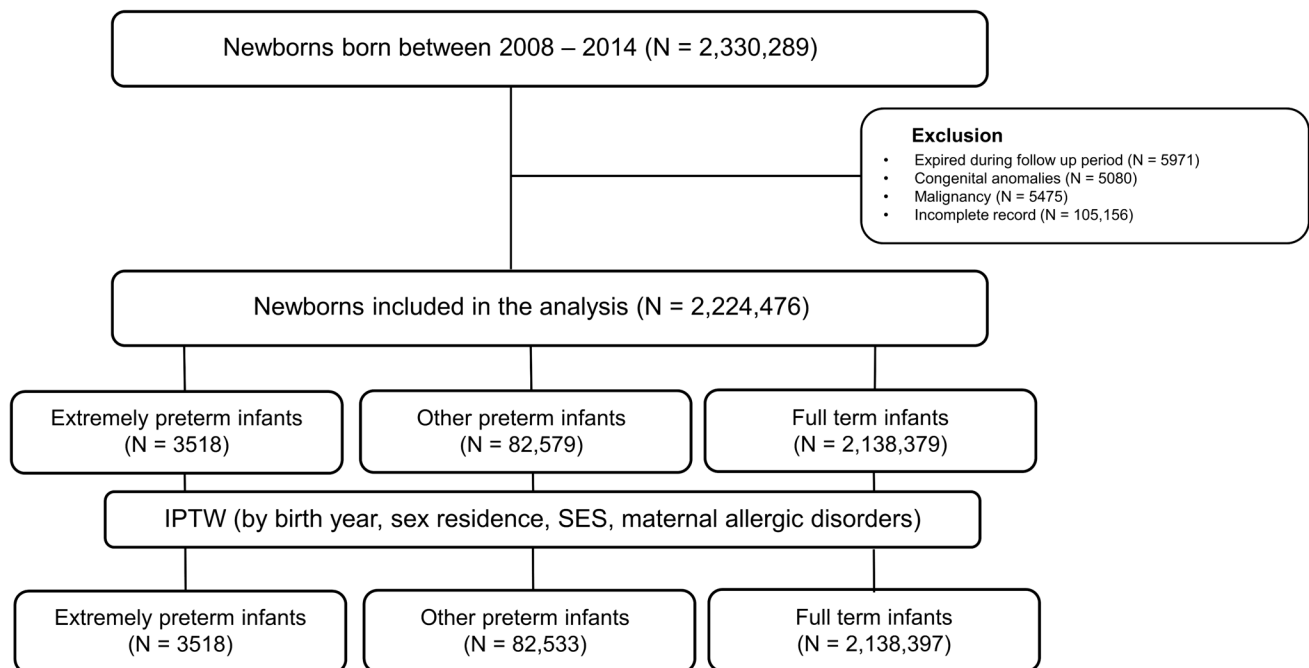
Fig. 1 Flow diagram of the study population. Abbreviations: IPTW, inverse probability of treatment-weighted; SES, socioeconomic status

Table 1 Baseline characteristics of the pediatric population before and after inverse probability of treatment weighting (IPTW)

