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Association of Childhood Blood eosinophils and Symptoms of Allergic disorders: A Cross-Sectional Study in Southern China

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Corresponding Author:	Xiaohua Douglas Zhang University of Macau Macau, MACAO
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Macau
Corresponding Author's Secondary Institution:	
First Author:	Xiaohua Douglas Zhang
First Author Secondary Information:	
Order of Authors:	Xiaohua Douglas Zhang
	Xiangqing Hou
	Wenting Luo
	Tianhao Chen
	Baoqing Sun
Order of Authors Secondary Information:	

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Abstract: The associations between blood eosinophils and subtypes of allergic symptoms remain understudied. This study was conducted to examine the associations between childhood blood eosinophils and subtypes of asthma, rhinitis and dermatitis, as well as the modifying effect of age. We obtained concurrent blood cell counts and serum

	Immunoglobulin E (IgE) test results in 5026 children (0-13, years) from the First Affiliated Hospital of Guangzhou Medical University during 2014-2019. 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). The association of eosinophils with allergic asthma/rhinitis is non-linear positively, with a plateau at levels of Q4 (≥0.51, 10^9/L). Conversely, exposure-response curves between eosinophils and the risk of non-allergic asthma and rhinitis are negatively linear, and especially, become statistically significant when levels of eosinophils are large than Q3 (≥0.30, 10^9/L). Compared with their counterparts, school-aged children (6-13, years) with higher level of blood eosinophils (≥0.35, 10^9/L) are 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) and allergic dermatitis (RERI not significant). We report that higher eosinophil counts are 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 accentuate in the school-aged child. These findings would contribute to providing novel insights in clinical administration relevance of allergic-related symptoms.
Suggested Reviewers:	Maggie Wang School of Public Health and Primary Care, Chinese University of Hong Kong, N.T., Hong Kong SAR Maggiew@cuhk.edu.hk
	Hao Luo Tianjin University, No.135 Yaguan Road, Haihe Education Park, Tianjin, China hluo@tju.edu.cn
	Guangyun Mao Wenzhou Medical College - Chashan Campus: Wenzhou Medical University mgy@wmu.edu.cn

Association of Childhood Blood eosinophils and Symptoms of Allergic disorders: A Cross-Sectional Study in Southern China

Running title: Childhood Blood Eosinophils and Allergic Symptoms

Xiangqing Hou[1*], Wenting Luo[2*], Tianhao Chen[1], Baoqing Sun[2✉], Xiaohua Douglas Zhang[1✉]

Affiliations: [1]Faculty of Health Sciences, University of Macau, Macau, China; [2]Department of Allergy and Clinical Immunology, State Key Laboratory of Respiratory Disease, National Clinical Research Center of Respiratory Disease, Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University, Guangdong, China.

* These authors contributed equally to this work.

✉**Corresponding Authors:**

Prof. Xiaohua Douglas Zhang; #E12-3021, Faculty of Health Sciences, University of Macau, Avenida da Universidade, Taipa, Macau, China; Telephone: +853-88224813; E-mail: douglaszhang@um.edu.mo.

Prof. Baoqing Sun; 151 Yanjiangxi Road, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University, Guangzhou, Guangdong, China; E-mail: sunbaoqing@vip.163.com.

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Abstract

The associations between blood eosinophils and subtypes of allergic symptoms remain understudied. This study was conducted to examine the associations between childhood blood eosinophils and subtypes of asthma, rhinitis and dermatitis, as well as the modifying effect of age. We obtained concurrent blood cell counts and serum Immunoglobulin E (IgE) test results in 5026 children (0-13, years) from the First Affiliated Hospital of Guangzhou Medical University during 2014-2019. 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). The association of eosinophils with allergic asthma/rhinitis is non-linear positively, 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 are negatively linear, and especially, become statistically significant when levels of eosinophils are large than Q_3 (≥0.30, 10^9/L). Compared with their counterparts, school-aged children (6-13, years) with higher level of blood eosinophils (≥0.35, 10^9/L) are 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) and allergic dermatitis (RERI not significant). We report that higher eosinophil counts are 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 accentuate in the school-aged child. These findings would contribute to providing novel insights in clinical administration relevance of allergic-related symptoms.

