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Age-related differences in IgE between childhood and adulthood allergic asthma: Analysis of NHANES 2005–2006

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ABSTRACT

Background: Asthma exhibits varying clinical features in children and adults. However, previous studies have mainly focused on the clinical significance of immunoglobulin E (IgE) in the diagnosis and treatment of asthma, disregarding the characteristics of IgE and its relevant factors.

Objective: This study aimed to gain a better understanding of the differences in the characteristics of IgE between childhood and adulthood allergic asthma (AA).

Methods: Patients with AA from the 2005 to 2006 National Health and Nutrition Examination Survey (NHANES) were divided into 3 groups based on their current age and onset age of AA: childhood AA (Group 1), childhood-onset adult AA (Group 2), and adulthood-onset AA (Group 3). Intragroup analysis and intergroup comparison were carried out, focusing on the characteristics and relevant factors of IgE, as well as the clinical relevance of total IgE (total IgE, tIgE) and allergen-specific IgE (allergen-specific IgE, sIgE).

Results: A total of 424 patients were analyzed, including 187 with childhood AA, 132 with childhood-onset adult AA, and 105 with adulthood-onset AA. The concentration of tIgE was found to be higher in Group 1 (268.0, 118.0–686.0 kU/L) than in Group 2 (224.0, 78.0–494.0 kU/L) and Group 3 (165.0, 74.4–350.5 kU/L). The sensitization rates did not differ between Group 1 and Group 2 but were higher compared with Group 3, particularly for *Alternaria*-sIgE (50.3% and 46.2% vs 15.2%) and *Aspergillus*-sIgE (43.9% and 37.1% vs 16.2%). In Group 1, there was a negative correlation between pollen-sIgEs and indoor allergens, but this correlation was not commonly observed in Group 2 and Group 3. On the other hand, in Group 1, environmental chemicals such as phthalates, polyaromatic hydrocarbons, trihalomethanes, and phenols showed a positive correlation with IgE. However, a greater number of chemicals was observed in Group 2 and Group 3, including cotinine, metals, trihalomethanes, phthalates, phenols, and other volatile organic compounds (VOCs). Furthermore, in Group 1, IgE was positively correlated with asthma-related issues such as emergency visits, absenteeism, limited activities, and medication needs. These correlations were less common in Group 2 and Group 3, particularly in Group 3.

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Conclusions: There are notable differences in the characteristics and environmental factors of IgE among childhood AA, childhood-onset adult AA, and adulthood-onset AA. Additionally, IgE plays a more significant role in childhood AA due to its higher concentration, fewer relevant environmental chemicals and greater clinical relevance. This may partially explain the age-related features of asthma.

Keywords: Asthma, Allergy and immunology, Immunoglobulin E, Omalizumab, Age groups

INTRODUCTION

Asthma has become a prevalent noncommunicable disease since the 1960s,[1] with allergic asthma (AA) being the most prominent type triggered by immunoglobulin E (IgE).[2] The clinical features of asthma vary with age, as well as onset age.[3] For instance, adulthood asthma has different risk factors and comorbidities, a lower prevalence, poorer therapeutic responses, and worse prognoses than childhood asthma.[4] In contrast, childhood asthma presents a higher incidence of thunderstorm asthma.[5] More importantly, recent studies suggest that the benefits of anti-IgE therapy (omalizumab) also vary in different age groups. In childhood asthma, omalizumab was found to be beneficial only for those who experienced exacerbations, while it was beneficial for both exacerbators and non-exacerbators in adulthood asthma.[6] Interestingly, discontinuing omalizumab resulted in a higher control rate for childhood asthma,[7] and no significant differences in asthma outcomes at 24 months were found regardless of whether omalizumab was discontinued or maintained.[8] These findings contrast with those in adulthood asthma, suggesting that age-related disparities in the clinical features of asthma may be linked to IgE. Therefore, analyzing the characteristics of IgE in different age groups may provide valuable insights into the diverse clinical features of asthma.

Currently, the clinical significance of IgE in childhood and adulthood asthma has not been consistently demonstrated. While some studies have indicated a stronger association between IgE and childhood asthma compared to adulthood asthma,[9-12] they primarily focused on the association between IgE and lung function, overlooking the differences in IgE itself and its relevant factors. Given the original function of IgE as a defense mechanism against environmental stimuli in epithelial and mucosal tissues and the increasing prevalence of allergies that cannot be explained by genetic variation,[1,13] it is believed that environmental changes have disrupted the evolved IgE immune regulation. Indeed, the relationship between environmental factors and asthma has sparked increasing interest,[14-16] particularly considering the significant impact of urbanization on human chemical exposure.[17] For instance, the association between household cleaners and asthma has been acknowledged for more than 2 decades.[18] These chemicals can damage the bronchial epithelial barrier,[19] and are correlated with IgE levels.[20] Furthermore, with over 350 000 chemicals present in human daily lives,[21] there is growing concern about their potential role in asthma. Therefore, understanding the age-related differences in the environmental factors affecting IgE is an important research topic, as it may provide insights into the underlying causes of the differences in clinical features of AA.