	Pre-IPTW				Post-IPTW			
	EP group $n=3518$ (0.2)	OP group $n=82,579$ (3.7)	FT group $n=2,138,379$ (96.1)	Maximum ASD	EP group $n=3549$ (0.2)	OP group $n=82,938$ (3.7)	FT group $n=2,138,358$ (96.1)	Maximum ASD
Variables included in IPTW								
Sex				0.07				0.03
Boys	1796 (51.0)	45,097 (54.6)	1,093,814 (51.1)		1877 (52.9)	43,303 (52.2)	1,096,585 (51.2)	
Girls	1722 (49.0)	37,482 (45.4)	1,044,565 (48.9)		1672 (47.1)	39,635 (47.8)	1,041,773 (48.7)	
Birth year				0.08				0.05
2008–2010	1235 (35.1)	32,362 (39.2)	821,608 (38.4)		1337 (37.7)	29,248 (35.3)	821,966 (38.4)	
2011–2014	2283 (64.9)	50,217 (60.8)	1,316,771 (61.6)		2212 (62.3)	53,690 (64.7)	1,316,393 (61.6)	
Residence				0.03				0.03
Metropolitan	1608 (45.7)	37,968 (46.0)	952,951 (44.6)		1563 (44.0)	37,532 (45.3)	954,128 (44.6)	
Rural	1910 (54.3)	44,611 (54.0)	1,185,428 (55.4)		1986 (56.0)	45,406 (54.7)	1,184,230 (55.4)	
SES				0.05				0.07
Q1	410 (11.7)	9368 (11.3)	226,689 (10.6)		366 (10.3)	8809 (10.6)	227,311 (10.6)	
Q2	795 (22.6)	18,420 (22.3)	495,053 (23.2)		822 (23.2)	19,200 (23.2)	494,359 (23.1)	
Q3	1429 (40.6)	32,164 (39.0)	856,067 (40.0)		1470 (41.4)	33,207 (40.0)	855,219 (40.0)	
Q4	884 (25.1)	22,627 (27.4)	560,570 (26.2)		891 (25.1)	21,722 (23.2)	561,469 (26.3)	
Maternal asthma	181 (5.1)	4172 (5.1)	94,938 (4.4)	0.03	173 (4.9)	3733 (4.5)	95,450 (4.5)	0.02
Maternal AD	82 (2.3)	1843 (2.2)	44,967 (2.1)	0.01	72 (2.0)	1758 (2.1)	45,077 (2.1)	<0.01
Variables not included in IPTW								
GDM	371 (10.6)	21,187 (25.7)	476,637 (22.3)	0.40	848 (23.9)	19,315 (23.3)	478,865 (22.4)	0.04
Cesarean section	2136 (60.7)	45,903 (55.6)	731,008 (24.2)	0.79	1221 (34.4)	28,649 (34.5)	748,858 (35.0)	0.23
PIH	120 (3.4)	4904 (5.9)	61,824 (2.9)	0.15	110 (3.1)	2375 (2.9)	64,242 (3.0)	0.01
IUGR	105 (3.0)	2899 (3.5)	6000 (0.3)	0.23	95 (2.7)	2621 (3.2)	6008 (0.3)	0.22
RDS	3017 (85.8)	18,020 (21.8)	11,485 (0.5)	3.39	2951 (83.2)	16,838 (20.3)	11,519 (0.5)	3.07
BPD	2620 (74.5)	4964 (6.0)	202 (<0.1)	2.41	2511 (70.8)	4612 (5.6)	204 (<0.1)	2.20
Pulmonary hypertension	258 (7.3)	745 (0.9)	708 (<0.1)	0.39	241 (6.8)	708 (0.9)	715 (<0.1)	0.38
Allergic proctocolitis	56 (1.6)	1044 (1.3)	25,830 (1.2)	0.03	74 (2.1)	1003 (1.2)	25,855 (1.2)	0.07
Birth weight, kg	1.1 (0.9, 2.0)	2.3 (1.9, 2.6)	3.2 (3.0, 3.5)	8.23	1.1 (0.9, 2.1)	2.3 (1.9, 2.6)	3.2 (3.0, 3.5)	8.10

Categorical variables are presented as number (%). Abbreviations: *IPTW*, inverse probability of treatment weighting; *EP*, extremely preterm; *OP*, other preterm; *FT*, full term; *SES*, socioeconomic status; *Q*, quartile; *AD*, atopic dermatitis; *ASD*, absolute standardized difference; *GDM*, gestational diabetes mellitus; *PIH*, pregnancy-induced hypertension; *IUGR*, intrauterine growth restriction; *RDS*, respiratory distress syndrome; *BPD*, bronchopulmonary dysplasia. Categorical variables are presented as number (%) and continuous variables are presented as median (Q1, Q3)

who, upon diagnosis, were prescribed high-potency topical steroids, methotrexate, or cyclosporine.

Covariates

Demographic data, including the child's sex, birth year, residence, and socioeconomic status (SES), were sourced from the NHIS database. Residence was classified into metropolitan or rural, with metropolitan areas including Seoul and the six major Korean cities, exceeding a population of 1 million. SES was inferred from health insurance premium quartiles, which are indicative of household income levels.

Maternal and perinatal conditions, such as delivery type, maternal gestational diabetes mellitus (GDM), and

pregnancy-induced hypertension (PIH), were linked to each child through maternal data in the NHIS database. Neonatal comorbidities, including respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), pulmonary hypertension, and allergic proctocolitis, were considered potential confounders and included in the analysis. However, given their prevalence in preterm infants, these comorbidities were excluded from the inverse probability of treatment-weighted (IPTW) analysis.

