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ORIGINAL ARTICLE

Childhood blood eosinophils and symptoms of allergic disorders: a cross-sectional study in Southern China

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ABSTRACT

Purpose: The relationship between childhood blood eosinophils and subtypes of allergic diseases remains understudied. This study aimed to examine the associations between childhood blood eosinophils and subtypes of asthma, rhinitis and dermatitis, as well as the modifying effect of age.

Methods: We obtained concurrent blood cell counts and serum Immunoglobulin E (IgE) test results in 5026 children (0–13, years) from First Affiliated Hospital of Guangzhou Medical University from 2014 to 2019. Generalized additive models with multivariable adjustments were utilized to model the exposure-response relationship between eosinophils and allergic symptoms. The robustness of the association was assessed in two age categories (<6, 6–13 years).

Results: The association of eosinophils with allergic asthma/rhinitis was positively nonlinear, with a plateau at levels of Q_4 (≥0.51, 10^9/L). Conversely, exposure-response curves between eosinophils and the risk of non-allergic asthma and rhinitis were negatively linear, and especially, became statistically significant when levels of eosinophils were larger than Q_3 (≥0.30, 10^9/L). Compared with their counterparts, school-aged children (6–13, years) with a higher level of blood eosinophils (≥0.35, 10^9/L) were more likely to suffer from allergic asthma [relative excess risk due to interaction (RERI), 2.51; 95% CI, 1.24–3.78], allergic rhinitis (RERI, 2.79; 95% CI, 1.14–4.45) but not allergic dermatitis (RERI not significant).

Conclusion: Higher eosinophil counts were associated with the increased risk of allergic subtype symptoms and the decreased risk of non-allergic subtypes in children. Moreover, the associations between eosinophils and allergic asthma/rhinitis were accentuated in the school-aged child. These findings may contribute to providing novel insights for clinical administration relevance of allergic-related symptoms.

KEY MESSAGES:

1. There was a positively nonlinear association between childhood eosinophils and allergic asthma/rhinitis.
2. Age modified the associations between eosinophils and allergy-related outcomes. The associations of eosinophil with allergic asthma/rhinitis accentuated in the school-aged child (6–13, years).

Abbreviations: IgE: immunoglobulin E; tIgE: total IgE; sIgE: specific IgE; AS: allergic asthma; AR: allergic rhinitis; AD: atopic dermatitis; CI: confidence interval; OR: odds ratio; Q_1: the first quartile; Q_2: the second quartile; Q_3: the third quartile; Q_4: the fourth quartile; RERI: relative excess risk due to interaction

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Children; allergic diseases; eosinophils; RERI; subtypes

Introduction

The prevalence of allergic diseases in China's rural and urban children has risen steadily in the past few decades that brings huge economic and health burdens [1,2]. It has been revealed that asthma [3], allergic rhinitis [4] and atopic dermatitis [5] are the most common inflammatory disorders which are strongly associated with allergic sensitization and subsequent many complications, for instance, cancer [6]. Therefore, some effective allergy prevention strategies, such as avoidance of contact with specific allergens or exposure to

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ambient air pollutants [7, 8], have been suggested in daily life. Although primary prevention strategies play an essential role in the prevention of allergic diseases, clinical administration and treatment are still a big challenge for well-trained physicians because of the serious and complex features of allergies [9]. Therefore, the identification of a measurement biomarker that can reflect the risks of various subtypes of allergic-related diseases may be beneficial for improved diagnosis and potential immunotherapy approaches to allergy. A prospective cohort study [10] suggested that age was associated with the progress of atopic diseases and allergic sensitization, moreover, untimely diagnosis and incomplete treatment for acute allergies during childhood would result in chronic diseases in adults, such as asthma or chronic bronchitis [11, 12]. Therefore, childhood is the critical period for clinical administration of various subtypes of allergic diseases.

It has been well considered that eosinophil counts are reliable and easily obtained biomarkers to predict the occurrence of allergic diseases, such as asthma [13]. The possible biological mechanism is that highly cytotoxic proteins stored in an eosinophil can result in tissue damage in inflammation [14]. A UK cohort study [15] revealed that blood eosinophil count was associated with improvement of predictive value for asthma outcomes assessment. Similarly, a multi-centre longitudinal study performed in China also reported that high blood eosinophil count was linked with increased risks of asthma [16]. However, very few epidemiological studies have examined the associations between childhood blood eosinophils and subtypes of allergic-related symptoms, and to our best knowledge, there is no study to investigate the joint associations of blood eosinophils and age with the symptoms of allergic disorders in children.

Using this large cross-sectional study of Chinese children, we comprehensively investigated the associations between blood eosinophils and the subtypes of allergic-related symptoms, and the modifying effect of age.

Materials and methods

Study design and data collection

The study population was based on a large cross-sectional study from Guangzhou city in southern China. The demographics data utilized in this study originated from long-term (2014–2019) longitudinal electronic medical records of patients enrolled in the First Affiliated Hospital of Guangzhou Medical University. All authors declared no potential conflicts of interest in this study.

The inclusion criteria were [1]: patients who had symptoms of allergy-related outcomes, such as asthma, rhinitis, dermatitis, etc. upon clinical examination [2]; patients who had completed total Immunoglobulin E (tIgE) or specific IgE (sIgE) tests [3]; patients who had complete peripheral blood cell counts [4]; patients who had at least one follow-up [5]; aged of 0–13 years. A total of 5026 subjects met the inclusion criteria and were enrolled in analysis of this study. Additionally, 5026 subjects contribute to 5588 observations during the study period, and the recurrence rate is 9.2%. The detailed follow-up information can be found in Supplementary Figure 1. Since the recurrence rate is relatively low (less than 10%), to avoid collinearity in the multivariable model due to duplicate medical records as well as retaining a large sample size, we just keep the first follow-up record in those recurrence patients and excluded other duplicate observations ($n = 562$).

