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Cord blood IgE predicts allergic sensitization, elevation of exhaled nitric oxide, and asthma in schoolchildren

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Abstract

Background: Few data are available in Asian children regarding the validity of cord blood immunoglobulin E (IgE) in predicting allergic sensitization and pulmonary function. The relationship between cord blood IgE and fraction of exhaled nitric oxide (FeNO) remains unknown. This study investigated the associations of cord blood IgE with allergic sensitization, FeNO, pulmonary function, and allergic diseases in Asian children.

Methods: Five hundred and sixty-six Asian children with valid cord blood IgE measurements at birth participated a 6-year follow-up visit including a questionnaire, serum total and allergen-specific IgE, FeNO measurement, and spirometry. Regression-based analyses with covariates adjustment were applied.

Results: Cord blood IgE levels were significantly associated with FeNO levels ($\beta = 0.131$, $p < .001$) and serum total IgE levels ($\beta = 0.325$, $p < .001$). Cord blood IgE levels were positively associated with allergic sensitization (adjusted odds ratio [AOR] = 2.22, $p < .001$), and sensitization to mites ($p = .002$), animals ($p = .023$), and foods ($p = .048$). Subjects with cord blood IgE ≥0.24 kU/L (the optimal cutoff) were significantly associated with an increased risk of allergic sensitization (AOR = 2.63, $p < .001$) and asthma (AOR = 2.35, $p = .024$) than those with cord blood IgE <0.24 kU/L. Subjects with cord blood IgE ≥0.24 kU/L had significantly higher FeNO levels than those with cord blood IgE <0.24 kU/L ($p = .028$). There were no significant associations between cord blood IgE levels and pulmonary function parameters.

Abbreviations: AOR, adjusted odds ratio; ATS, American Thoracic Society; BMI, body mass index; CGMH, Chang Gung Memorial Hospital; CI, confidence interval; ERS, European Respiratory Society; FEF_{25-75}, forced expiratory flow at 25%–75%; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IgE, immunoglobulin E; ISAAC, International Study of Asthma and Allergies in Childhood; LIGHTS, Longitudinal Investigation of Global Health in Taiwanese Schoolchildren; NTD, new Taiwan dollar; PEF, peak expiratory flow; ROC, receiver-operator characteristic; SD, standard deviation.

Conclusion: Cord blood IgE ≥0.24 kU/L predicts allergic sensitization, FeNO elevation, and asthma among Asian schoolchildren, suggesting cord blood IgE would be useful for identifying newborns at risk of subsequent allergic sensitization and allergic airway inflammation.

KEYWORDS
allergic sensitization, asthma, cord blood IgE, exhaled nitric oxide, pulmonary function

1 | INTRODUCTION

The rising prevalence of allergic diseases worldwide represents an important health problem. Early identification of children at high risk of allergic diseases could be helpful for physicians to recommend preventive measures and apply early interventions. Cord blood immunoglobulin E (IgE) has been considered as a potential marker for years due to its predictability for allergic diseases, but the results are controversial.[1] Several studies have reported that elevated cord blood IgE may predict allergic diseases and/or allergic sensitization in childhood,[2–9] whereas other studies failed to find it as a good predictor.[10–14]

The inconsistent results observed in previous studies when using cord blood IgE as a predictor for atopy may be explained in part by the different definitions of atopy (or allergic sensitization). Some studies suggested that cord blood IgE may not be a sensitive predictor of atopy when atopy was defined based on clinical symptoms without objective measurements of allergic sensitization.[10,11] In contrast, cord blood IgE could serve as a useful predictor of allergic sensitization when atopy was defined by a positive skin prick test[4–6] or detectable allergen-specific IgE to at least one of the test allergens.[14,15] However, the role of cord blood IgE in predicting sensitization to specific allergens in childhood remains unclear. Furthermore, ethnic differences in cord blood IgE levels were reported previously,[16,17] but few data are available in Asian children regarding the validity of cord blood IgE levels in predicting allergic sensitization.