Furthermore, neonatal comorbidities, such as RDS, BPD, patent ductus arteriosus (PDA), pulmonary hypertension, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), hypothyroidism, neonatal sepsis, neonatal jaundice, and retinopathy of prematurity (ROP), were investigated as risk factors for asthma and AD. Online Resource 2 provides comprehensive details of variables.

Statistical analysis

We employed the IPTW based on the propensity score (PS) to mitigate selection bias for assessing the incidence of asthma and AD among the three population subgroups. This approach involved creating a pseudo-dataset, in which each participant was weighted according to the IPTW. Then, the dataset was subjected to regression analysis. The PS for each subgroup was determined using a logistic regression model incorporating baseline demographic information (sex, birth year, residence, and SES) and maternal factors (maternal asthma, maternal AD, GDM, cesarean section, PIH, and intrauterine growth restriction (IUGR)).

Baseline demographic characteristics and comorbidities across groups were compared using a one-way analysis of variance for continuous variables and the chi-squared test for categorical variables. We calculated the maximum absolute standardized difference (ASD) for each variable to assess the balance of characteristics among the groups, considering the maximum ASD of < 0.1 indicative of well-balanced variables between the groups.

Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for the risk of developing asthma and AD were derived from Cox proportional hazards models. A multivariate Cox regression analysis was conducted to adjust for potential confounders specific to each disease. For asthma, variables such as RDS, BPD, and pulmonary hypertension were adjusted. Regarding AD, adjustments were made for allergic proctocolitis. The assumption of proportional hazards was verified using log-minus-log plots.

The incidence of asthma and AD by age was depicted using Kaplan–Meier survival curves, with differences among subgroups assessed using the log-rank test. Additionally, logistic regression analysis was employed to identify major risk factors for diseases. A p-value < 0.01 indicated

statistical significance. Statistical analyses were conducted using the SAS Enterprise Guide (version 7.1, SAS Institute Inc., Cary, NC, USA).

Sensitivity analysis

An additional sensitivity analysis was conducted to validate our statistical analysis. We divided the study population into three groups according to BW: extremely low birth weight (ELBW) including those with BW < 1 kg, low birth weight (LBW) including those with BW < 2.5 kg, and normal birth weight (NBW). We selected children who were assigned birth codes regarding BW. The IPTW with covariates, such as sex, birth year, residence, SES, maternal allergic disorders, GDM, cesarean section, PIH, and IUGR, was included

Table 2 Generalized linear model presenting the association between preterm birth and pediatric chronic disease (asthma and AD)

	N (%)	Crude model	Adjusted model[d]
Asthma[a,b,c]			
FT group	367,673 (17.2)	Reference	Reference
OP group	18,044 (21.8)	2.05 (1.93–2.17)	1.51 (1.41–1.63)
EP group	1133 (32.0)	1.30 (1.28–1.32)	1.24 (1.22–1.26)
Early asthma[a,b,c]			
FT group	66,588 (3.1)	Reference	Reference
OP group	3050 (3.7)	1.19 (1.15–1.24)	1.10 (1.06–1.15)
EP group	190 (5.3)	1.78 (1.55–2.06)	1.15 (0.97–1.36)
Severe asthma[a,b,c]			
FT group	20,437 (1.0)	Reference	Reference
OP group	1230 (1.5)	1.59 (1.50–1.69)	1.40 (1.32–1.50)
EP group	107 (3.0)	3.47 (2.87–4.20)	1.62 (1.28–2.05)
AD[a,b,c]			
FT group	513,769 (24.0)	Reference	Reference
OP group	17,949 (21.6)	0.73 (0.68–0.79)	0.73 (0.67–0.79)
EP group	656 (18.5)	0.88 (0.87–0.89)	0.88 (0.87–0.89)
Early AD[a,b,c]			
FT group	307,050 (14.4)	Reference	Reference
OP group	10,088 (12.2)	0.83 (0.81–0.85)	0.83 (0.81–0.85)
EP group	336 (9.5)	0.64 (0.57–0.71)	0.63 (0.57–0.71)
Severe AD[a,b,c]			
FT group	137,784 (6.4)	Reference	Reference
OP group	4565 (5.5)	0.83 (0.81–0.86)	0.83 (0.81–0.86)
EP group	150 (4.2)	0.63 (0.54–0.74)	0.63 (0.53–0.73)

Abbreviations: *EP*, extremely preterm; *OP*, other preterm; *FT*, full term; *AD*, atopic dermatitis