This study aimed to investigate the differences in characteristics, environmental factors, and clinical relevance of IgE in patients with AA across different age groups, which was achieved by analyzing the 2005–2006 dataset of the National Health and Nutrition Examination Survey (NHANES at www.cdc.gov/nchs/nhanes).

METHODS

Study design and population

The NHANES is a long-term research program that examines a nationally representative sample of approximately 5000 people each year in the United States. The program (NHANES 2005–2006) was approved by the NCHS Ethics Review Board

(Protocol #2005–06). The NHANES 2005–2006 project examined 10 348 participants and additionally investigated allergy-related issues, which included related questions and analytes, especially total IgE (tIgE) and allergen-specific IgE (sIgE). Thus, the dataset was obtained for the purpose of analysis in this study.

Inclusion and exclusion process

In this study, asthma was defined through 2 questions: 1) "Has a doctor or other health professional ever told you that you have asthma?" and 2) "Do you still have asthma?".[22] Patients with asthma were classified as having AA if they were sensitized to at least 1 aeroallergen according to sIgE, which was the inclusion criterion of this study. However, children under the age of 6 were excluded from the study because their wheezing could be caused by respiratory infections and other conditions, as per the guidelines set out by the Global Initiative for Asthma (GINA).[23]

Sample collection and examination

Human specimens, including blood and urine, as well as environmental samples, such as household dust and water, were collected by trained staff at the mobile examination centers and in participants' homes, respectively. All analyses were conducted using a standardized protocol by NHANES contract laboratories and were quality controlled using multiple methods.

Serum samples were analyzed for tIgE and sIgE using the Pharmacia Diagnostics ImmunoCAP 1000 System (Kalamazoo, Michigan). In addition to tIgE, a total of 15 aeroallergen-sIgEs were detected, including *D. farinae*, *D. pteronyssinus*, *cat*, *dog*, *rat*, *mouse*, *cockroach*, *ragweed*, *oak*, *birch*, *rye grass*, *Bermuda grass*, *thistle*, *Alternaria*, and *Aspergillus*. The NHANES measured tIgE and sIgE in units of kU/L and kU_A/L, respectively. Then, the unit of tIgE was converted to match the unit of globulin (g/L), and the proportion of tIgE was calculated (1 IU = 2.42 ng), with the aim of evaluating the impact of basal globulin concentration when comparing tIgE. In addition, sIgE was defined as positive (or allergic sensitization) if it exceeded the threshold of 0.35 kU_A/L, which is in line with global standards.[24] The whole percentage of sIgE was calculated by adding together each sIgE.

Environmental factors, including biological and chemical agents from the environment, were analyzed as potential factors that were correlated with IgE. The analytes included (in blood) cotinine, metals, polyfluoroalkyl substances, trihalomethanes (THMs) and other volatile organic compounds (VOCs); (in urine) arsenics, metals, phenols, parabens, phthalates, polyaromatic hydrocarbons (PAHs), THMs and other VOCs; (in household dust) allergens (*Der f1*, *Der p1*, *Fel d1*, *Can f1*, *Rat n1*, *Mus m1*, *Bla g1*, *Bla g2*, *Alt a1* and *Aspergillus*) and endotoxin; and (in water) THMs and other VOCs. Notably, different sample types allowed for the detection of various types of VOCs, resulting in a more comprehensive analysis of VOCs.

Asthma-related issue assessment

One questionnaire regarding a history of respiratory health was administered to the survey participants to investigate symptoms that may be related to asthma. In this study, the presence of wheezing and wheezing-related functional impairments and medical treatment in the past year were evaluated through 6 questions. The responses were recoded into 2 categorical variables during analysis. The primary question, which required all participants to answer, was recoded as "Wheezing or whistling in the past year". The secondary questions required the participants who reported wheezing or whistling to answer and were recoded as "Go to emergency due to wheezing", "Miss school or work due to wheezing", "Limit activities due to wheezing", "Disturb sleep due to wheezing", and "Need wheezing medication".