Keywords: 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 and brings huge economic and health burdens[1,2]. Allergic and autoimmune disorders are common diseases that are characterized by complicated clinical symptoms and hard to diagnose and cure, particularly in young people[3]. It has been revealed that asthma[4], allergic rhinitis[5] and atopic dermatitis[6] are the most common inflammatory disorders which are strongly associated with allergic sensitization. Therefore, some effective allergy prevention strategies, such as avoidance of contact with specific allergens or exposure to ambient air pollutants[7], 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. Therefore, effective identification of the subtypes of allergic-related symptoms would contribute to the appropriate deployment of limited medical resources as well as guiding diagnosis and treatment. A prospective cohort study[8] suggests that age is associated with the progress of atopic diseases and allergic sensitization, and a recent review[9] reports that autoimmune diseases are more frequent in the youngster. In comparison with adults, children have higher risks of autoimmune diseases and more severe symptoms resulting from the lack of autoantibodies[10]. 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 is beneficial and quite necessary to examine easily accessed biomarkers that are associated with allergy-related outcomes for clinical administration and specific treatments. 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 eosinophil can result in tissue damage in inflammation[14]. A UK cohort study[15] reveals that blood eosinophil count is associated with improvement of predictive value for asthma outcomes assessment. Similarly, a multi-center longitudinal study performed in China also reports that high blood eosinophil count is 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 investigate 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 in Guangzhou city, in southern China. The data utilized in this study was originated from long-term (2014-2019) longitudinal electronic medical records of patients enrolled in the First Affiliated Hospital of Guangzhou Medical University.

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) test; (3) patients who had completed peripheral blood cell counts test; (4) patients who had at least one follow-up; (5) initial hospital visit between January 2014 and August 2019; (6) aged of 0-13 years. Finally, a total of 5026 subjects satisfying inclusion criteria were analyzed in this study. Additionally, 5026 subjects contribute to 5588 observations during the study period, and the recurrence rate is 9.2%. Since the recurrence rate is relatively lower (less than 10%), to avoid the collinearity in the multivariable model due to duplicate medical records as well as retain a large sample size, we just keep the first follow-up record in those recurrence patients and excluded other duplicate observations (n=562).

All blood samples were collected in the First Affiliated Hospital of Guangzhou Medical University between January 2014 and August 2019. Serum IgE samples were sent to the central laboratory for diagnosis using ImmuoCAP (Thermo Fisher Scientific Inc., California, USA). TIgE and 99 sIgE, including 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]. At the same time, cell count test was carried out for peripheral blood samples. 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 patient's medical records which were downloaded from the Medical Data Information Detection System in the First Affiliated Hospital of Guangzhou Medical University.

Assessment of age groups, higher eosinophils and allergy-related outcomes

Age was categorized into six classes (0~, 2~, 4~, 6~, 8~, 10~13 years) to describe the characteristics of subjects

in the present study (**Supplemental Table 1**). Moreover, we recognized ages of 6 as the cut-off point to assess the reliability of the association between eosinophils and allergic diseases because the school-aged child (6-13, years) has a large prevalence of allergic diseases than early childhood (<6, years). According to previous research, 0.35 (10^9/L) was a widely accepted classification criterion[18] to distinguish higher and lower eosinophil levels. Additionally, the present study also found that the exposure-response curve between eosinophils and the risks of allergic asthma/rhinitis is gradually becoming more stable when the level of eosinophils large than 0.35 kU/L. Therefore, based on the cut-off value of 0.35, we separate the subjects into two populations with higher and lower eosinophils.

The diagnosis flowchart can be seen in **Figure 1**. There are six subtypes of allergic-related symptoms in this study: 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 as 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[19]. Additionally, patients who had the clinical diagnosis of asthma, rhinitis, dermatitis but not with any allergic sensitization reaction were defined as non-allergic subtypes.