Numbers are expressed with an adjusted hazard ratio (95% confidence interval)

[a]$p < 0.001$ in post hoc analysis (EP group vs. OP group), [b]$p < 0.001$ in post hoc analysis (EP group vs. FT group), [c]$p < 0.001$ in post hoc analysis (OP group vs. FT group)

[d]Adjusted for RDS, BPD, and pulmonary hypertension for asthma; adjusted for allergic proctocolitis for AD
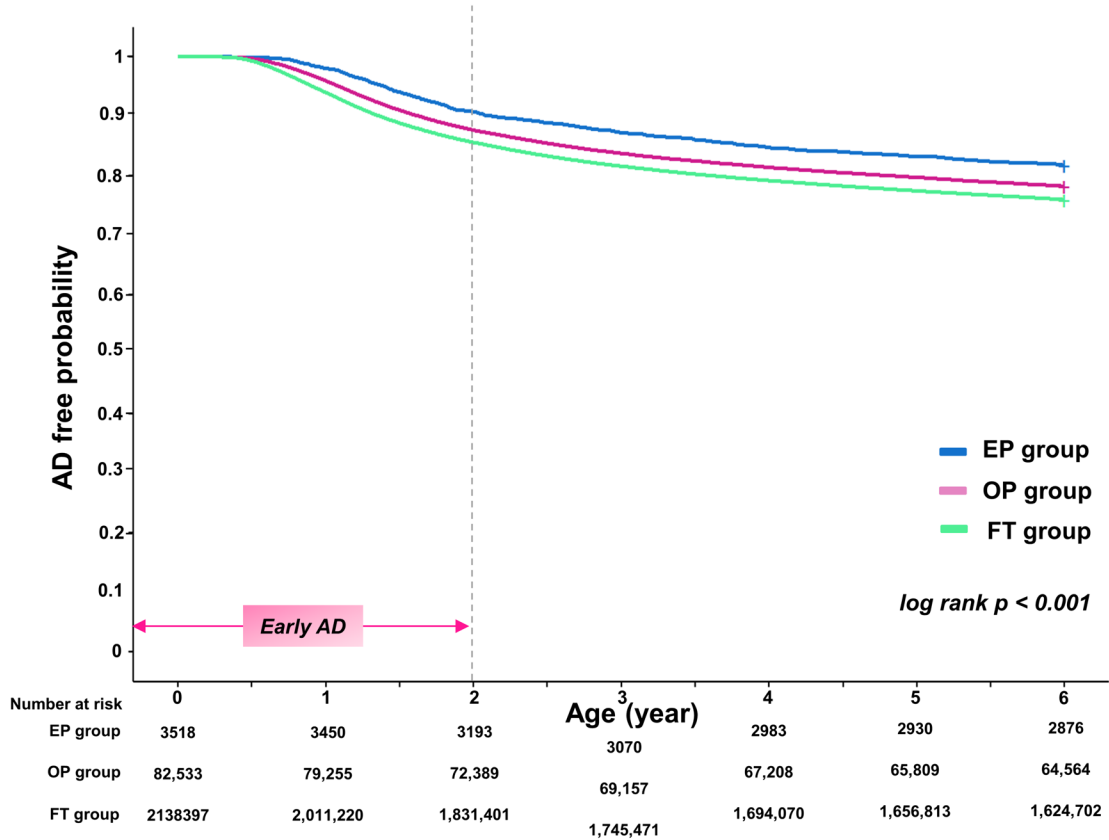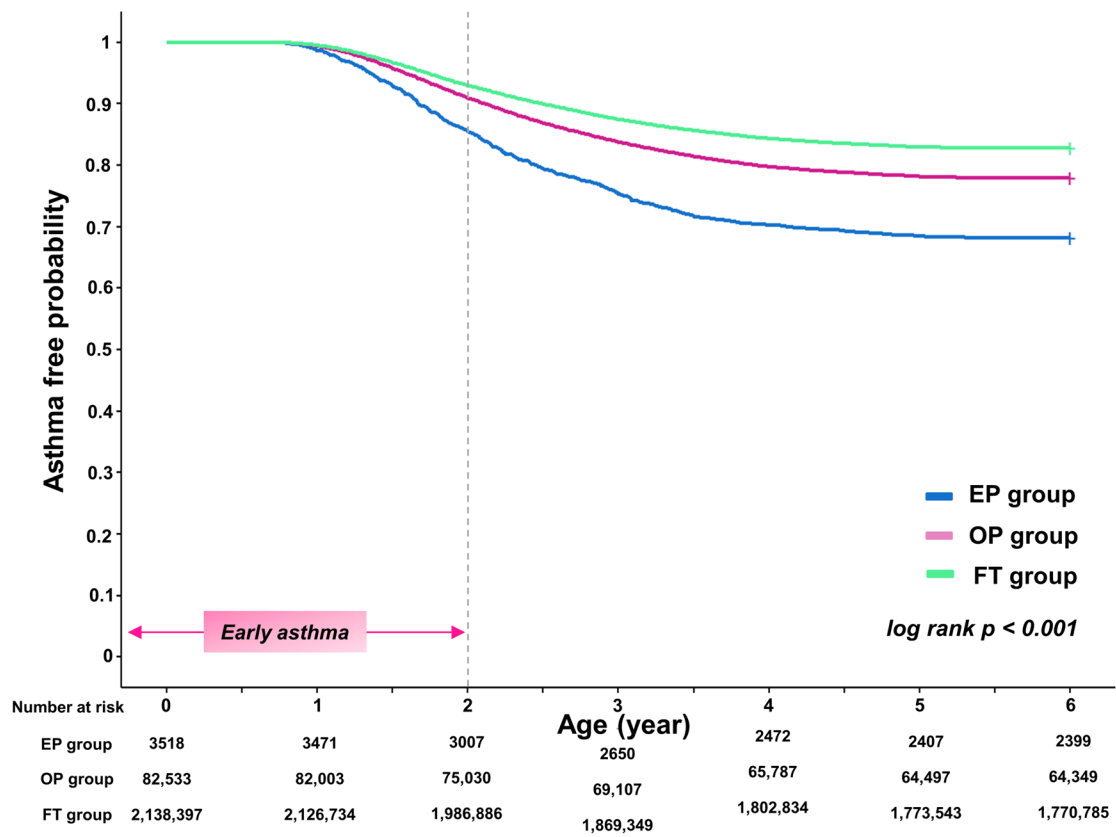
◄**Fig. 2** The Kaplan–Meier curve presenting the risk of asthma and AD according to the degree of prematurity. **a** Risk of asthma. **b** Risk of AD. The *x*-axis represents the age of the population, and the *y*-axis represents the disease-free probability. The number of children at risk of each study group is included. Abbreviations: EP, extremely preterm infants; OP, other preterm infants; FT, full-term infants; AD, atopic dermatitis