Grouping and statistical analysis

The variables of interest were tIgE and sIgE, and all analyses were stratified by age group. The patients were divided into 3 groups based on their current age and onset age of AA. Group 1 consisted of patients with childhood AA (current age: 6–17 years old). Group 2 consisted of patients with childhood-onset adult AA (current age: 18 years old and above, onset age: below 18 years old). Group 3 consisted of patients with adulthood-onset AA (current age: 18 years old and above, onset age: 18 years old and above). This grouping

strategy was determined based on the analysis of the onset age (Figure S1). Before the formal analysis, patients with tIgE levels over 1000 kU/L were assessed for the presence of skin problems, sinus infections, malignancy, white blood cell counts, C-reactive protein and globulin concentration to rule out potential hyper-IgE syndrome, and no suspected patients were identified. Furthermore, the differences in the male to female ratio, tIgE, and sIgE between children (6–11 years old) and adolescents (12–17 years old) were tested and found to be nonsignificant.

Qualitative data are presented as frequencies (percentages), and quantitative data are presented as medians (interquartile ranges, IQRs) after undergoing normality testing. Kruskal-Wallis and chi-square tests, followed by Fisher's least significant difference (LSD) multiple comparisons, were performed to evaluate the intergroup differences in the concentration of tIgE, the positive rates of sIgE, the concentration of environmental analytes, and the proportion of asthma-related issues. Spearman correlation was used to assess the correlation among sIgEs, and between IgE and environmental factors as well as asthma-related issues. The intergroup comparison of the correlation coefficients was conducted using MedCalc based on the Fisher *z*-transformation and *z* test.[25] Multiple linear regression was conducted to evaluate the regression coefficients of each sIgE to tIgE. The final model was built using the stepwise method and was additionally checked and processed for multicollinearity. All analyses and plotting were performed using GraphPad Prism 9 and MedCalc Software. Statistical signifi-cance was set at a two-tailed $P < 0.05$.

RESULTS

General characteristics

A total of 424 patients over 6 years old with AA were analyzed, including 187 (44.1%) with childhood AA (Group 1), 132 (31.1%) with childhood-onset adult AA (Group 2), and 105 (24.8%) with

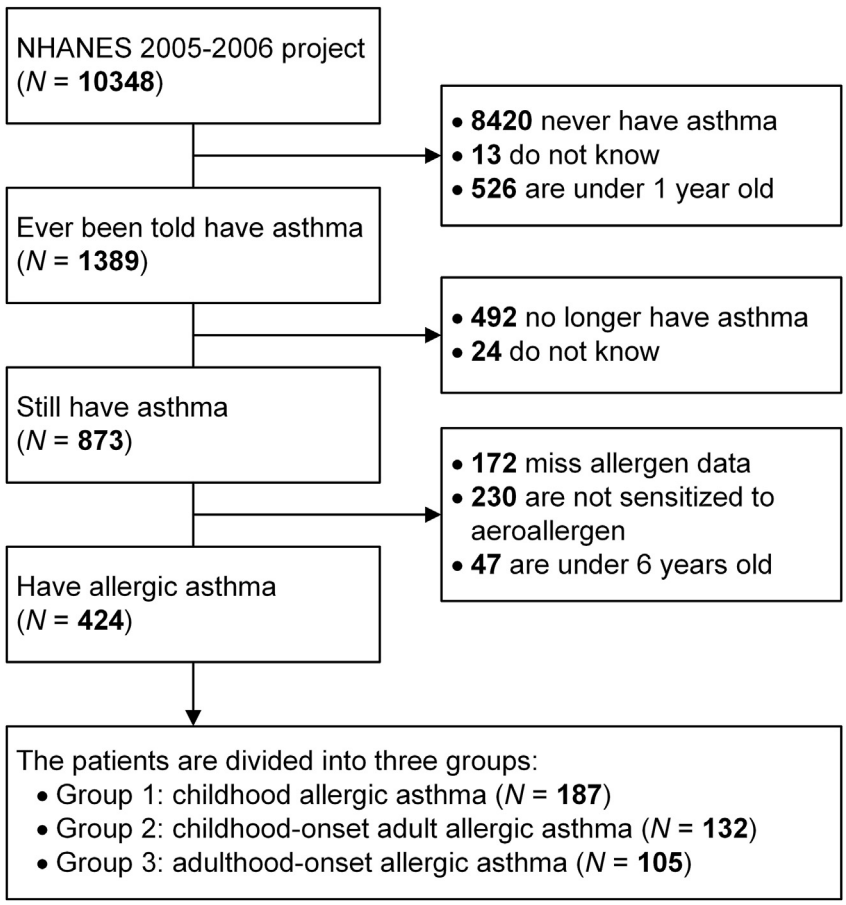


Fig. 1 The inclusion and exclusion process of this study

adulthood-onset AA (Group 3) (Fig. 1). The general characteristics of the patients are summarized in Table 1. In summary, the concentration of tIgE and its proportion in globulin were higher in Group 1 than in Group 2 and Group 3. Additionally, the percentage of sIgE in tIgE was higher in both Group 1 and Group 2 than in Group 3.