Statistics analysis

Peripheral blood cells were described as median (1^{st} quartile, 3^{rd} 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 was applied to investigate the associations between blood eosinophils and allergy-related outcomes. Eosinophil counts were classified into four categories by quartile to examine the trend of such associations. 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 two age categories (<6, 6-13). 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 modeling the relative excess risk due to interaction (RERI) using the method of variance estimates recovery, and 95% confidence interval (CI) of RERI including 0 indicates 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, US). Figures were drawn with R-studio 1.2.5001 (Copyright 2009-2018 R-studio, Inc.). All tests were two-sided and $p<0.05$ was considered as significant.

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.

Results

Study population characteristics

A total of 5026 children from Guangzhou city during January 2014 to August 2019 were included in final analysis in this study, 3305(65.8%) of them were boys, and the median (P_{25}, P_{75}) age were 4(2, 6) years. Among all patients, 12.4%, 8.0%, and 2.3% were diagnosed as 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 show that the early childhood (<6, years) tends to have higher monocyte and lymphocyte counts, while having less eosinophils and neutrophils than the school-aged child (6-13, years). As shown in Table 1, the school-aged child is more sensitive to allergic sensitization than early childhood ($P<0.001$). Moreover, the prevalence of allergic disorders including asthma, rhinitis, dermatitis is comparatively higher ($P<0.001$) in the school-aged child, and similar results are also observed in non-allergic rhinitis.

Individual Association between Age and Allergy-related outcomes

There exists 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 become stable when age is more than 6 years (**Figure 2, Supplemental Table 1**). Similarly, the exposure-response curve between age and non-allergic asthma depicts slightly positive association and achieves significance when age less than 4 years (**Figure 2**). However, the exposure-response curves suggest that children aged 6-8 years are more likely to suffer from non-allergic rhinitis (**Figure 2, Supplemental Table 1**). Additionally, a significant "U" shaped association between age and the risks of dermatitis can be observed when controlling for other confounders (**Figure 2**).

Individual Association between eosinophil counts and Allergy-related outcomes

We classified eosinophil counts into four categories by quartiles to performed trend tests. **Table 2 and Figure 2**

show that eosinophil count is 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, obvious negative relationship between eosinophil count and non-allergic asthma/rhinitis can be observed in this study (**Figure 2**), and the trend test achieve statistical significance (**Table 2**, P_{trend}<0.001). Compared with the first quartile of eosinophil counts, the highest quartile (Q_4) of eosinophil counts is 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 is significantly reduced when exposed to Q_4.

Stratified analyses are 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 demonstrate that there are consistent associations between allergic-subtype symptoms and eosinophil levels in each stratum (**Table 2, Supplemental 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 are reliable in different age group or gender. No significant associations between eosinophils and non-allergic dermatitis are observed in this study.

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

The individual association of eosinophil count and age on symptoms of allergy-related outcomes has been comprehensively demonstrated in this study. 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**) show that the greatest risks of allergic asthma, allergic rhinitis and allergy dermatitis are observed in the school-aged child with high level of eosinophil (≥0.35, 10^9/L). Moreover, significant additive interactions between age and eosinophils are identified in allergic asthma and allergic rhinitis (95% CIs of RERI excluding 0), though there is 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) are higher than 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 is 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 exhibit significance (**Table 3**). Additionally, the results also suggest that no obvious joint associations of age and eosinophils with non-allergic dermatitis are observed.

Discussion

To our knowledge, 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 in children. Overall, our findings contribute to the established evidence regarding the associations between eosinophil and allergy-related outcomes, and especially emphasize the joint association of age and eosinophil with asthma, rhinitis and dermatitis. Firstly, we reveal that there is a positive association between childhood eosinophils and allergic-subtype symptoms. The association of eosinophils with allergic asthma/rhinitis is slightly non-linear, with a plateau at levels of Q_4 (≥0.51, 10^9/L). Secondly, the highest adjusted OR of allergic asthma/rhinitis/dermatitis is 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) has the greatest risks of non-allergic asthma and rhinitis. Lastly, the associations of eosinophil and allergic asthma/rhinitis accentuate in the school-aged child, additionally, both significant multiplicative and additive interactions between age and eosinophil on non-allergic asthma/rhinitis are identified in this study.