in the analysis. Then, the association between BW and diseases (asthma and AD) was validated and expressed as HR with 95% CI using the Cox proportional hazards model.

Results

Participants' characteristics

Among the study cohort of 2,224,476 individuals, 3518 (0.2%) were categorized as EP, 82,579 (3.7%) were categorized as OP, and 2,138,379 (96.1%) were categorized as FT (Table 1). Maternal asthma prevalence was lowest in the FT group compared to the EP and OP groups (5.1% in EP, 5.1% in OP, and 4.4% in FT; $p < 0.001$). Similarly, maternal AD was the commonest in the EP group, followed by the OP and FT groups (2.3% in EP, 2.2% in OP, and 2.1% in FT; $p < 0.001$). The frequencies of cesarean section, PIH, and IUGR were significantly higher among preterm infant groups than in the FT group. Before applying the IPTW, the maximum ASD for GDM, cesarean section, PIH, and IUGR exceeded 0.1. However, after IPTW adjustment, all baseline demographic characteristics were well balanced with a maximum ASD of < 0.1 except for IUGR.

Median BW was 3.2 kg (Q1, Q3: 3.0, 3.5) for the FT group, 2.3 kg (Q1, Q3: 1.9, 2.6) for the OP group, and 1.1 kg (Q1, Q3: 0.9, 2.1) for the EP group. The incidence of neonatal morbidities, including RDS, BPD, pulmonary hypertension, and allergic proctocolitis, was significantly higher in the EP group compared to the other groups ($p < 0.001$).

Incidence and risk of pediatric asthma and AD

Table 2 presents the incidence of diseases and the results of regression analysis. The incidence of asthma was the highest in the EP group, followed by the OP group, and then the FT group (32.0% vs. 21.8% vs. 17.2%, $p < 0.001$). This pattern was consistent for both early-onset and severe asthma, with the highest incidence in the EP group, followed by the OP and FT groups. Conversely, the incidence of AD was the highest in the FT group, followed by the OP and EP groups (24.0% vs. 21.6% vs. 18.5%, $p < 0.001$). The Kaplan–Meier curves illustrated the incidence of asthma and AD across the three groups over the observation period from ages 0 to 6 years (Fig. 2). Asthma was the most prevalent in the EP

group, while AD was the most prevalent in the FT group (log-rank $p < 0.001$).