Total IgE and allergen-specific IgE

The most common indoor allergens were *D. pteronyssinus* (58.0%) and *D. farinae* (57.8%), while *rye grass* (56.8%) and *ragweed* (49.3%) were the most common outdoor allergens. Interestingly, the positive rates of sIgEs were not significantly different between Group 1 and Group 2. However, Group 3 had significantly lower positive rates for several sIgEs compared with Group 1 and Group 2, particularly *Alternaria*-sIgE (3.0- to 3.3-fold) and *Aspergillus*-sIgE (2.3- to 2.7-fold), and no sIgE showed a higher rate in Group 3 (Fig. 2). Additionally, the analysis showed that *Aspergillus*-sIgE had the highest regression coefficient to tIgE in Group 1 ($\beta = 28.9$, 95% CI 22.5–35.4, $P < 0.001$) and Group 2 ($\beta = 53.6$, 95% CI 39.3–67.9, $P < 0.001$) after adjustment, but this was not observed in Group 3 (Figure S2). Furthermore, the bivariate correlation analysis showed potential differences in sensitization patterns between the groups (Figure S3). Specifically, a negative correlation between dust mite-sIgEs and *Alternaria*-sIgE in Group 1 was not observed in Group 2 and Group 3, and a positive correlation between dust mite-sIgEs and pollen-sIgEs (*ragweed* and *rye grass*) in Group 2 was not observed in Group 1 and Group 3. Further intergroup comparisons showed stronger correlations between sIgEs in Group 1 and Group 2 than in Group 3.

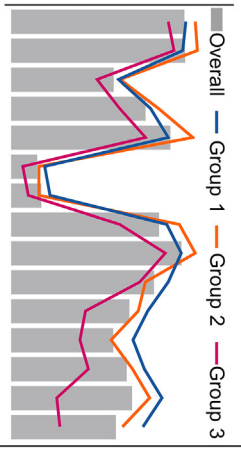
Association between IgE and household dust analytes

The correlation between IgE and household dust analytes was more significant in Group 1 (Fig. 3). Specifically, indoor allergens (*Der f1*, *Der p1*, *Bla g2*, *Fel d1*, *Rat n1*) from household dust were negatively correlated with pollen-sIgEs in Group 1, whereas this correlation was not commonly observed in Group 2 and Group 3. Further intergroup comparisons confirmed the

Characteristics median (IQR) or n (%)	Overall (N = 424)	Group 1 (N = 187, 44.1 %)	Group 2 (N = 132, 31.1 %)	Group 3 (N = 105, 24.8 %)	*P* value
Age (year)	19 (14–40)	13 (10–16)[b,c]	32 (21–45)[a,c]	47 (34–62)[a,b]	<0.001
Sex, male					0.003
Male	217 (51.2)	111 (59.4)[c]	65 (49.2)	41 (39.0)[a]	
Female	207 (48.8)	76 (40.6)	67 (50.8)	64 (61.0)	
Onset age of asthma (year)	8 (3–17)	5 (1–8)[b,c]	7 (2–12)[a,c]	32 (24–46)[a,b]	<0.001
Globulin (g/L)	29 (27–32)	29 (26–31)[b,c]	29 (27–33)[a]	29 (27–33)[a]	0.02
Total IgE (kU/L)	227.0 (90.7–528.8)	268.0 (118.0–686.0)[b,c]	224.0 (78.0–494.0)[a]	165.0 (74.4–350.5)[a]	<0.001
tIgE/globulin ratio (millionth)	17.6 (7.5–42.7)	23.2 (11.0–58.5)[b,c]	16.8 (6.6–42.9)[a]	13.2 (6.2–25.8)[a]	<0.001
sIgE/tIgE ratio (%)	17.5 (8.3–33.8)	21.8 (11.1–36.4)[c]	17.6 (9.3–30.5)[c]	10.9 (4.6–27.6)[a,b]	<0.001

Table 1. The General characteristics of the patients. *Group 1: childhood allergic asthma; Group 2: childhood-onset adult allergic asthma; Group 3: adulthood-onset allergic asthma. sIgE: allergen-specific immunoglobulin E; tIgE: total immunoglobulin E.* [a]$P < 0.05$ *vs. Group 1.* [b]$P < 0.05$ *vs. Group 2.* [c]$P < 0.05$ *vs. Group 3*