Serum IgE samples were sent to the central laboratory for diagnosis using ImmuoCAP (Thermo Fisher Scientific Inc., California, USA). TIgE and 99 sIgE to common inhalant allergens (house dust mite, dermatophagoides farinae, aspergillus fumigatus, cat dander, dog dander, mugwort, etc.) and food allergens (egg white, milk, wheat, peanut, shrimp, soy, crab, etc.) were tested in this place, and all allergic information was stored in the serum bank of Allergy Information Repository (AIR-SKLRD) located in the First Affiliated Hospital of Guangzhou Medical University [17]. We obtained concurrent specific or total IgE test results and basophils, neutrophils, eosinophils, lymphocytes and monocyte levels of the participants. Demographic information such as age and gender were extracted from the patient's medical records which were downloaded from the Medical Data Information Detection System in the First Affiliated Hospital of Guangzhou Medical University.

Ethics approval and consent to participate

All participants or their parents provided oral and written informed consent for participating in this study, and in conformity with the ethics approval by the First Affiliated Hospital of Guangzhou Medical University ethics committee (Reference number: GYFYY-2016-73).

Definition of allergy-related outcomes

The diagnosis flowchart can be seen in Figure 1. The pre-diagnosis of allergies in this study was obtained from electronic medical records which included

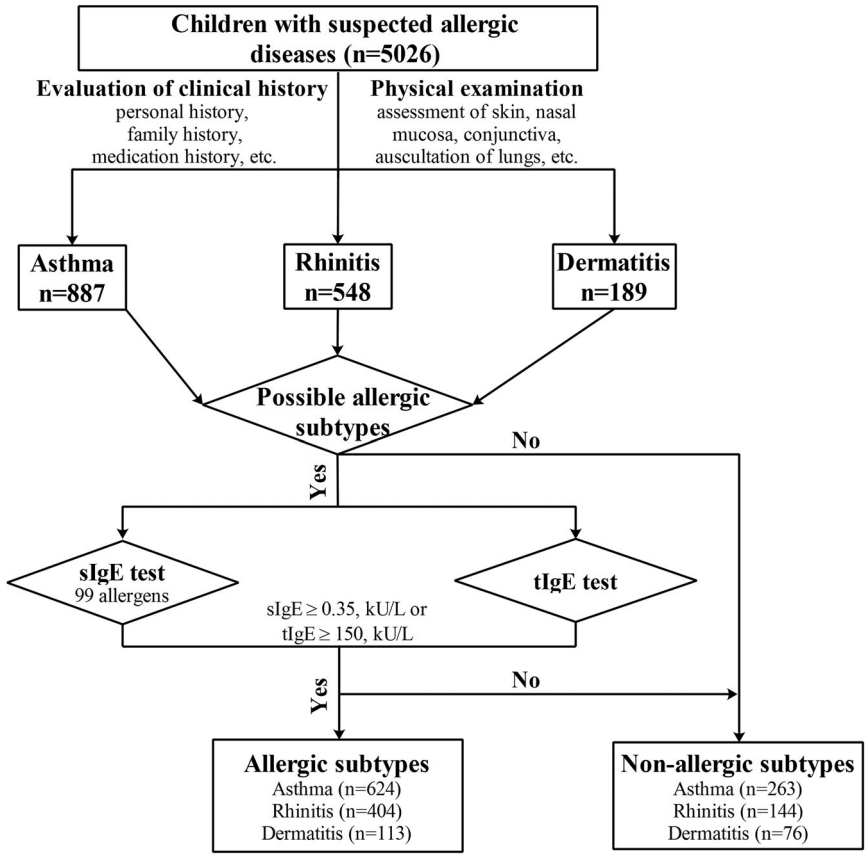

Figure 1. Diagnostic flowchart of allergic disorders.

information about a patient's clinical history, physical examination and diagnoses results and treatment plans. In combination with IgE test results, a total of six subtypes of allergic-related symptoms were defined in this study, including allergic asthma, non-allergic asthma, allergic rhinitis, non-allergic rhinitis, allergic dermatitis and non-allergic dermatitis. The diagnosis of allergic disorders in this study should meet two criteria [1]. patients who were diagnosed with asthma, rhinitis or dermatitis based on the clinical history and physical examination [2]. patients who were allergic to at least one allergen (sIgE >0.35, kU/L) or tIgE is more than 150, kU/L [18]. Additionally, patients who had the clinical diagnosis of asthma, rhinitis, and dermatitis but not any allergic sensitization reaction were defined as non-allergic subtypes.

Statistical analysis

Peripheral blood cells were described as median (1st quartile, 3rd quartile) because their distribution was skewed. The Kruskal-Wallis tests were conducted to compare the blood cells among different age stages. The allergy-related outcomes were presented as frequency (percentage) and Chi-square tests were utilized to compare the proportion among various age groups.

Logistic regression models were applied to investigate the associations between blood eosinophils and allergy-related outcomes. The trend tests of eosinophil count with the risks of various subtypes of allergic diseases were also estimated and stratified by age group and gender in this study. Eosinophil counts (10^9/L) were classified into four categories by quartile to examine the trend of such associations and the corresponding groupings are as follows [1]: Pools: <0.10, 0.11–0.29, 0.30–0.50, ≥0.51 [2]. <6 years: <0.10, 0.11–0.26, 0.27–0.49, ≥0.50 [3]. 6–13, years: <0.17, 0.18–0.32, 0.33–0.60, ≥0.61 [4]. Boys: <0.11, 0.12–0.29, 0.30–0.51, ≥0.52 [5]. Girls: <0.10, 0.11–0.22, 0.23–0.47, ≥0.48. According to previous research, 0.35 (10^9/L) was a widely accepted classification criterion [19] to distinguish between higher and lower eosinophil levels. Additionally, the present study also confirmed that the exposure-response curve between eosinophils and the risks of allergic asthma/rhinitis was gradually became more stable when the level of eosinophils large than 0.35 kU/L. Therefore, based on the cut-off value of 0.35, we separated the subjects into two

populations with higher and lower eosinophils. Additionally, generalized additive models with multivariable adjustments were utilized to model the exposure-response relationship between blood eosinophils and allergy-related outcomes, and the robustness of the association was assessed in the two age categories. To comprehensively examine the joint associations of age and eosinophil count with allergy-related outcomes, we used multiplicative and additive scales to estimate the interactions. The additive effects were evaluated by modelling the relative excess risk due to interaction (RERI) using the method of variance estimates recovery, and a 95% confidence interval (CI) of RERI including 0 indicated no significant interaction [20,21].