Regression analysis indicated that both preterm groups had a significantly higher risk of asthma (aHR for the EP group 1.24, 95% CI 1.22–1.26; aHR for the OP group 1.51, 95% CI 1.41–1.63). Notably, the OP group exhibited a significant risk for both early-onset and severe asthma during preschool ages (aHR 1.10, 95% CI 1.06–1.15 for early-onset asthma; aHR 1.40, 95% CI 1.32–1.50 for severe asthma). Regarding AD, preterm infants demonstrated a significantly lower risk (aHR for the OP group 0.73, 95% CI 0.67–0.79; aHR for the EP group 0.88, 95% CI 0.87–0.89). This association remained significant for both early-onset and severe AD.

Risk factors for pediatric asthma and AD

Analysis revealed several neonatal comorbidities associated with the later development of asthma and AD (Table 3). Cardiorespiratory conditions, such as RDS, BPD, PDA, and pulmonary hypertension, significantly increased the risk of asthma. Specifically, BPD emerged as a significant risk factor for both severe and early-onset asthma (odds ratio (OR) 1.36, 95% CI 1.21–1.37 for severe asthma; OR 1.55, 95% CI 1.30–1.85 for early asthma), while it was associated with a decreased risk of AD (OR 0.86, 95% CI 0.80–0.92). Neonatal sepsis, jaundice, and ROP were also identified as significant risk factors for later asthma. Online Resource 3 provides association between pediatric asthma and atopic dermatitis according to baseline characteristics of the pediatric population and neonatal comorbidities.

Sensitivity analyses

The analysis included participants with ELBW (0.2%, $n = 4025$) and LBW (2.5%, $n = 54,867$) (Online Resource 4). Children born small had a significantly elevated risk of asthma and a decreased risk of AD, aligning with the main results (Table 4).

Discussion

In our study, we explored the risk of asthma and AD in preterm infants, leveraging nationwide medical claims data from Korea. Our analysis not only assessed the overall risk associated with asthma and AD but also examined their onset and severity across different degrees of prematurity according to GA. We found that preterm infants exhibit a significantly higher risk of developing asthma and a relatively lower risk of AD compared to the FT control group. Moreover, our findings indicate an increased vulnerability among preterm children to both early-onset and severe forms

Table 3 Logistic regression analysis presenting the association between neonatal comorbidities and pediatric chronic disease (asthma and AD)

Comorbidity	Asthma	Early asthma	Severe asthma	AD	Early AD	Severe AD
RDS	1.09 (1.05–1.14)	1.16 (1.06–1.26)	1.11 (0.98–1.27)	0.91 (0.88–0.95)	0.89 (0.84–0.93)	0.93 (0.87–1.00)
BPD	1.29 (1.21–1.37)	1.36 (1.20–1.55)	1.55 (1.30–1.85)	0.86 (0.80–0.92)	0.81 (0.74–0.89)	0.77 (0.67–0.88)
PDA	1.12 (1.06–1.18)	1.01 (0.90–1.13)	1.36 (1.17–1.59)	0.95 (0.90–1.00)	0.93 (0.87–1.00)	0.88 (0.79–0.98)
Pulmonary hypertension	1.16 (1.01–1.33)	1.29 (0.98–1.70)	1.25 (0.87–1.85)	1.10 (0.94–1.28)	1.10 (0.91–1.35)	1.01 (0.74–1.36)
NEC	0.93 (0.83–1.04)	0.90 (0.71–1.15)	0.68 (0.48–0.97)	0.87 (0.77–0.99)	0.97 (0.82–1.14)	0.73 (0.56–0.94)
IVH	1.02 (0.96–1.08)	0.98 (0.86–1.11)	0.88 (0.73–1.06)	1.00 (0.94–1.06)	0.98 (0.91–1.06)	1.04 (0.93–1.16)
Hypothyroidism	1.15 (1.08–1.23)	1.02 (0.88–1.18)	1.14 (0.93–1.38)	1.08 (1.01–1.16)	1.04 (0.95–1.13)	1.11 (0.98–1.26)
Neonatal sepsis	1.07 (1.03–1.13)	0.99 (0.90–1.10)	1.30 (1.13–1.48)	1.04 (0.99–1.09)	1.06 (0.99–1.12)	1.07 (0.98–1.16)
Neonatal jaundice	1.04 (1.00–1.08)	1.07 (0.98–1.17)	1.04 (0.91–1.19)	1.04 (0.99–1.08)	1.07 (1.01–1.12)	1.08 (1.00–1.16)
ROP	1.09 (1.05–1.13)	1.06 (0.97–1.14)	1.20 (1.06–1.35)	1.04 (1.00–1.07)	1.03 (0.98–1.08)	1.00 (0.94–1.07)