sIgE, n (%)	Overall (N = 424)	Group 1 (N = 187)	Group 2 (N = 132)	Group 3 (N = 105)	Positive rate (%) 0 15 30 45 60	*P* value
D. farinae	245 (57.8)	109 (58.3)	81 (61.4)	55 (52.4)		0.37
D. pteronyssinus	246 (58.0)	107 (57.2)	82 (62.1)	57 (54.3)		0.46
Cockroach	145 (34.2)	67 (35.8)	48 (36.4)	30 (28.6)		0.37
Cat	191 (44.8)	87 (46.5)	65 (49.2)	38 (36.2)		0.11
Dog	225 (53.1)	98 (52.4)	80 (60.6)	47 (44.8)		0.05
Rat	37 (8.7)	21 (11.2)	12 (9.2)	4 (3.8)		0.10
Mouse	42 (10.0)	24 (12.9)	12 (9.2)	6 (5.7)		0.14
Ragweed	209 (49.3)	97 (51.9)[c]	74 (56.1)[c]	38 (36.2)[a,b]		0.006
Rye grass	241 (56.8)	106 (56.7)	81 (61.4)	54 (51.4)		0.31
Bermuda grass	202 (47.6)	98 (52.4)	59 (44.7)	45 (42.9)		0.21
Oak	167 (39.4)	85 (45.5)[c]	56 (42.4)[c]	26 (24.8)[a,b]		0.002
Birch	144 (34.0)	76 (40.6)[c]	44 (33.3)	24 (22.9)[a]		0.009
Thistle	163 (38.5)	83 (44.4)[c]	53 (40.5)[c]	27 (25.7)[a,b]		0.006
Alternaria	171 (40.3)	94 (50.3)[c]	61 (46.2)[c]	16 (15.2)[a,b]		< 0.001
Aspergillus	148 (34.9)	82 (43.9)[c]	49 (37.1)[c]	17 (16.2)[a,b]		< 0.001



[a] $P < 0.05$ vs Group 1; [b] $P < 0.05$ vs Group 2; [c] $P < 0.05$ vs Group 3.

Fig. 2 The positive rates of sIgE among the 3 groups. Group 1: childhood allergic asthma; Group 2: childhood-onset adult allergic asthma; Group 3: adulthood-onset allergic asthma

significantly lower coefficients in Group 1 ($P < 0.05$). Additionally, a negative correlation was observed between endotoxin and IgE (tIgE, *dog*-sIgE, *rat*-sIgE and *mouse*-sIgE) in Group 1. In contrast, a positive correlation (*rat*-sIgE) was observed in Group 3. Notably, the concentrations of most analytes did not differ among the groups, while *Mus m 1* was higher in Group 1 than in Group 3 (median 1.16 vs 0.86 ng/ml, $P = 0.007$).

Association between IgE and environmental chemicals

Phthalates, THMs and phenols were positively correlated with tIgE in Group 1, while more chemicals, including cotinine, metals, THMs, phthalates, phenols and other VOCs (such as phenylglyoxylic acid and cysteines), were positively correlated in Group 2 and Group 3 (Fig. 4). Further analysis between the relevant chemicals of 3 representative sIgEs (*D. pteronyssinus*-sIgE, *rye grass*-sIgE and *Aspergillus*-sIgE) showed that more chemicals were correlated with sIgE in Group 1 than in Group 2 and Group 3, which contrasted with tIgE. Notably, most of the listed chemicals showed no significant differences in their concentrations between the 3 groups, while a few showed significantly lower concentrations in Group 1.

Association between IgE and asthma-related issues

The levels of tIgE and several sIgEs were positively correlated with issues in Group 1, including emergency visits, absenteeism from school or work, limited activities, and the need for wheezing medication (Fig. 5). However, most of these findings were not observed in Group 2 and Group 3, and further intergroup comparison confirmed the significantly higher coefficients in Group 1. Additionally, the correlation coefficients were found to be the lowest in Group 3. Notably, the proportions of patients experiencing wheezing in the past year were not significantly different among the groups.

Further analysis evaluated the relationship between asthma-related issues and household dust analytes, as well as the chemicals listed above (Table S1). In Group 1, *Aspergillus* showed a positive correlation with wheezing ($r = 0.18$, $P = 0.03$). In Group 2, none of the household dust analytes showed a correlation with asthma-related issues, but several chemicals were positively correlated. In Group 3, *Aspergillus* and several chemicals were positively correlated with asthma-related issues. However, no potential regulatory or mediating relationships were found among these environmental factors, IgE, and asthma-related issues.