The fraction of exhaled nitric oxide (FeNO) levels serves as a noninvasive marker of allergic airway inflammation in children.[18] Previous studies by our group and others have demonstrated the positive association between allergic sensitization and FeNO levels.[19–22] However, to our knowledge, there has been no study investigating the relationship between cord blood IgE and FeNO levels in a population setting. In addition to FeNO levels, some studies reported that atopy, especially sensitization to individual allergens, was associated with impaired pulmonary function.[23–25] The relationship between cord blood IgE and childhood pulmonary function remains unclear.[9,26]

The objective of this study was to investigate the associations of cord blood IgE levels with allergic sensitization, FeNO, pulmonary function, and allergic diseases in a population-based sample of Asian children, and to determine an optimal cutoff value of cord blood IgE.

Key Message

The role of cord blood IgE in predicting allergic sensitization, FeNO, pulmonary function, and allergic diseases remains unclear. This population-based cohort study of 566 Asian children has identified an optimal cutoff value of cord blood IgE at 0.24 kU/L in predicting allergic sensitization, elevated FeNO levels, and asthma. Cord blood IgE levels are not predictive of childhood pulmonary function.

2 | METHODS

2.1 | Study subjects

This study included 566 children participating in the Longitudinal Investigation of Global Health in Taiwanese Schoolchildren (LIGHTS) study, a prospective population-based cohort study designed to longitudinally investigate the effects of early-life environmental exposures and genetic predisposition on childhood allergic outcomes.[27–29] In the LIGHTS cohort, 1513 children born in 2010–2011 in the Chang Gung Memorial Hospital attended a 6-year follow-up visit. A total of 566 children with valid cord blood IgE measurements at birth were included in the current study. The perinatal health information was obtained from the electronic medical records in the Chang Gung Memorial Hospital, Taiwan. Parents of the participants answered a modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.[30] Data collected in the questionnaire included general health information, demographics and clinical data. An interview conducted by pediatricians was applied to all subjects. Blood samples were drawn for subsequent measurement of serum total and allergen-specific IgE. Measurements of FeNO and pulmonary function were performed in standard procedures. This study was approved by the Institutional Review Board of Chang Gung Medical Foundation (No.201600334A3), and the parents of each subject provided written informed consent.

2.2 | Cord blood IgE

Cord blood was collected by needle puncture from the umbilical cord vein at birth, and separated serum was frozen before analyses. The

level of cord blood IgE was quantified by a fluoroenzyme immunoassay using ImmunoCAP® Total IgE Low Range (Phadia, Uppsala, Sweden).

2.3 | Primary and secondary outcomes

The primary outcome was allergic sensitization at 6 years of age. The secondary outcomes were FeNO, pulmonary function, and allergic diseases or symptoms.

2.4 | Total and allergen-specific serum IgE

Serum total IgE was determined by ImmunoCAP® (Phadia, Uppsala, Sweden). Allergic sensitization was defined as a positive Phadiatop Infant test result (≧0.35 PAU/L) (Phadia, Uppsala, Sweden), detecting allergen-specific IgE against a mix of common inhalant and food allergens.[31] Serum levels of allergen-specific IgE were measured using an automated microfluidic-based multiplexed immunoassay system (BioIC™ Allergen-specific IgE Detection Kit- AD40 Panel; Agnitio Science and Technology, Hsinchu, Taiwan). The following six categories were included for subsequent analysis: (1) mites: Dermatophagoides pteronyssinus, Dermatophagoides farinae, and Blomia tropicalis; (2) animals: dog dander, cat dander, chicken feather and skin, and duck feather and skin; (3) cockroaches: mixed classes; (4) pollen: timothy grass, bermuda grass, short ragweed, common mugwort, goldenrod, eucalyptus, and acacia; (5) foods: cow's milk, goat's milk, egg white, egg yolk, crab, shrimp, codfish, salmon, blue mussel, soybean, wheat, white potato, peanut, almond, garlic, taro, cheddar cheese, baker's yeast, kiwi, tomato, and carrot; and (6) latex.

2.5 | FeNO and pulmonary function

FeNO measurement was performed by chemiluminescence analyzer (CLD 88sp NO analyzer®, Ecomedics, Duernten, Switzerland) according to the 2005 American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations for standardized single-breath online measurement.[32] The subjects inhaled to near total lung capacity over a period of 2–3 s and exhaled for at least 4 s with a constant flow rate of 50 ml/s for the achievement of a stable NO plateau.[32] Pulmonary function was measured by spirometry (Spirolab II®, Medical International Research, Roma, Italy) following the standardized performance proposed by ATS/ERS task force as well.[33] The parameters including forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC ratio, forced expiratory flow at 25%–75% (FEF_{25-75}), and peak expiratory flow (PEF) were measured.