Adjusted for sex, residence, socioeconomic status, maternal asthma, maternal AD, maternal GDM, cesarean section, PIH

Numbers are expressed as odds ratios (95% confidence interval). Abbreviations: *AD*, atopic dermatitis; *RDS*, respiratory distress syndrome; *BPD*, bronchopulmonary dysplasia; *NEC*, necrotizing enterocolitis; *IVH*, intraventricular hemorrhage; *PDA*, patent ductus arteriosus; *ROP*, retinopathy of prematurity

of asthma. In our study, the prevalence of asthma and the incidence of early-onset and severe asthma were higher in the EP group than in the OP group. Thus, the lower the GA, the higher the prevalence of asthma, early-onset asthma, and severe asthma. Additionally, the presence of cardiorespiratory comorbidities, such as RDS, BPD, PDA, and pulmonary hypertension, in the neonatal period was identified as a significant risk factor for asthma in preschool-aged children.

Asthma is coded as J45 when it is confirmed through a pulmonary function test, but pulmonary function tests are difficult in children. Additionally, diagnosing asthma is challenging because wheezing is frequent in children aged < 6 years. For coding asthma in children under 6 years, we use the "asthma prediction index" [20, 21]. Asthma was diagnosed and coded as J45 in patients with ≥ 2 wheezing episodes (clinically or coded R06.2) or bronchiolitis diagnosis if parents have asthma or high IgE. According to the Korean pediatric asthma treatment guidelines, treatment adjustment and step-down are performed at least in 2-month intervals after diagnosis [22, 23]. We suggest that patients visiting the hospital 2–3 times in at least 3-month intervals can be accurately diagnosed with asthma; thus, we set this criteria. Although these strict standards may have decreased the number of enrollees, it is believed that there was no major error given that the prevalence rate was similar to the results of other cohort studies. Our results align with those of Sol et al. [9], who reported asthma prevalence of 26.5% in children aged < 2 years and 25.8% in children aged < 6 years, corroborating our findings.

Regarding AD, our incidence was higher than that reported by a previous study: 17.2% in patients aged < 2 years and 7.3% in those aged < 5 years [24]. J20 code is used when simple eczematous skin lesions persist for > 6 weeks and are accompanied by itching [25]. Only patients who consistently visited the hospital according to the guidelines received treatment for AD and were coded as AD each time they were selected as study subjects to rule out the possibility that simple eczematous lesions or other differential diseases were misdiagnosed as AD [26, 27].

The main symptom of asthma is airway hyperresponsiveness, with still unclarified underlying mechanisms. Several studies showed that bronchial hyperresponsiveness can occur in premature infants due to various reasons. Clemm et al. [28] showed that exposure to tracheal intubation and oxygen therapy could induce structural deformations possibly resulting in airway hyperresponsiveness. Another potential cause of asthma may be that preterm infants with GA < 32 weeks are born with a structurally immature respiratory system. Preterm children lack sufficient time for alveolar maturation, mainly occurring after 32 weeks of GA, and receiving large quantities of maternal transplacental antibodies that could be protective against frequent respiratory infections [29–32]. This increases the risk of respiratory infections and can lead to bronchial hyperresponsiveness. Additionally, the inflammatory response caused by proinflammatory cytokines, such as TNF-α and IL-6, occurring in RDS also causes bronchial hyperresponsiveness. Moreover, the high incidence of RDS in premature infants might contribute to the high incidence of asthma [33]. Delaying treatment for asthma can lead to impaired lung function in adulthood. Thus, early diagnosis and management of asthma are critical to estimate the prognosis for lung function [34].