All data management and statistical analyses were performed using SAS 9.4 (Copyright 2002–2012 by SAS Institute Inc., Cary, NC, USA). Figures were drawn with R-studio 1.2.5001 (Copyright 2009–2018 R-studio, Inc.). All tests were two-sided and a value of $p < 0.05$ was considered statistically significant.

Results

Study population characteristics

Age was categorized into six classes (0–1, 2–3, 4–5, 6–7, 8–9, 10–13 years) to describe the characteristics of subjects in the present study (Table 1). Moreover, we recognized the age of 6 as the cut-off point to assess the reliability of the association between eosinophils and allergic diseases because school-aged child (6–13, years) has a large prevalence of allergic diseases than early childhood (<6, years). A total of 5026 children were included in the final analysis of this study, 3305(65.8%) of them were boys, and the median (P_{25}, P_{75}) age was 4(2, 6) years. Among all patients, 12.4%, 8.0%, and 2.3% were diagnosed with allergic asthma, allergic rhinitis, and allergic dermatitis. The median (P_{25}, P_{75}) value of tIgE was 92.4(31.1, 294.9) kU/L.

When comparing peripheral blood cells between different age groups (Table 1), the results showed that early childhood (<6, years) tends to have higher monocyte and lymphocyte counts, while having fewer eosinophils and neutrophils than the school-aged child (6–13, years). As shown in Table 1, the school-aged child was more sensitive to allergic sensitization than in early childhood ($p < 0.001$). Moreover, the prevalence of allergic disorders including asthma, rhinitis, and dermatitis was comparatively higher ($p < 0.001$) in the school-aged child, and similar results were also observed in non-allergic rhinitis.

The relationship between age and allergy-related outcomes

There existed an obvious positive association between age and the risk of allergic asthma/rhinitis in children when controlling for gender, levels of basophil, neutrophil, eosinophil, lymphocyte, monocyte, and the association became stable when age was more than 6 years (Figure 2). Similarly, the exposure-response curve between age and non-allergic asthma depicted a slightly positive association and achieved significance when age was less than 4 years (Figure 2). However, the exposure-response curves suggest that children aged 6–8 years were more likely to suffer from non-allergic rhinitis (Figure 2). Additionally, a significant '*U*' shaped association between age and the risks of dermatitis can be observed when controlling for other confounders (Figure 2).

The relationship between eosinophil counts and allergy-related outcomes

We classified eosinophil counts into four categories by quartiles to perform trend tests. Table 2 **and** Figure 2 showed that eosinophil count was positively associated with the risks of allergic asthma, allergic rhinitis and allergic dermatitis when controlling for age, gender, cell counts of basophil, neutrophil, lymphocyte and monocyte ($P_{trend}<0.001$). Conversely, an obvious negative relationship between eosinophil count and non-allergic asthma/rhinitis can be observed in this study (Figure 2), and the trend test achieved statistical significance (Table 2, $P_{trend}<0.001$). Compared with the first quartile of eosinophil counts, the highest quartile (Q_4) of eosinophil counts was strongly linked with increased risks of allergic-subtype symptoms (asthma, rhinitis and dermatitis) when controlling for other confounders. Conversely, compared with the lower quartile of eosinophils (Q_1–Q_3), the adjusted odds ratio (OR) for the risks of non-allergic asthma/rhinitis was significantly reduced when exposed to Q_4.

Stratified analyses were performed to evaluate the reliability of the association between eosinophil level and allergy-related outcomes in two strata of age (<6, 6–13 years) and different gender. The results demonstrated that there were consistent associations between allergic-subtype symptoms and eosinophil levels in each stratum (Table 2). However, the association of higher eosinophils with the decreased risks of non-allergic rhinitis can only be observed in school-aged children or boys. Additionally, the association between eosinophils and non-allergic asthma were reliable in different age groups or gender. No

Table 1. Characteristics of subjects in various age groups.

Label	Total ($n = 5026$)	Age, years						P^c
		<6 ($n = 3627$)			6–13 ($n = 1399$)			
		0–1	2–3	4–5	6–7	8–9	10–13	
Gender								0.020
Boys	3305 (65.8)	834 (72.8)	787 (61.9)	729 (60.2)	409 (66.5)	261 (70.4)	285 (69.0)	
Girls	1721 (34.2)	312 (27.2)	484 (38.1)	481 (39.8)	206 (33.5)	110 (29.6)	128 (31.0)	
tIgE, kU/L								<0.001
<150	3079 (61.3)	945 (82.5)	846 (66.6)	710 (58.7)	274 (44.6)	140 (37.7)	164 (39.7)	
≥150	1947 (38.7)	201 (17.5)	425 (33.4)	500 (41.3)	341 (55.4)	231 (62.3)	249 (60.3)	
Sensitization[a]	2164 (43.1)	377 (32.9)	574 (45.2)	553 (45.7)	278 (45.2)	186 (50.1)	196 (47.5)	<0.001
Peripheral blood cells, 10 [9]/L								
Basophils	0.03 (0.01,0.10)	0.03 (0.01,0.09)	0.02 (0.00,0.07)	0.03 (0.00,0.10)	0.03 (0.00,0.10)	0.04 (0.00,0.10)	0.03 (0.00,0.10)	0.028
Neutrophils	3.60 (2.60,5.10)	3.20 (2.10,4.70)	3.70 (2.60,5.30)	3.70 (2.70,5.50)	3.70 (2.70,5.20)	3.50 (2.70,4.80)	3.60 (2.80,4.90)	0.033
Eosinophils	0.30 (0.10,0.50)	0.20 (0.10,0.42)	0.23 (0.10,0.46)	0.30 (0.14,0.55)	0.40 (0.20,0.62)	0.39 (0.16,0.60)	0.30 (0.11,0.53)	<0.001
Lymphocytes	3.60 (2.70,4.90)	5.40 (4.10,7.00)	3.90 (3.00,4.90)	3.40 (2.70,4.20)	3.20 (2.50,3.90)	2.80 (2.30,3.40)	2.60 (2.10,3.20)	<0.001
Monocyte	0.60 (0.50,0.80)	0.80 (0.60,1.10)	0.70 (0.50,0.80)	0.60 (0.40,0.80)	0.60 (0.40,0.70)	0.50 (0.40,0.70)	0.50 (0.40,0.70)	<0.001
Diagnosis								
Asthma[b]								
AS	624 (12.4)	28 (2.4)	110 (8.7)	170 (14.0)	135 (22.0)	83 (22.4)	98 (23.7)	<0.001
Non-AS	263 (5.2)	39 (3.4)	76 (6.0)	67 (5.5)	41 (6.7)	18 (4.9)	22 (5.3)	0.271
Rhinitis[b]								
AR	404 (8.0)	8 (0.7)	41 (3.2)	107 (8.8)	101 (16.4)	75 (20.2)	72 (17.4)	<0.001
Non-AR	144 (2.9)	7 (0.6)	34 (2.7)	41 (3.4)	23 (3.7)	21 (5.7)	18 (4.4)	<0.001
Dermatitis[b]								
AD	113 (2.3)	28 (2.4)	11 (0.9)	21 (1.7)	18 (2.9)	17 (4.6)	18 (4.4)	<0.001
Non-AD	76 (1.5)	28 (2.4)	12 (0.9)	15 (1.2)	10 (1.6)	3 (0.8)	8 (1.9)	0.968