2.6 | Allergic diseases

Current allergic symptoms and diagnoses of allergic diseases were assessed using the ISAAC questionnaire. Asthma was defined as having the presence of wheeze in the last 12 months (current wheeze) and physician-diagnosed asthma. Allergic rhinitis and atopic eczema were defined as the presence of symptoms in the last 12 months and ever having the two diseases, respectively.

2.7 | Statistical analysis

All data analyses were performed using the SAS version 9.4 for Windows (SAS Institute, Cary, NC). Cord blood IgE, serum total IgE, and FeNO values were log10-transformed to obtain approximate normality. Multivariate analyses using linear regression were carried out to assess the associations of cord blood IgE values with FeNO and pulmonary function parameters. Multivariate logistic regression was employed to determine the associations of cord blood IgE values with allergic sensitization. The adjusted covariates were listed as follows: age, gender, height, body mass index (BMI, weight (kg)/height squared (m^2)), birth order (i.e., if the subject is first born or not), season of birth, maternal and paternal allergic diseases (i.e., physician-diagnosed asthma, allergic rhinitis, or atopic eczema), exclusive breastfeeding ≧3 months, and exposure to household passive smoking and pet in the first year of life, which were similar to those adjusted in previous relevant studies.[3–5,7] Receiver-operator characteristic (ROC) curves were generated to assess the overall validity of cord blood IgE for predicting allergic sensitization. Youden index was applied to determine the optimal cutoff value. A p-value <.05 was considered statistically significant.

3 | RESULTS

3.1 | Subject characteristics

Cord blood IgE was measured in 566 children (321 boys; age: 6.5 ± 0.4 years). Table 1 shows the characteristics of the study subjects. The mean cord blood IgE level was 0.97 ± 4.15 kU/L. Total and specific IgE levels, FeNO levels, and pulmonary function parameters were available in 536 (94.7%), 548 (96.8%), and 565 (99.8%) of 566 subjects, respectively. There were no significant differences in gender, BMI, birth order, parental allergic diseases, exclusive breastfeeding, exposure to passive smoking and pet, serum total IgE levels, allergic sensitization, FeNO levels, and allergic diseases between the 566 study subjects and the 1513 original cohort participants (Table S1). The 566 study subjects tended to have slightly higher age (6.5 ± 0.4 vs. 6.4 ± 0.4 years), greater height (119.3 ± 5.4 vs. 118.5 ± 5.7 cm), higher FVC (1.22 ± 0.23 vs. 1.19 ± 0.24 L) and FEV_1 (1.11 ± 0.22 vs. 1.09 ± 0.22 L), and a higher proportion of birth in winter (34.8% vs. 23.5%).

3.2 | Association of cord blood IgE with allergic sensitization, FeNO, and pulmonary function

There was a significant positive association between cord blood IgE levels and serum total IgE levels at school age (β = 0.325, 95%

TABLE 1 Characteristics of study subjects

Characteristic	Sample size	Data[a]
Age (year)	566	6.5 ± 0.4
Gender	566	
Male		321 (56.7)
Female		245 (43.3)
Height (cm)	566	119.3 ± 5.4
BMI (kg/m^2)	566	15.9 ± 2.4
Birth order, first born	566	343 (60.6)
Season of birth	566	
Spring		130 (23.0)
Summer		110 (19.4)
Autumn		129 (22.8)
Winter		197 (34.8)
Maternal asthma	561	41 (7.3)
Maternal allergic diseases	566	262 (46.3)
Paternal asthma	559	30 (5.4)
Paternal allergic diseases	565	299 (52.9)
Exclusive breastfeeding	566	282 (49.8)
Passive smoking	565	175 (31.0)
Pet exposure	566	117 (20.7)
Cord blood IgE (kU/L)	566	0.97 ± 4.15
Serum total IgE (kU/L)	536	335.1 ± 565.3
Allergic sensitization	536	358 (66.8)
Sensitization to mites	535	300 (56.1)
Sensitization to animals	535	65 (12.2)
Sensitization to cockroaches	535	18 (3.4)
Sensitization to pollen	535	89 (16.6)
Sensitization to foods	535	164 (30.7)
Sensitization to latex	535	5 (0.9)
FeNO (ppb)	548	16.6 ± 19.8
Pulmonary function	565	
FVC (L)		1.22 ± 0.23
FEV_1 (L)		1.11 ± 0.22
FEV_1/FVC ratio (%)		91.4 ± 6.4
FEF_{25-75} (L/s)		1.50 ± 0.42
PEF (L/s)		2.09 ± 0.63
Allergic diseases		
Asthma	558	38 (6.8)
Allergic rhinitis	562	271 (48.2)
Atopic eczema	564	120 (21.3)