DISCUSSION

In this study, we examined the differences in IgE between childhood AA (Group 1), childhood-onset adult AA (Group 2), and adulthood-onset AA (Group 3), with the objective of identifying

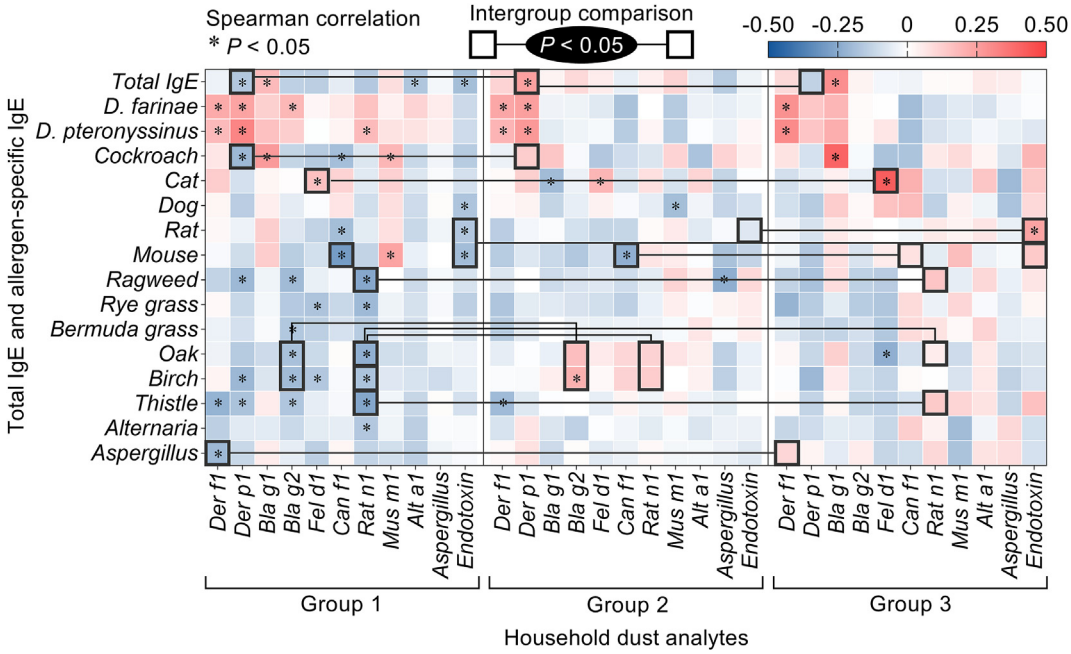


Fig. 3 The correlation between IgE and household dust analytes among the 3 groups. Group 1: childhood allergic asthma; Group 2: childhood-onset adult allergic asthma; Group 3: adulthood-onset allergic asthma

potential reasons for the age-related differences in the clinical features of asthma. Our findings revealed that the concentration of tIgE was highest in Group 1, which was confirmed by the basal globulin concentration. In addition, the percentage of sIgE was higher in Group 1 and Group 2 than in Group 3, indicating that more unknown sIgE, nonspecific IgE or nonfunctional IgE may appear in Group 3.

This study revealed interesting findings regarding sIgE. Similar sensitization rates and the highest regression coefficient of *Aspergillus*-sIgE were observed in both Group 1 and Group 2, indicating that the 2 groups have similar allergen profiles. This finding aligns with a previous study that showed persistent sensitization profiles over time.[26] However, this raises the question of whether the sensitization pattern was similar between the 2 groups. To address this, the study further examined the correlations between sIgEs and found a negative correlation between dust mite-sIgE and *Alternaria*-sIgE, as well as a lack of correlation between dust mite-sIgE and the most prevalent pollen-sIgEs (*ragweed* and *rye grass*) in Group 1 compared with Group 2. This suggests potentially different sensitization patterns. The cluster analysis for longitudinal patterns of sIgE responses supports this, as separate clusters for dust mites and grass were formed at the age of 3 years, and the sensitization patterns became more complex and intersected more as age increased.[27] Therefore, the sensitization pattern observed in Group 2 may be considered the long-term pattern of Group 1, which requires further clarification in cohort studies.

Unexpectedly, the sensitization rates of several allergens were found to be higher in Group 1 and Group 2 than in Group 3. This difference was particularly significant for allergens such as *Alternaria* and *Aspergillus*. Moreover, the highest regression coefficient of *Aspergillus*-sIgE to tIgE was not observed in Group 3. These findings highlight the distinct allergen profiles in adulthood-onset AA, suggesting that fungi may have a significant role as allergens for sensitization in childhood. Additionally, a decade of data from Beijing (2010–2020) revealed a gradual shift, with fungal allergens surpassing dust mites as the most common aeroallergens in children.[28] On the other hand, a previous study demonstrated an association between *Aspergillus* sensitization and current childhood asthma.[29] Therefore, although not currently included in routine testing, fungal allergens are expected to gain importance as a future research topic.[30]

This study examined the relationship between the concentrations of household allergens and IgE.