The potential biological mechanism of the association between eosinophil and allergies has been well established by previous studies. Eosinophil-Associated Diseases (EADs) has become a hot research topic recently, not only it will induce inflammation of immune system, but also can result in chronic organ damage[14]. It has been emphasized that eosinophil as potential end-stage effector and blood immune biomarkers plays a major role in the development of allergic inflammation in the airways and skin tissue, it commonly joints with mast cells to induce autoimmune disorders, such as asthma and chronic spontaneous urticaria[22]. Additionally, it has been suggested that the 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 aging as well as the age-dependent differential immune activation commonly induce complicated allergic symptoms in various age groups[23]. Therefore, better understanding in the roles of eosinophil and age on the occurrence of allergic-related diseases might provide new therapeutic and health-care strategies.

Several epidemiological studies confirm that the higher level of eosinophil increases the risks of allergic diseases, especially asthma[15] and rhinitis[24]. For instance, a cross-sectional study[25] performed in the UK discovers that eosinophil increases the occurrence 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 report that there is 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 demonstrates that there is 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[9], our data also suggest that the risks of asthma and rhinitis significantly increases as children get older during early childhood, and become stable when age is 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.

The independent associations of age and eosinophil on allergies have been well demonstrated in previous studies[27,28]. Nevertheless, to the best of our knowledge, the joint association of eosinophil and age on the subtypes of allergic-related symptoms remains unknown, particularly in children. A large study[29] derived from routine medical record data reports that blood eosinophilia (>0.4) and older age are independent risk factors associated with future asthma attacks. Furthermore, a longitudinal study[26] reports that blood eosinophil count, together with type 2 inflammatory biomarker, is 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 emphasize that compared with their counterparts, there are increasing risks of allergic subtype symptoms (asthma, rhinitis and dermatitis) when exposed to high level of eosinophil in the school-aged child. To our knowledge, we are the first to discover that there are 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 strong immune system and it is the critical period to subsequent challenge that stimulates a latent immune response[30], thus when getting into contact with the immune effector of eosinophil[31], it might strengthen 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[4,5]. 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.

The major clinical implications of the present study are based on public health. Firstly, 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. Secondly, the comprehensive analysis of the association between eosinophil and the symptoms of allergies in early and school-aged childhood would be beneficial to clinical management in child allergies. Thirdly, the assessment of joint associations between age and eosinophil contributes to the understanding of the development of pathogenesis for childhood allergy.

Some limitations should also be considered. In this study, the enrolled participants come from a single center in Guangzhou might limit the generalizability of our conclusions. However, these study samples of ours come from the serum bank of Allergy Information Repository (AIR-SKLRD), which is located 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 make our results more reliable. Additionally, the present study only investigates IgE-mediated allergic subtypes that are mainly characterized by urticaria in the skin, rhinitis and asthma. Therefore, future research should examine IgE-independent allergies which are commonly presented as gastrointestinal disorder.

Conclusions

In conclusion, current results have demonstrated that eosinophil and age independently and jointly play important roles in the occurrence of various symptoms of allergic disorders. The higher eosinophil counts are 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 are significantly additive interactions existing between eosinophil and age, as well as emphasize their joint effect on the clinical policy relevance of allergies administration in children.

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Figure legends:

Figure 1. Diagnostic flowchart of allergic disorders.

Figure 2. Associations of age and eosinophils with the risks of asthma, rhinitis and dermatitis based on spline regression models.

Note: 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.

Figure 3. Adjusted combined effects of age and eosinophils on the risks of asthma, rhinitis and dermatitis.

Note: 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.

List of 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; CI, confidence interval; RERI, relative excess risk due to interaction.

Declarations

Ethics approval and consent to participate: All participants or their parents provided an 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. Xiangqing Hou, Baoqing Sun and Xiaohua Douglas Zhang had full access to the data in the study and had final responsibility for the decision to submit for publication.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author (email: douglaszhang@um.edu.mo) on reasonable request.