tIgE: total IgE; AS: allergic asthma; non-AS: non-allergic asthma; AR: allergic rhinitis; non-AR: non-allergic rhinitis; AD: allergic dermatitis; non-AD: non-allergic dermatitis.

[a]Allergic to at least one allergen of 99 allergens.

[b]Allergic asthma/rhinitis/dermatitis was defined as those who were diagnosed with asthma/rhinitis/dermatitis, and allergic to at least one specific allergen or total IgE ≥ 150, kU/L; Non-allergic asthma/rhinitis/dermatitis was defined as those who suffered from asthma/rhinitis/dermatitis and without allergic sensitization reaction.

[c]The comparison between school-aged children (6–13, years) and early childhood (<6 years).

significant associations between eosinophils and non-allergic dermatitis were observed in this study.

Joint associations between eosinophil counts and age on allergy-related outcomes

This study has comprehensively demonstrated the individual association of eosinophil count and age with symptoms of allergy-related outcomes. Therefore, it is necessary to investigate the joint association of eosinophil count and age with the risks of allergic disorders. The results (Table 3, Figure 3) showed that the greatest risks of allergic asthma, allergic rhinitis and allergy dermatitis were observed in the school-aged child with a high level of eosinophil (≥0.35, 10^9/L). Moreover, significant additive interactions between age and eosinophils were identified in allergic asthma and allergic rhinitis (95% CIs of RERI excluding 0), though there was no obvious multiplicative interaction between them ($P_{interaction}$>0.05). Additionally, the adjusted OR of allergic dermatitis in the school-aged child (aOR, 4.82; 95%CI, 2.83–8.20) was higher than in early childhood (aOR, 2.23; 95%CI, 1.32–3.76) when exposed to high eosinophils count, and no significant interactions between eosinophils and age on allergic dermatitis can be observed in this study.

Furthermore, compared with their counterparts, the school-aged child with low eosinophil counts was more probable to suffer from non-allergic asthma (aOR, 1.53; 95%CI, 1.09–2.14) and rhinitis (aOR, 2.73; 95%CI, 1.79–4.15), and both the multiplicative and additive interactions exhibited significance (Table 3). Additionally, the results also suggested that no obvious joint associations of age and eosinophils with non-allergic dermatitis were observed.

Discussion

The present study is the first one to comprehensively examine the individual and joint associations of age and childhood blood eosinophil with the symptoms of allergic disorders. Overall, our findings contributed to the established evidence regarding the associations between eosinophil and allergy-related outcomes, and especially emphasized the joint association of age and eosinophil with asthma, rhinitis and dermatitis. First, we revealed that there was a positive association between childhood eosinophils and allergic-subtype symptoms. The association of eosinophils with allergic asthma/rhinitis was slightly non-linear, with a plateau at levels of Q_4 (≥0.51, 10^9/L). Second, the highest adjusted OR of allergic asthma/rhinitis/dermatitis was