Abbreviations: BMI, body mass index; FEF_{25-75}, forced expiratory flow at 25%–75%; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IgE, immunoglobulin E; PEF, peak expiratory flow; ppb, parts per billion.

[a]Data are shown as mean ± standard deviation or number (%), as appropriate.

confidence interval [CI]: 0.223–0.426, $p < .001$), after adjusting for age, gender, height, BMI, birth order, season of birth, parental allergic diseases, exclusive breastfeeding, and exposure to passive smoking and pet. Table 2 shows the adjusted odds ratios (AOR) of the associations between cord blood IgE levels and allergic sensitization at school age. Elevated cord blood IgE levels were significantly associated with a higher likelihood of allergic sensitization (AOR = 2.22, 95% CI: 1.54–3.20, $p < .001$) and IgE sensitization to mites (AOR = 1.68, 95% CI: 1.21–2.33, $p = .002$), animals (AOR = 1.69, 95% CI: 1.07–2.65, $p = .023$), and foods (AOR = 1.39, 95% CI: 1.01–1.94, $p = .048$) (Table 2). The associations between cord blood IgE and sensitization to specific allergens are shown in Table S2. Specifically, elevated cord blood IgE levels were significantly associated with a higher likelihood of sensitization to Dermatophagoides pteronyssinus, Dermatophagoides farinae, dog dander, egg yolk, garlic, and baker's yeast (Table S2).

Table 3 shows the associations of cord blood IgE levels with FeNO and pulmonary function parameters at school age. A significant positive association was found between cord blood IgE and FeNO levels ($\beta = 0.131$, 95% CI: 0.057–0.204, $p < .001$) (Table 3). There were no statistically significant associations between cord blood IgE levels and pulmonary function parameters (Table 3). Similar results were found when pulmonary function parameters were calculated as percentage of predicted values (Table S3). One may argue that the use of anti-inflammatory medications for asthma may affect FeNO levels. Nevertheless, the association between cord blood IgE and FeNO levels remained significant after additionally adjusting for anti-inflammatory medications (Table S4).

3.3 | Validity of cord blood IgE in predicting allergic sensitization, FeNO, and allergic diseases

A ROC curve was generated to determine the validity and the optimal cutoff value of cord blood IgE for predicting allergic sensitization at school age. The area under the ROC curve was 0.675 (95% CI: 0.626–0.723), indicating a modest discriminative accuracy. At the optimal cutoff value of 0.24 kU/L, the sensitivity, specificity, positive predictive value, and negative predictive value were 59.8%, 64.0%, 77.0%, and 44.2%, respectively.

Subjects with cord blood IgE ≥0.24 kU/L (the optimal cutoff) were significantly associated with an increased risk of allergic sensitization compared with those with cord blood IgE <0.24 kU/L (77.0% vs. 55.8%; AOR = 2.63, 95% CI: 1.78–3.89, $p < .001$). In addition, subjects with cord blood IgE ≥0.24 kU/L had significantly higher FeNO levels (median: 11.5 ppb, IQR: 3.5–25.1) than those with cord blood IgE <0.24 kU/L (median: 8.8 ppb, IQR: 3.0–19.1; $p = .028$) (Figure 1A). Subjects with cord blood IgE ≥0.24 kU/L were also associated with a higher risk of asthma (9.1% vs. 4.2%; AOR = 2.35, 95% CI: 1.12–4.94, $p = .024$) and current wheeze (17.4% vs. 9.1%; AOR = 2.03, 95% CI: 1.19–3.45, $p = .009$) than those with cord blood IgE <0.24 kU/L (Table 4).