Competing interests: All authors declare no potential conflicts of interest.

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Authors' contributions: Xiangqing Hou, Wenting Luo, Baoqing Sun and Xiaohua Douglas Zhang designed the study. Wenting Luo, Tianhao Chen completed the data management and data cleaning as well as interpretation. Xiangqing Hou and Xiaohua Douglas Zhang performed the statistical analysis. Xiangqing Hou and Wenting Luo drafted the manuscript. Xiangqing Hou, Baoqing Sun and Xiaohua Douglas Zhang edited the manuscript. All authors contributed to critically revision of the manuscript, and approved the final version.

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Table1. Characteristics of subjects in various age groups

Label	Total (n=5026)	Age, years		*P* value
		<6 (n=3627)	6-13 (n=1399)	
Gender				0.020
Boys	3305(65.8)	2350(64.8)	955(68.3)	
Girls	1721(34.2)	1277(35.2)	444(31.7)	
Total IgE, kU/L				<0.001
<150	3079(61.3)	2501(69.0)	578(41.3)	
≥150	1947(38.7)	1126(31.0)	821(58.7)	
Allergic sensitization¶	2164(43.1)	1504(41.5)	660(47.2)	<0.001
Peripheral blood cells, 10^9/L				
Basophils	0.03(0.01,0.10)	0.03(0.01,0.09)	0.03(0.00,0.10)	0.028
Neutrophils	3.60(2.60,5.10)	3.50(2.50,5.20)	3.60(2.70,5.00)	0.033
Eosinophils	0.30(0.10,0.50)	0.26(0.10,0.50)	0.33(0.17,0.60)	<0.001
Lymphocytes	3.60(2.70,4.90)	4.00(3.10,5.40)	2.90(2.30,3.60)	<0.001
Monocyte	0.60(0.50,0.80)	0.70(0.50,0.90)	0.50(0.40,0.70)	<0.001
Diagnosed diseases				
Asthma§				
Allergic asthma	624(12.4)	308(8.5)	316(22.6)	<0.001
Non-allergic asthma	263(5.2)	182(5.0)	81(5.8)	0.271
Rhinitis§				
Allergic rhinitis	404(8.0)	156(4.3)	248(17.7)	<0.001
Non-allergic rhinitis	144(2.9)	82(2.3)	62(4.4)	<0.001
Dermatitis§				
Allergic dermatitis	113(2.3)	60(1.7)	53(3.8)	<0.001
Non-allergic dermatitis	76(1.5)	55(1.5)	21(1.5)	0.968

¶: Allergic to at least one allergen of 99 allergens.
§: Allergic asthma/rhinitis/dermatitis was defined as those who diagnosed as 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.

Table2. OR (95% CIs)[¶] for allergic disorders by quartiles of eosinophil count in different age groups

Label	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	¶*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
<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
Rhinitis					
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

Note: 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: 1st quartile (n=1259), <0.10, 10^9/L; 2nd quartile (n=1237), 0.11-0.29, 10^9/L; 3rd quartile (n=1333), 0.30-0.50, 10^9/L; 4th quartile (n=1197), ≥0.51, 10^9/L.

b: 1st quartile (n=997), <0.10, 10^9/L; 2nd quartile (n=828), 0.11-0.26, 10^9/L; 3rd quartile (n=888), 0.27-0.49, 10^9/L; 4th quartile (n=914), ≥0.50, 10^9/L.

c: 1st quartile (n=351), <0.17, 10^9/L; 2nd quartile (n=347), 0.18-0.32, 10^9/L; 3rd quartile (n=382), 0.33-0.60, 10^9/L; 4th quartile (n=319), ≥0.61, 10^9/L.

¶:Adjusted for Basophils, Neutrophils, Lymphocytes, Monocyte, Gender and/or Age.