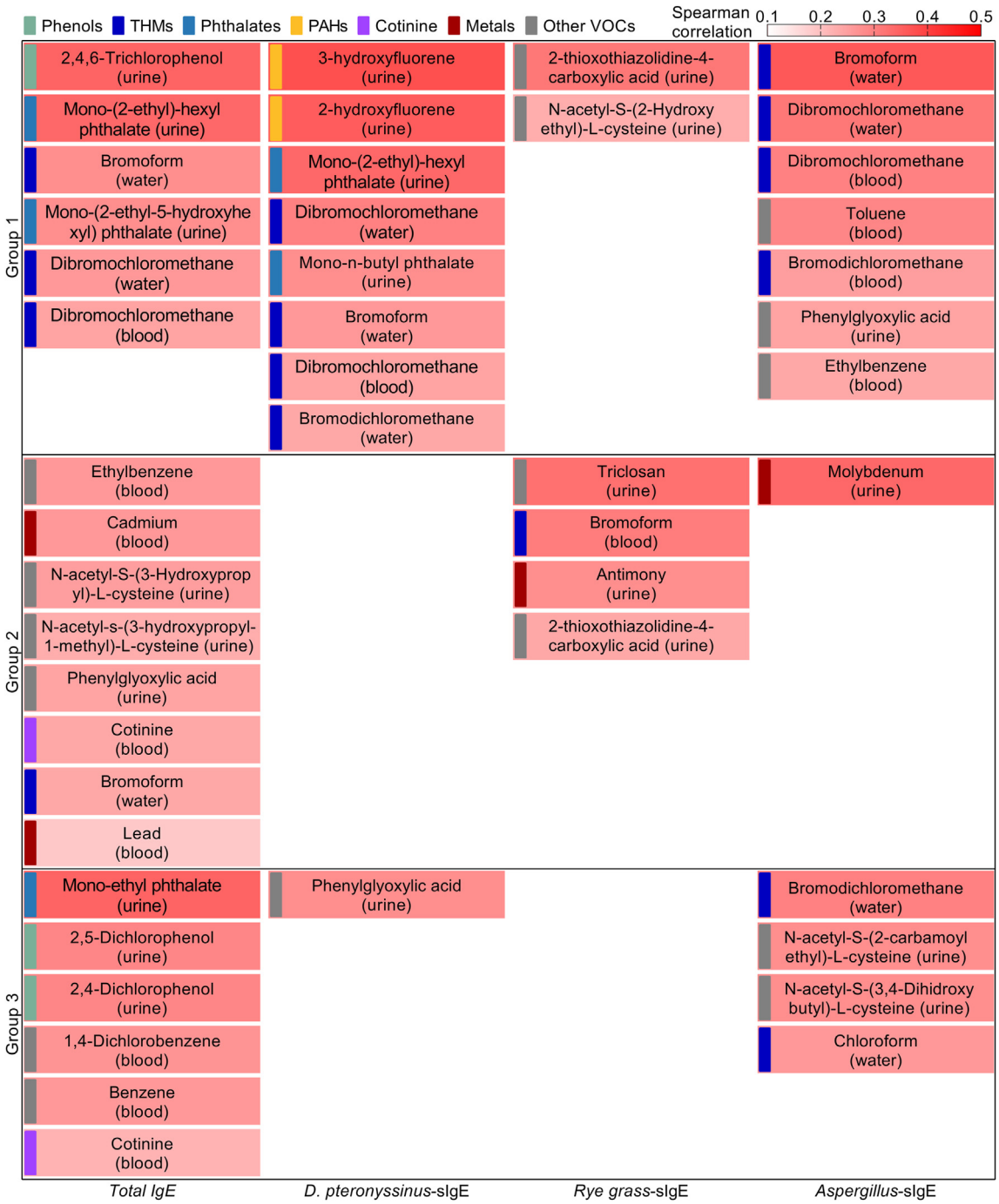


Fig. 4 Chemicals correlated with tIgE and sIgE among the 3 groups. Group 1: childhood allergic asthma; Group 2: childhood-onset adult allergic asthma; Group 3: adulthood-onset allergic asthma. Spearman correlation. sIgE: allergen-specific immunoglobulin E; THMs: trihalomethanes; PAHs: polyaromatic hydrocarbons; VOCs: volatile organic compounds

The results showed a positive correlation between the concentration of allergens in household dust and sIgE of the same allergen, which aligns with current knowledge.[31] However, a broad negative correlation between the concentration of indoor allergens and outdoor allergen-sIgEs as well as significantly lower coefficients were observed in Group 1, which was not common in Group 2 and Group 3. The possible reason for this difference may still be attributed to the different sensitization patterns discussed earlier, suggesting that children with higher indoor allergen exposure levels may be more inclined toward the dust mite cluster and less inclined toward the grass cluster.[27] Unfortunately,