Unlike asthma, we found that the risk of AD was higher in the FT group. Moreover, the EP group had the lowest incidence and aHRs for early and severe AD. Some previous studies showed conflicting results as to whether preterm birth increases the risk of AD [35, 36]. The significance between

AD and the degree of prematurity has not yet been clarified. There are many studies showing that the skin barrier and immune response affect the development of AD [19].

Compared with other studies, our study was based on the most recent births (over 2 million) in a nationwide population representing the general pediatric population (a large-scale national study). In our study, the risk of AD was higher in the FT group. We suggest that still developing immune response might contribute to atopic sensitization. As GA increases, the fetal immune response to specific antigens strengthens, and the intestinal non-immune defense system matures [37, 38]. Consistent with the findings of Mitselou et al. [39], preterm birth is associated with a reduced risk of sensitization to food or inhalant allergens compared to FT births. This diminished risk of allergen sensitization could be attributed to early microbial exposure, fostering an enhanced Th-1-type adaptive immune response [40]. Therefore, we speculate that the earlier exposure to allergens in

Table 4 Sensitivity analysis of the association between population subgroup and pediatric chronic disease (asthma and AD) according to birth weight

	Adjusted model[a]
Asthma	
NBW group	Reference
LBW group	1.17 (1.14–1.20)
ELBW group	1.43 (1.32–1.55)
Early asthma	
NBW group	Reference
LBW group	1.06 (0.99–1.12)
ELBW group	0.99 (0.80–1.24)
Severe asthma	
NBW group	Reference
LBW group	1.39 (1.26–1.52)
ELBW group	2.28 (1.74–3.00)
AD	
NBW group	Reference
LBW group	0.89 (0.87–0.91)
ELBW group	0.77 (0.71–0.84)
Early AD	
NBW group	Reference
LBW group	0.84 (0.82–0.87)
ELBW group	0.76 (0.68–0.85)
Severe AD	
NBW group	Reference
LBW group	0.87 (0.83–0.90)
ELBW group	0.52 (0.43–0.64)

Abbreviations: *FT*, full term; *LBW*, low birth weight; *ELBW*, extremely low birth weight; *NBW*, normal birth weight; *AD*, atopic dermatitis

[a]Adjusted for RDS, BPD, and pulmonary hypertension for asthma and adjusted for allergic proctocolitis for AD

FT infants might account for their increased risk of both early-onset and severe AD.

Individuals with AD may suffer from diverse issues, including chronic fatigue from insomnia, psychological distress, and a diminished quality of life [41]. While AD may improve with age, severe cases are less likely to resolve spontaneously and persistent AD increases may precede the development of other diseases, such as allergic rhinitis and asthma [42, 43]. It is called as "allergic march." Therefore, effectively managing AD is crucial to preventing its progression.

Our study also explored risk factors for asthma and AD among neonatal comorbidities, finding that cardiopulmonary complications, such as RDS, PDA, BPD, and pulmonary hypertension, significantly predict the later development of asthma. Although the precise mechanisms underlying asthma development remain unclear, early lung injury — including exposure to repetitive oxygen therapy and tracheal intubation — might play a contributory role.

This study has several limitations. First, the reliance on medical claims data, collected primarily for reimbursement purposes, might influence the accuracy of the diagnoses coded by physicians. Second, the lack of data on allergic history or environmental factors (e.g., exposure to house dust mites or sanitation status) limits our analysis. Third, our observation period extended only until the preschool age, precluding the identification of asthma and AD that may emerge during pre-adolescence. Additionally, detection bias is a concern. Since preterm birth is likely associated with increased medical treatment, children born preterm may be more likely to be diagnosed with asthma or AD, thereby biasing results.

Despite these limitations, this study analyzed a large nationwide population to estimate the risk of asthma and AD in preterm infants in Korea, covering 6 years including both infancy and toddlerhood. We differentiated the population by GA and categorized asthma and AD into early-onset and severe forms. Preterm birth was significantly associated with asthma and inversely associated with AD. Further studies regarding its clinical mechanism are required, as well as studies for targeted respiratory and dermal management and prevention of asthma and AD for this high-risk population.

Conclusion

Preterm children exhibit a significantly higher risk of asthma but a lower risk of AD compared to their FT counterparts. Emphasizing long-term respiratory care for preterm infants, especially those with cardiopulmonary comorbidities, is crucial for asthma prevention. Conversely, to prevent the development of AD, more attention should be paid to FT children. Continued and larger research for prevention is needed.

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Data availability The data presented in this study are available on request from the corresponding author.

Declarations

Conflict of interest The authors declare no competing interests.

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