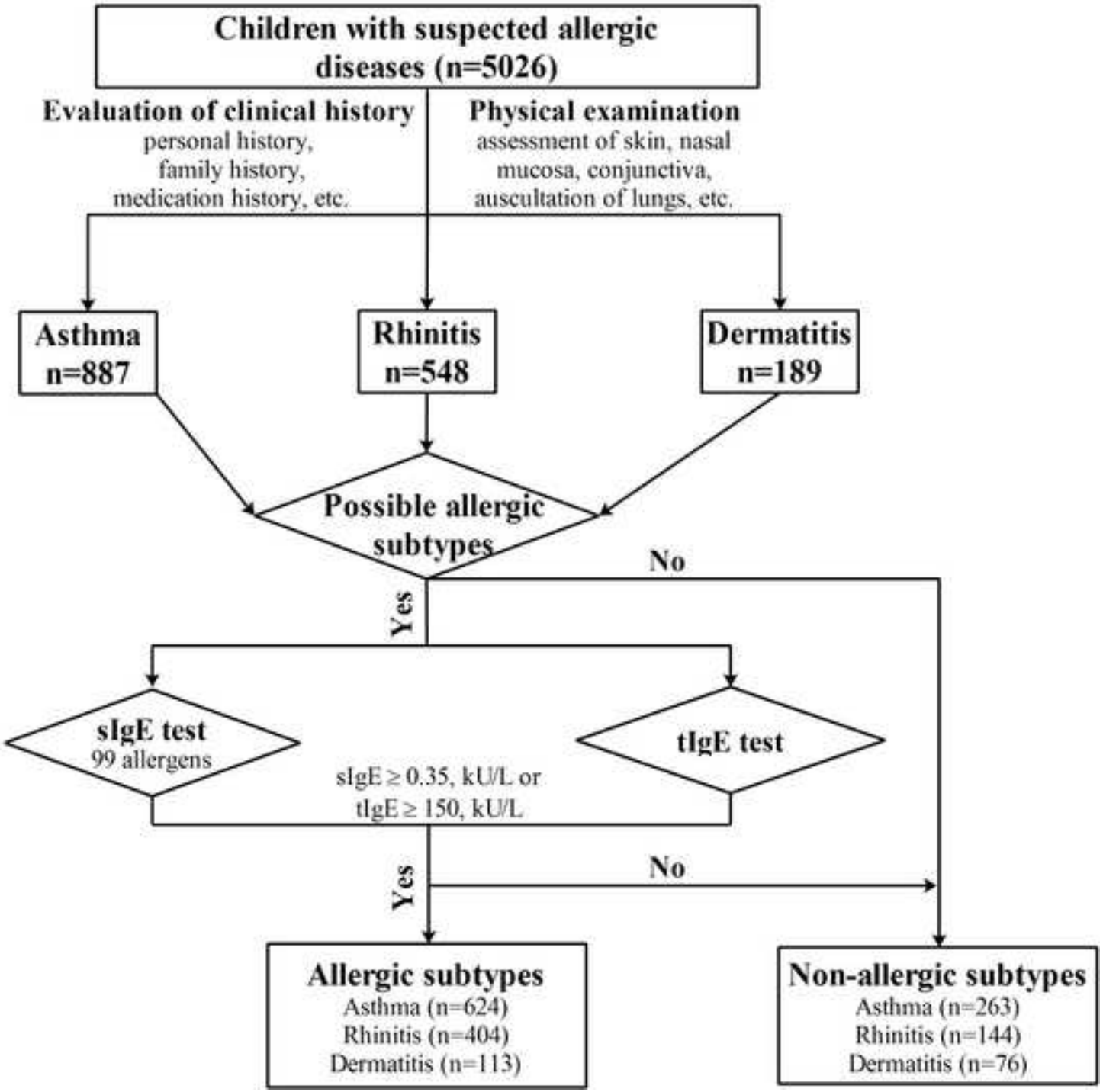
Table3. Joint Associations between eosinophil counts and age on allergy-related outcomes

Age, years	Eosinophils ≥0.35, 10^9/L	Cases/ Controls	Prevalence, %	*Crude*		*Adjusted*§	
				OR (95% CI)	*p*-value	OR (95% CI)	*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)							

Note: 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.