Previous studies have suggested that cord blood IgE above 0.5 kU/L may predict allergic diseases and sensitization in childhood.[2–7] We thereby assessed the validity of cord blood IgE at the cutoff value of 0.5 kU/L in predicting allergic sensitization and FeNO

TABLE 2 Association of cord blood IgE with allergic sensitization

Category of allergen	N	(%)	AOR (95% CI)[a]	p[b]
Allergic sensitization	358	(66.8)	2.22 (1.54, 3.20)	**<.001**
Sensitization to mites	300	(56.1)	1.68 (1.21, 2.33)	**.002**
Sensitization to animals	65	(12.2)	1.69 (1.07, 2.65)	**.023**
Sensitization to cockroaches	18	(3.4)	1.25 (0.55, 2.84)	.596
Sensitization to pollen	89	(16.6)	1.24 (0.81, 1.90)	.332
Sensitization to foods	164	(30.7)	1.39 (1.01, 1.94)	**.048**
Sensitization to latex	5	(0.9)	0.49 (0.09, 2.83)	.429

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; IgE, immunoglobulin E.

[a]Adjusted covariates include age, gender, height, body mass index, birth order, season of birth, parental allergic diseases, exclusive breastfeeding ≧3 months, and exposure to household passive smoking and pet in the first year of life.

[b]$p < .05$ is in bold.

TABLE 3 Association of cord blood IgE with FeNO and pulmonary function parameters

Variable	N	β (95% CI)[a]	p[b]
FeNO (ppb)	548	0.131 (0.057, 0.204)	**<.001**
FVC (L)	565	0.002 (−0.023, 0.026)	.894
FEV_1 (L)	565	0.003 (−0.020, 0.026)	.785
FEV_1/FVC ratio (%)	565	−0.021 (−0.960, 0.918)	.965
FEF_{25-75} (L/s)	565	0.004 (−0.049, 0.058)	.872
PEF (L/s)	565	0.027 (−0.052, 0.106)	.503

Abbreviations: CI, confidence interval; FEF_{25-75}, forced expiratory flow at 25%–75%; FeNO, fraction of exhaled nitric oxide; FEV_1: forced expiratory volume in 1 s; FVC, forced vital capacity; IgE, immunoglobulin E; PEF, peak expiratory flow; ppb, parts per billion.

[a]Adjusted covariates include age, gender, height, body mass index, birth order, season of birth, parental allergic diseases, exclusive breastfeeding ≧3 months, and exposure to household passive smoking and pet in the first year of life.

[b]$p < .05$ is in bold.

levels in our study subjects. At the cutoff of 0.5 kU/L, the sensitivity, specificity, PPV, and NPV for predicting allergic sensitization were 33.2%, 78.7%, 75.8%, and 36.9%, respectively. Subjects with cord blood IgE ≥0.5 kU/L were significantly associated with an increased risk of allergic sensitization than those with cord blood IgE <0.5 kU/L (75.8% vs. 63.1%; AOR = 1.73, 95% CI: 1.12–2.69; $p = .014$). However, there was no statistically significant difference in FeNO levels between subjects with cord blood IgE ≥0.5 kU/L and those <0.5 kU/L ($p = .079$) (Figure 1B). Likewise, there were no statistically significant differences in the risk of allergic diseases or allergic symptoms between subjects with cord blood IgE ≥0.5 kU/L and those <0.5 kU/L (Table 4).

4 | DISCUSSION

This population-based cohort study investigated the associations of cord blood IgE with allergic sensitization, FeNO, pulmonary function, and allergic diseases among 566 Asian children. The major finding is the significant association of cord blood IgE levels with allergic sensitization and FeNO levels at school age. This study has identified an optimal cutoff value of cord blood IgE at 0.24 kU/L in predicting allergic sensitization, elevated FeNO levels, and asthma. Cord blood IgE levels are not predictive of childhood pulmonary function in this population study.