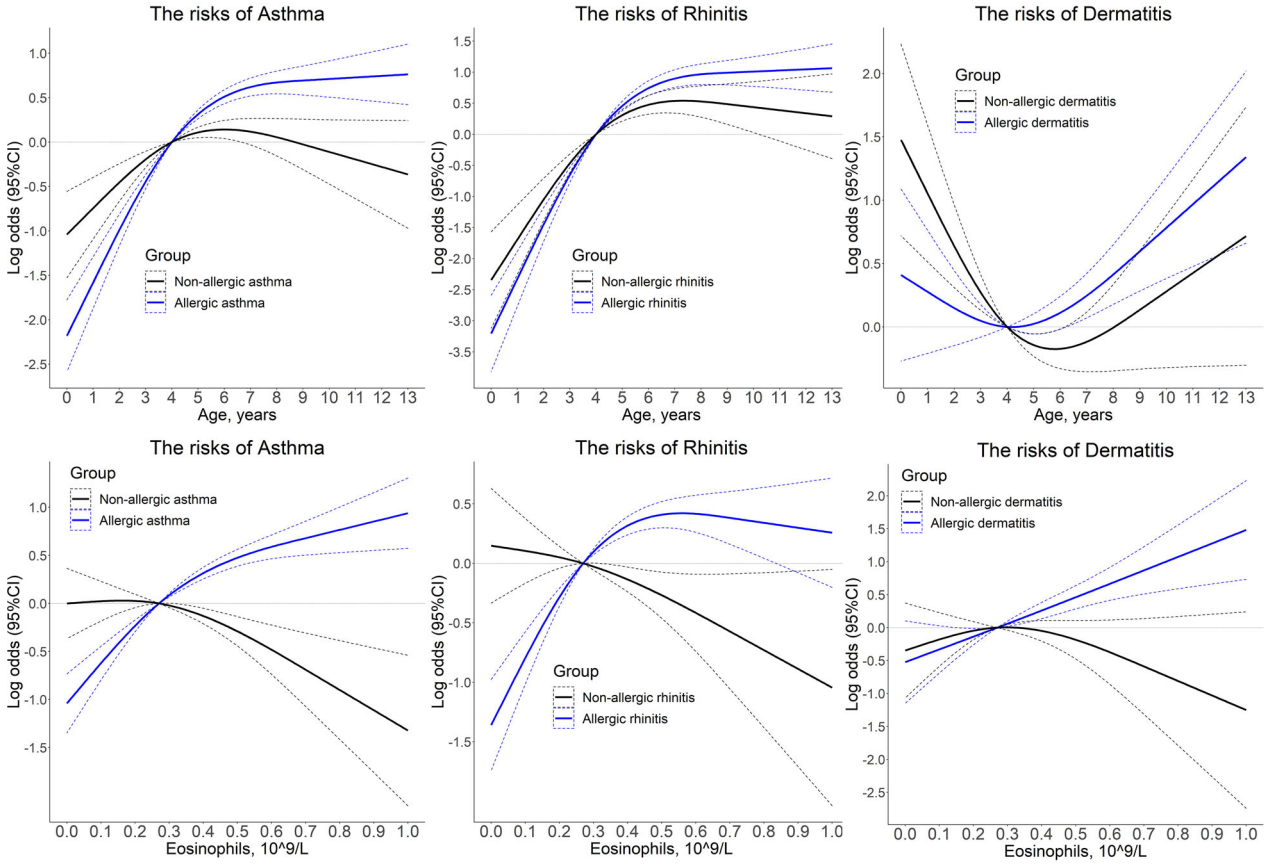

Figure 2. Associations of age and eosinophils with the risks of asthma, rhinitis and dermatitis based on spline regression models. All estimates are adjusted for gender, basophils, neutrophils, eosinophils, lymphocytes, monocyte and age/eosinophils. It is shown by the blue solid line with the 95% confidence interval.

observed in the school-aged child with a high level of eosinophil (≥0.35, 10^9/L), and the school-aged child with a low level of eosinophil (<0.35, 10^9/L) had the greatest risks of non-allergic asthma and rhinitis. Lastly, the associations of eosinophil and allergic asthma/rhinitis were accentuated in the school-aged child, additionally, both significant multiplicative and additive interactions between age and eosinophil on non-allergic asthma/rhinitis were identified in this study. In comparison with others, the major novelty of ours perhaps is we first proposed identifying children at high risk of various subtypes of allergic diseases by the combination of routine data from electronic medical records.

The major clinical implications of the present study are based on public health. Initially, although the association of eosinophil with allergies has been well discussed, identifying which subgroups would be more sensitive to different allergy-related subtypes is essential for guiding intervention when medical resources are limited. Then, the comprehensive analysis of the association between eosinophils and the symptoms of allergies in early and school-aged childhood may be beneficial for the clinical management of child allergies. Besides, the assessment of joint associations between age and eosinophil contributes to the understanding of the development of pathogenesis for childhood allergy.

The potential biological mechanism of the association between eosinophils and allergies has been well established by previous studies. Eosinophil-Associated Diseases (EADs) have become a hot research topic recently, not only it will induce inflammation of the immune system, but also can result in chronic organ damage [14]. It has been emphasized that eosinophil as a potential end-stage effector and blood immune biomarker plays a major role in the development of allergic inflammation in the airways and skin tissue, it commonly joints with mast cells to induce inflammatory diseases, such as asthma and chronic spontaneous urticaria [22]. Additionally, it has been suggested that allergic disorders, which are characterized by eosinophilia and increased immunoglobulin E (IgE) levels, are strongly linked with age. The existence of changes in normal immunity with ageing as well as the age-dependent differential immune activation

Table 2. OR (95% CIs)[A] for allergic disorders by quartiles of eosinophil count.Rhinitis