§: Adjusted for Gender, Basophils, Neutrophils, Lymphocytes, Monocyte.

Figure



Figure

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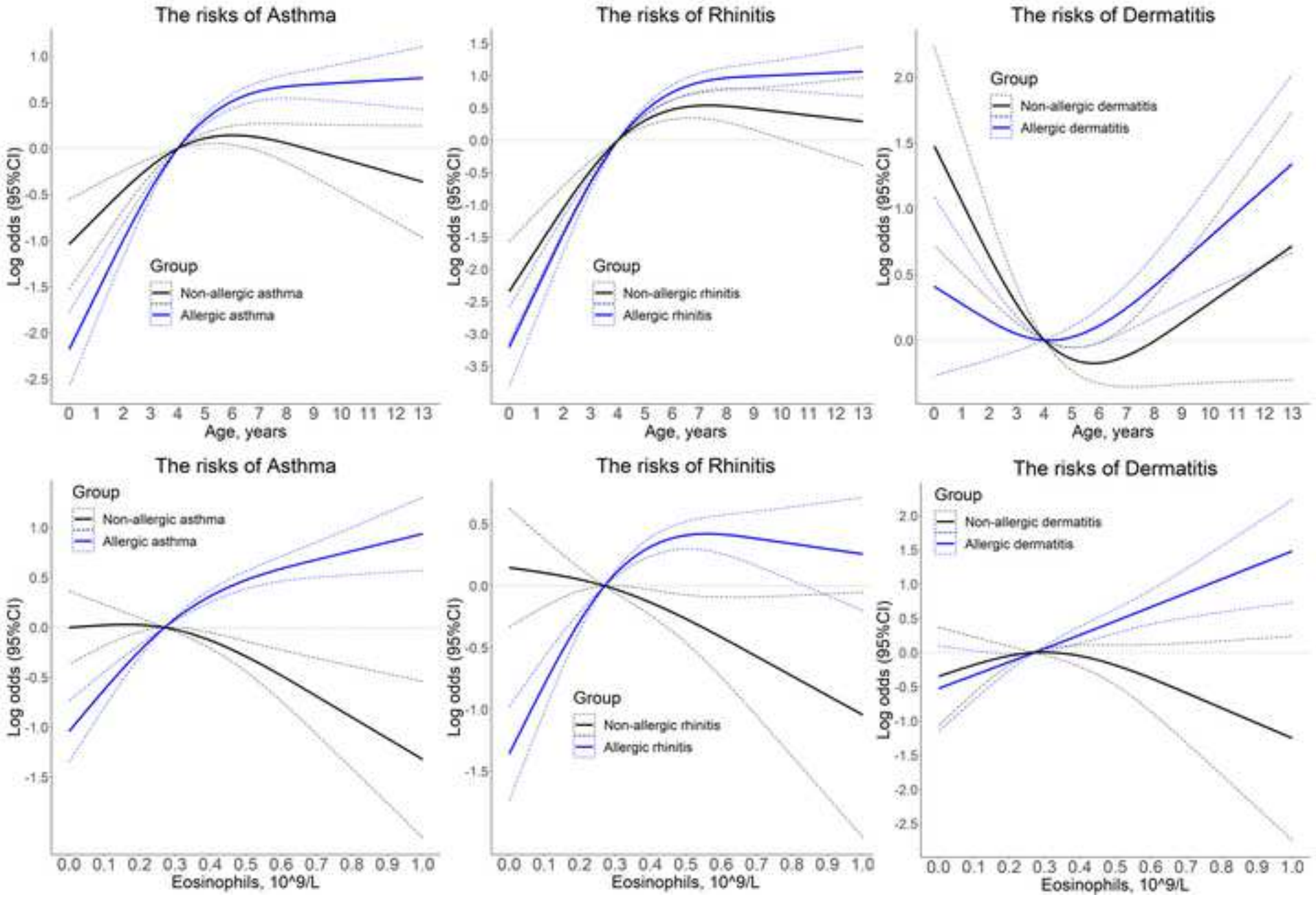

Figure

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