To our knowledge, this is the first study to investigate the relationship between cord blood IgE levels and FeNO levels. Our data have demonstrated that increased cord blood IgE is significantly associated with FeNO elevation in schoolchildren. The finding implies that allergic airway inflammation may be, at least in part, determined innately and suggests the potential role of cord blood IgE levels in predicting the development of allergic airway inflammation in childhood. Our finding also lends supportive evidence for the association between allergic sensitization and FeNO, as documented by previous studies.[19–22]

The current study provides evidence of a statistically significant association between increased cord blood IgE levels and subsequent development of allergic sensitization, specifically sensitization to mites, animals, and foods. Our findings in Asian children are in accordance with previous studies in Western countries.[4–9] Ferguson et al.[4] found that elevated cord blood IgE levels were associated with positive skin test reactions against aeroallergen, but not food allergens, at 7 years of age in a Canadian birth cohort at high risk of allergic diseases. Croner et al.[8] reported that high cord blood IgE levels in Swedish neonates were associated with serum IgE sensitization to food allergens at 18–24 months of age. Genetic influence on total IgE levels and allergic sensitization has been documented through a number of genome-wide association studies.[34,35] The association between cord blood IgE levels and subsequent allergic sensitization identified in this study implies that allergic sensitization is genetically predetermined.

There remains considerable debate about the optimal cutoff values of cord blood IgE for predicting atopy in childhood.[1,6] The current study has indicated that cord blood IgE levels ≥0.24 kU/L in Asian children were associated with a 2.6-fold increased risk of allergic sensitization, specifically sensitization to mites, animals, and foods, at 6 years

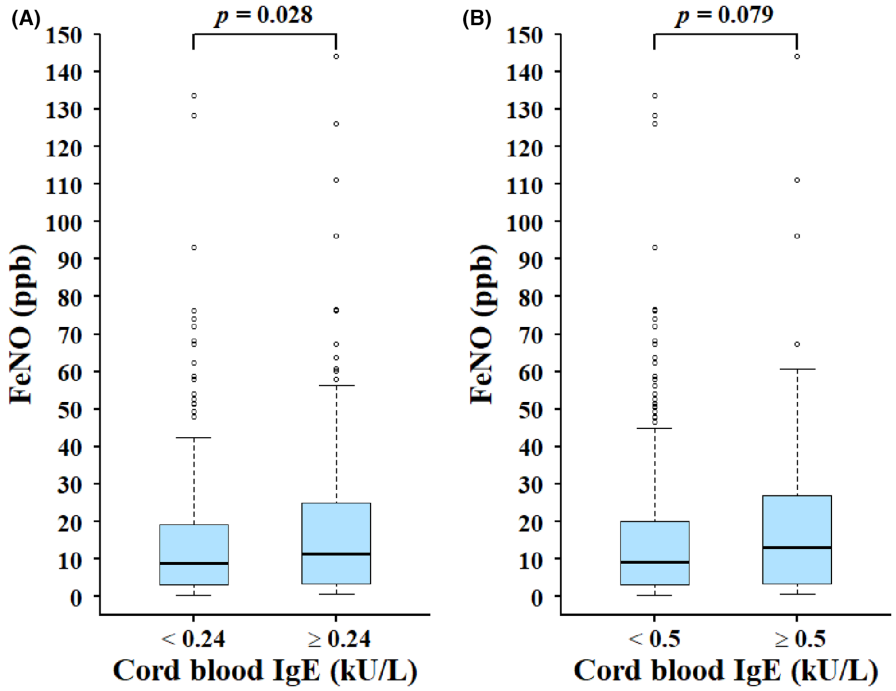

FIGURE 1 Association between cord blood IgE and FeNO based on two different cutoff values of cord blood IgE: (A) 0.24 kU/L and (B) 0.5 kU/L. FeNO, fraction of exhaled nitric oxide; IgE: immunoglobulin E. Adjusted covariates include age, gender, height, body mass index, birth order, season of birth, parental allergic diseases, exclusive breastfeeding ≧3 months, and exposure to household passive smoking and pet in the first year of life.