Label	First quartile	Second quartile	Third quartile	Fourth quartile	$^{A}P_{trend}$
Pooled[a]					
Asthma					
AS	1.00 (1.00,1.00)	1.42 (1.03,1.97)	2.85 (2.12,3.83)	4.13 (3.08,5.55)	<0.001
Non-AS	1.00 (1.00,1.00)	1.00 (0.72,1.39)	0.85 (0.61,1.20)	0.39 (0.25,0.60)	<0.001
Rhinitis					
AR	1.00 (1.00,1.00)	1.82 (1.22,2.71)	3.33 (2.30,4.81)	3.26 (2.24,4.74)	<0.001
Non-AR	1.00 (1.00,1.00)	0.56 (0.36,0.89)	0.71 (0.46,1.08)	0.30 (0.17,0.53)	<0.001
Dermatitis					
AD	1.00 (1.00,1.00)	1.41 (0.74,2.70)	1.81 (0.97,3.37)	3.60 (1.99,6.51)	<0.001
Non-AD	1.00 (1.00,1.00)	1.99 (1.03,3.84)	1.29 (0.62,2.65)	1.30 (0.61,2.77)	0.898
Stratum1					
<6, years[b]					
Asthma					
AS	1.00 (1.00,1.00)	1.59 (1.05,2.42)	3.17 (2.16,4.64)	3.94 (2.67,5.81)	<0.001
Non-AS	1.00 (1.00,1.00)	1.06 (0.71,1.58)	1.04 (0.69,1.56)	0.55 (0.33,0.91)	0.049
Rhinitis					
AR	1.00 (1.00,1.00)	2.15 (1.23,3.77)	2.99 (1.74,5.12)	3.43 (1.98,5.95)	<0.001
Non-AR	1.00 (1.00,1.00)	0.65 (0.34,1.22)	1.21 (0.70,2.11)	0.49 (0.23,1.05)	0.349
Dermatitis					
AD	1.00 (1.00,1.00)	1.61 (0.70,3.68)	1.69 (0.73,3.90)	3.50 (1.59,7.72)	0.002
Non-AD	1.00 (1.00,1.00)	1.78 (0.81,3.93)	1.58 (0.69,3.61)	1.57 (0.65,3.77)	0.409
6–13, years[c]					
Asthma					
AS	1.00 (1.00,1.00)	1.35 (0.81,2.25)	2.74 (1.72,4.37)	4.68 (2.95,7.43)	<0.001
Non-AS	1.00 (1.00,1.00)	0.81 (0.45,1.47)	0.52 (0.28,0.97)	0.18 (0.08,0.41)	<0.001
AR	1.00 (1.00,1.00)	1.52 (0.87,2.65)	3.42 (2.06,5.67)	2.95 (1.76,4.96)	<0.001
Non-AR	1.00 (1.00,1.00)	0.43 (0.22,0.84)	0.31 (0.16,0.63)	0.16 (0.07,0.38)	<0.001
Dermatitis					
AD	1.00 (1.00,1.00)	1.38 (0.47,4.05)	2.28 (0.85,6.15)	4.42 (1.71,11.43)	<0.001
Non-AD	1.00 (1.00,1.00)	2.90 (0.82,10.32)	0.72 (0.14,3.64)	0.88 (0.19,4.09)	0.310
Stratum2					
Boys[d]					
Asthma					
AS	1.00 (1.00,1.00)	1.49 (1.00,2.23)	2.76 (1.92,3.98)	4.13 (2.87,5.95)	<0.001
Non-AS	1.00 (1.00,1.00)	1.39 (0.89,2.17)	1.11 (0.70,1.75)	0.57 (0.32,0.99)	0.038
Rhinitis					
AR	1.00 (1.00,1.00)	1.72 (1.02,2.89)	3.71 (2.32,5.95)	3.65 (2.26,5.91)	<0.001
Non-AR	1.00 (1.00,1.00)	0.46 (0.25,0.86)	0.59 (0.34,1.03)	0.23 (0.11,0.49)	<0.001
Dermatitis					
AD	1.00 (1.00,1.00)	0.91 (0.41,2.04)	1.07 (0.49,2.30)	2.80 (1.40,5.60)	0.001
Non-AD	1.00 (1.00,1.00)	1.53 (0.62,3.77)	1.20 (0.47,3.07)	1.23 (0.46,3.29)	0.865
Girls[e]					
Asthma					
AS	1.00 (1.00,1.00)	1.31 (0.75,2.30)	3.15 (1.91,5.20)	4.17 (2.53,6.89)	<0.001
Non-AS	1.00 (1.00,1.00)	0.64 (0.38,1.08)	0.82 (0.48,1.38)	0.37 (0.18,0.75)	0.017
Rhinitis					
AR	1.00 (1.00,1.00)	2.15 (1.16,3.98)	2.82 (1.54,5.16)	2.71 (1.45,5.05)	0.001
Non-AR	1.00 (1.00,1.00)	0.68 (0.34,1.36)	0.87 (0.45,1.71)	0.44 (0.19,1.03)	0.119
Dermatitis					
AD	1.00 (1.00,1.00)	3.45 (1.06,11.28)	4.86 (1.55,15.30)	6.12 (1.91,19.65)	0.001
Non-AD	1.00 (1.00,1.00)	2.79 (1.05,7.45)	1.52 (0.49,4.73)	1.50 (0.46,4.88)	0.845

AS: allergic asthma; non-AS: non-allergic asthma; AR: allergic rhinitis; non-AR: non-allergic rhinitis; AD: allergic dermatitis; non-AD: non-allergic dermatitis.
[a]First quartile ($n = 1259$), <0.10, 10^9/L; second quartile ($n = 1237$), 0.11–0.29, 10^9/L; third quartile ($n = 1333$), 0.30–0.50, 10^9/L; fourth quartile ($n = 1197$), ≥0.51, 10^9/L.
[b]First quartile ($n = 997$), <0.10, 10^9/L; second quartile ($n = 828$), 0.11–0.26, 10^9/L; third quartile ($n = 888$), 0.27–0.49, 10^9/L; fourth quartile ($n = 914$), ≥0.50, 10^9/L.
[c]First quartile ($n = 351$), <0.17, 10^9/L; second quartile ($n = 347$), 0.18–0.32, 10^9/L; third quartile ($n = 382$), 0.33–0.60, 10^9/L; fourth quartile ($n = 319$), ≥0.61, 10^9/L.
[d]First quartile ($n = 813$), <0.11, 10^9/L; second quartile ($n = 736$), 0.12–0.29, 10^9/L; third quartile ($n = 933$), 0.30–0.51, 10^9/L; fourth quartile ($n = 823$), ≥0.52, 10^9/L.
[e]First quartile ($n = 494$), <0.10, 10^9/L; second quartile ($n = 363$), 0.11–0.22, 10^9/L; third quartile ($n = 437$), 0.23–0.47, 10^9/L; fourth quartile ($n = 427$), ≥0.48, 10^9/L.
[A]adjusted for basophils, neutrophils, lymphocytes, monocyte, gender, and/or age.

commonly induces complicated allergic symptoms in various age groups [23]. Therefore, a better understanding of the roles of eosinophils and age on the occurrence of allergic-related diseases might provide new therapeutic and healthcare strategies.

Several epidemiological studies confirmed that a higher level of eosinophil increased the risks of allergic diseases, especially asthma [15] and rhinitis [24]. For instance, a cross-sectional study [25] performed in the UK suggests that eosinophils increase the occurrence

Table 3. Joint associations between eosinophil counts and age on allergy-related outcomes.

Age, years	Eosinophils ≥0.35, 10^9/L	Cases/ Controls	Prevalence, %	*Crude* OR (95% CI)	*Crude* *p*-value	*Adjusted*[a] OR (95% CI)	*Adjusted*[a] *p*-value
AS							
<6	No	125/2115	5.6	1.00 (1.00,1.00)	Ref.	1.00 (1.00,1.00)	Ref.
<6	Yes	183/1204	13.2	2.57 (2.03,3.26)	<0.001	2.62 (2.05,3.35)	<0.001
6–13	No	98/609	13.9	2.72 (2.06,3.60)	<0.001	2.23 (1.67,2.98)	<0.001
6–13	Yes	218/474	31.5	7.78 (6.11,9.91)	<0.001	6.36 (4.94,8.20)	<0.001
Interaction of age and eosinophils					0.561		0.639
RERI (95% CI) =2.51 (1.24,3.78)							
Non-AS							
<6	No	126/2114	5.6	1.00 (1.00,1.00)	Ref.	1.00 (1.00,1.00)	Ref.
<6	Yes	56/1331	4.0	0.71 (0.51,0.97)	0.034	0.68 (0.49,0.94)	0.021
6–13	No	61/646	8.6	1.58 (1.15,2.18)	0.005	1.53 (1.09,2.14)	0.014
6–13	Yes	20/672	2.9	0.50 (0.31,0.81)	0.005	0.47 (0.28,0.76)	0.002
Interaction of age and eosinophils					0.009		0.010
RERI (95% CI) = −0.74 (−1.33,−0.15)							
AR							
<6	No	70/2170	3.1	1.00 (1.00,1.00)	Ref.	1.00 (1.00,1.00)	Ref.
<6	Yes	86/1301	6.2	2.05 (1.48,2.83)	<0.001	2.06 (1.48,2.86)	<0.001
6–13	No	87/620	12.3	4.35 (3.14,6.03)	<0.001	3.39 (2.41,4.77)	<0.001
6–13	Yes	161/531	23.3	9.40 (6.99,12.64)	<0.001	7.24 (5.30,9.87)	<0.001
Interaction of age and eosinophils					0.809		0.860
RERI (95% CI) =2.79 (1.14,4.45)							
Non-AR							
<6	No	56/2184	2.5	1.00 (1.00,1.00)	Ref.	1.00 (1.00,1.00)	Ref.
<6	Yes	26/1361	1.9	0.75 (0.47,1.19)	0.220	0.76 (0.47,1.23)	0.263
6–13	No	49/658	6.9	2.90 (1.96,4.30)	<0.001	2.73 (1.79,4.15)	<0.001
6–13	Yes	13/679	1.9	0.75 (0.41,1.37)	0.348	0.70 (0.38,1.32)	0.274
Interaction of age and eosinophils					0.007		0.007
RERI (95% CI) = −1.78 (−3.01,−0.56)							
AD							
<6	No	28/2212	1.3	1.00 (1.00,1.00)	Ref.	1.00 (1.00,1.00)	Ref.
<6	Yes	32/1355	2.3	1.87 (1.12,3.11)	0.017	2.23 (1.32,3.76)	0.003
6–13	No	17/690	2.4	1.95 (1.06,3.58)	0.032	1.73 (0.92,3.26)	0.089
6–13	Yes	36/656	5.2	4.34 (2.63,7.16)	<0.001	4.82 (2.83,8.20)	<0.001
Interaction of age and eosinophils					0.655		0.579
RERI (95% CI) =1.86 (−0.23,3.94)							
Non-AD							
<6	No	33/2207	1.5	1.00 (1.00,1.00)	Ref.	1.00 (1.00,1.00)	Ref.
<6	Yes	22/1365	1.6	1.08 (0.63,1.86)	0.787	1.09 (0.62,1.90)	0.773
6–13	No	15/692	2.1	1.45 (0.78,2.69)	0.238	1.43 (0.75,2.74)	0.276
6–13	Yes	6/686	0.9	0.59 (0.24,1.40)	0.229	0.61 (0.25,1.50)	0.281
Interaction of age and eosinophils					0.079		0.095
RERI (95% CI) = −0.91 (−2.11,0.29)							

Ref.: Reference; AS: allergic asthma; non-AS: non-allergic asthma; AR: allergic rhinitis; non-AR: non-allergic rhinitis; AD: allergic dermatitis; non-AD: non-allergic dermatitis.
[a]Adjusted for gender, basophils, neutrophils, lymphocytes, monocyte.

of asthma and associated symptoms, and tIgE in adults. Besides, it has been suggested that allergy patients with a higher level of eosinophil commonly have poor symptom control and further exacerbations in the progress of allergic diseases [26]. Consistent with previous findings, we reported that there was a significant positive association between eosinophil (by quartile) and allergic-related outcomes (asthma, rhinitis and dermatitis) in children when controlling for other confounders. Additionally, the exposure-response curve also demonstrated that there was a significant linear association between eosinophil count and the risk of allergic dermatitis, as well as a slightly non-linear association between eosinophil counts and the risk of allergic asthma/rhinitis. To our knowledge, we are the first to disclose such associations in children. Just like previous research [27], our data also suggested that the risks of asthma and rhinitis significantly increased as children got older during early childhood, and became stable when age was more than 6 years. In comparison with others, we are the first to discover the 'U' shape association between age and the risks of dermatitis, and the exposure-response curve decreases steeply in early childhood and swiftly increases as children get school-age periods.

Previous studies demonstrated the independent associations of age and eosinophil on allergies have been well demonstrated in previous studies [28,29]. Nevertheless, the joint association of eosinophil and age on the subtypes of allergic-related symptoms remains unknown, particularly in children. A large study [30] derived from routine medical record data