TABLE 4 Association of cord blood IgE with allergic diseases and allergic symptoms based on two different cutoff values of cord blood IgE: 0.24 and 0.5 kU/L

	Cord blood IgE						Cord blood IgE					
	≧0.24 kU/L		<0.24 kU/L				≧0.5 kU/L		<0.5 kU/L			
Variable	*N*	(%)	*N*	(%)	AOR (95% CI)[a]	*p*[b]	*N*	(%)	*N*	(%)	AOR (95% CI)[a]	*p*[b]
Allergic diseases												
Asthma	27	9.1	11	4.2	2.35 (1.12, 4.94)	**.024**	14	8.3	24	6.2	1.40 (0.69, 2.86)	.353
Allergic rhinitis	153	51.0	118	45.0	1.13 (0.78, 1.62)	.521	83	48.5	188	48.1	0.84 (0.57, 1.24)	.381
Atopic eczema	62	20.7	58	21.9	0.91 (0.59, 1.39)	.657	37	21.6	83	21.1	0.98 (0.62, 1.55)	.941
Allergic symptoms												
Current wheeze	52	17.4	24	9.1	2.03 (1.19, 3.45)	**.009**	26	15.4	50	12.7	1.11 (0.65, 1.88)	.712
Current rhinitis	215	71.7	176	66.9	1.13 (0.77, 1.65)	.529	121	70.8	270	68.9	0.97 (0.64, 1.47)	.889
Current eczema	87	28.9	83	31.3	0.88 (0.6, 1.28)	.507	53	31.0	117	29.6	1.03 (0.68, 1.54)	.903

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; IgE, cord blood immunoglobulin E.

[a]Adjusted covariates include age, gender, height, body mass index, birth order, season of birth, parental allergic diseases, exclusive breastfeeding ≧3 months, and exposure to household passive smoking and pet in the first year of life.

[b]$p < .05$ is in bold.

of age. Furthermore, this study suggested that cord blood IgE levels ≥0.24 kU/L were predictive of allergic airway inflammation, in terms of elevated FeNO levels, and asthma in childhood. In constrast, 0.5 kU/L as the optimal cutoff previously suggested in Western countries was not predictive of elevated FeNO levels and allergic diseases in the current study. Further investigations to validate predictive performance of the optimal cutoff suggested by this study would be warranted.

There was no significant association of cord blood IgE levels and pulmonary function parameters in this population sample of Asian children. This finding was in line with a population-based birth cohort in the United States which observed no associations between cord blood IgE and pulmonary function parameters.[9] In a German study involving children with different wheezing patterns, Lau et al.[26] found that FEV_1/FVC ratio in children with current wheeze and persistent wheeze was inversely influenced by cord blood IgE levels. Further study is needed to determine whether cord blood IgE levels are associated with specific wheeze phenotypes.

This study has several strengths, including a prospective follow-up cohort and objective measurements of allergic sensitization, FeNO, and pulmonary function in a population-based sample of children. However, there are some limitations in this study. First, whether the findings in this study of Asian children are applicable to other non-Asian populations needs to be confirmed. Second, selection bias might be a concern but may not be be severe in the present

study, given the relatively small differences across characteristics between subjects in the current study and the original cohort. Third, although several important risk factors have been taken into account in the analysis, it remains possible that some unmeasured confounding factors may explain in part the observed associations.

5 | CONCLUSION

This study demonstrates that cord blood IgE ≥0.24 kU/L predicts allergic sensitization, FeNO elevation, and asthma among Asian schoolchildren. Specifically, cord blood IgE levels ≥0.24 kU/L were associated with a 2.6-fold increased risk of allergic sensitization, particularly sensitization to mites, animals, and foods, at 6 years of age. This study suggests that cord blood IgE levels would be useful for early identification of newborns at risk of subsequent allergic sensitization and allergic airway inflammation at school age.

AUTHOR CONTRIBUTIONS

Hsin-Ju Lee: Conceptualization (equal); formal analysis (equal); writing – original draft (equal); writing – review and editing (equal). **Hui-Ju Tsai:** Funding acquisition (supporting); resources (supporting); writing – review and editing (supporting). **Hsin-Yi Huang:** Formal analysis (equal); writing – original draft (supporting); writing – review and editing (supporting). **Chun-Chun Gau:** Data curation (supporting); writing – review and editing (supporting). **Chia-Hua Ho:** Data curation (supporting); writing – review and editing (supporting). **Jing-Long Huang:** Funding acquisition (supporting); resources (supporting); writing – review and editing (supporting). **Tsung-Chieh Yao:** Conceptualization (equal); funding acquistion (lead); formal analysis (supporting); supervision (lead); writing - original draft (equal); writing - review and editing (lead).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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