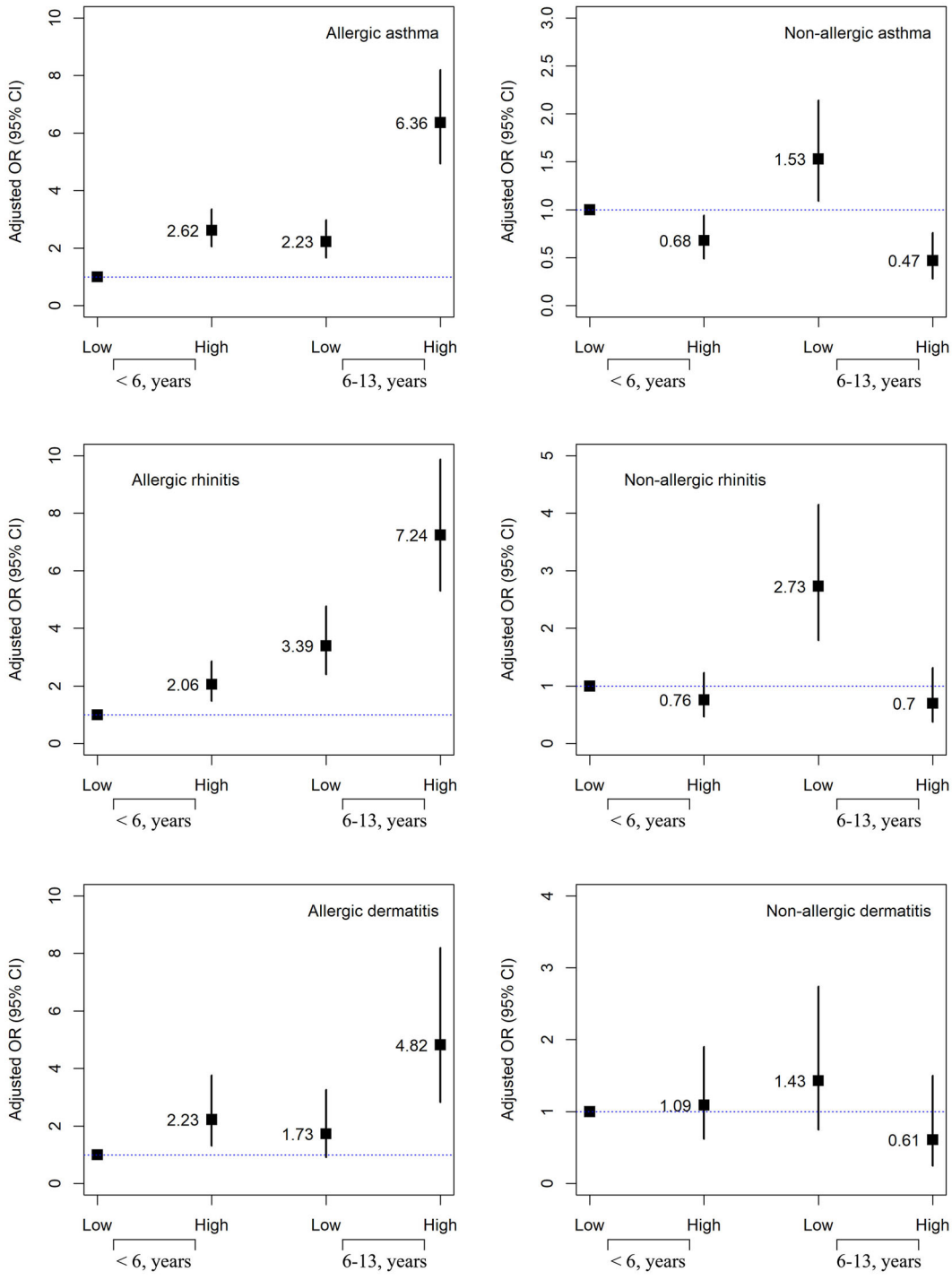

Figure 3. Adjusted combined effects of age and eosinophils on the risks of asthma, rhinitis and dermatitis. All estimates are adjusted for gender, basophils, neutrophils, eosinophils, lymphocytes and monocyte. Error bars represent 95% confidence intervals of ORs. Low indicates eosinophils <0.35, 10^9/L; High indicates eosinophils ≥ 0.35, 10^9/L.

reported that blood eosinophilia (>0.4) and older age were independent risk factors associated with future asthma attacks. Furthermore, a longitudinal study [26] reported that blood eosinophil count, together with type 2 inflammatory biomarker, was effective to predict the acute visits for asthma in adolescents, and the optimal cut point of eosinophil count is altered by age. In contrast to prior studies, our findings emphasized that compared with their counterparts, there were increased risks of allergic subtype symptoms (asthma, rhinitis and dermatitis) when exposed to a high level of eosinophil in the school-aged child. Moreover, we are the first to discover that there were significant additive interactions between eosinophil

count and age on allergic asthma/rhinitis in children. The possible biological explanation is that the school-aged childhood has formulated a strong immune system and it is the critical period to subsequent challenges that stimulates a latent immune response [31], thus when getting into contact with the immune effector of eosinophil [32], it might strengthen the immune response in organs and airway tissues, hence increases the risks of allergy. Additionally, both additive and multiplicate interactions can be observed between age and eosinophil count on non-allergic asthma and rhinitis. To date, the biological mechanism of the progress of non-allergic subtype symptoms throughout childhood and its recurrence in adulthood is still poorly understood [3,4]. In this regard, we speculate that the school-aged children with lower eosinophil count, having the highest risks of non-allergic asthma/rhinitis in this study, might correlate with specific sub-phenotyping.

Some limitations should also be considered. The most important one may be that the patients' diagnosis was obtained from the electronic medical records, and we could not get some pulmonary function parameters. The enrolled participants coming from a single centre in Guangzhou might limit the generalisability of our conclusions. However, these study samples of ours come from the serum bank of the Allergy Information Repository (AIR-SKLRD), which is in the First Affiliated Hospital of Guangzhou Medical University. The AIR-SKLRD has become the largest dataset of allergic patient information in southern China [17], and the participants in this study had better representativeness of Chinese children, thus making our results more reliable. Additionally, the present study only investigated IgE-mediated allergic subtypes that were mainly characterized by urticaria in the skin, rhinitis and asthma. Therefore, future research should examine IgE-independent allergies which are commonly presented as a gastrointestinal disorder. The cross-sectional study design let us can't calculate the risk ratios, thus we used odds ratios (ORs) to measure the association between the exposure and outcomes in this study.

Conclusions

Current results have demonstrated that eosinophils and age independently and jointly played important roles in the occurrence of various symptoms of allergic disorders. The higher eosinophil counts were associated with the increased risks of allergic-subtype symptoms and the decreased risks of non-allergic subtypes in children. Our findings also have discovered that there were significantly additive interactions between eosinophil and age and emphasize their joint effect on the clinical policy relevance of allergies administration in children.

Ethical approval

All participants or their parents provided oral and written informed consent for participating in this study, and in conformity with the ethics approval by the First Affiliated Hospital of Guangzhou Medical University ethics committee (reference number: GYFYY-2016-73).

Consent for publication

The funders had no roles in study design, data collection, data analysis, interpretation and writing of the report. XH and BS had full access to the data in the study and had final responsibility for the decision to submit it for publication.

Patient and public involvement

Study participants or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Author contributions

XH, WL and BS designed the study. WL and TC completed the data management and data cleaning as well as interpretation. XH performed the statistical analysis. XH, WL and HG drafted the manuscript. XH, Ganhui and BS edited the manuscript. All authors contributed to the critical revision of the manuscript and approved the final version.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability statement

The datasets used and/or analysed during this study are available from the corresponding author (email: sunbaoqing@vip.163.com) on reasonable request.

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