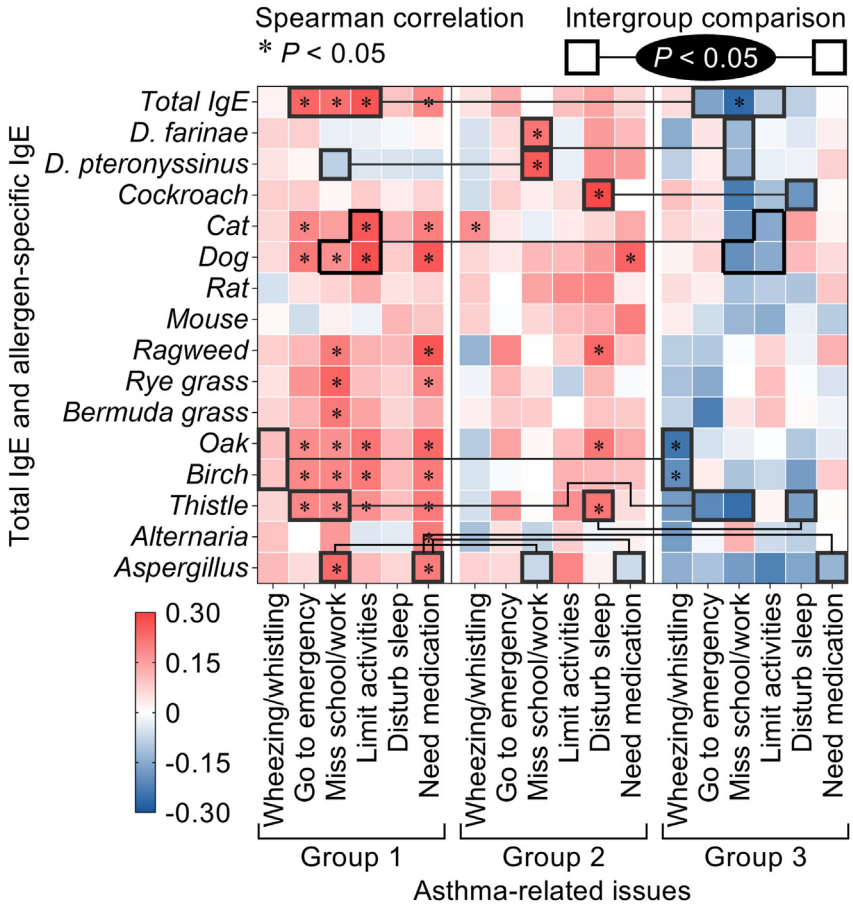


Fig. 5 The correlation between sIgE and asthma-related issues. Group 1: childhood allergic asthma; Group 2: childhood-onset adult allergic asthma; Group 3: adulthood-onset allergic asthma

this study was unable to determine any potential negative correlation between exposure to outdoor allergens and indoor allergen-sIgE due to a lack of data. Another notable finding was the association between the concentration of endotoxin in household dust and IgE, which differed between Group 1 and Group 3. This difference may be attributed to the inclination of Th1 and Th2 responses in distinct age groups.[32] Furthermore, although the concentration of allergens showed a positive correlation with their sIgEs, they were not commonly correlated with asthma-related issues. However, this study did find a correlation between IgE and asthma-related issues, suggesting that the relationship between the concentration of allergens and symptoms can be complex, as previously reported.[33]

In addition, the correlation between chemical exposures and IgE showed that phthalates, PAHs, THMs and phenols were positively correlated with tIgE or sIgE in Group 1. Specifically, phthalates are used as plasticizers in various industries and have become ubiquitous pollutants in air and dust.[34] The association between phthalates and allergic diseases as well as IgE has been reported in several studies,[35-37] and its possible mechanism is that phthalate exposure could disrupt the balance of innate and adaptive immunity and produce epigenetic modifications.[38-40] On the other hand, PAHs are classified as atmospheric particulate matter (PM 2.5), and their effects on IgE have already been reported; that is, they can enhance B-cell differentiation in an isotype-specific way and promote IgE production,[41,42] which mainly occurs in younger age groups.[43] This is in line with our results that PAHs are positively correlated with *D. pteronyssinus* IgE only in Group 1. The mechanism is that PAHs can not only carry allergens but also activate aryl hydrocarbon receptors to promote Th2 and Th17 responses.[44] Another point that needs to be emphasized is that there is an association between disinfection byproducts (THMs and

phenols) and IgE in Group 1 in this study. While a few studies have indicated similar associations,[45,46] the underlying mechanism remains unclear. One of the possible reasons could be that they may damage the epithelial barrier similar to other chemical cleaners,[19] leading to microbial dysbiosis and exposure to allergens. In fact, it can be impossible to kill harmful insects or microorganisms without damaging human cells, and the most well-known example is the association between antibiotics and allergies.[47] Therefore, these chemicals may have long been underestimated as allergy-promoting factors, and their health relevance needs to be carefully assessed. Additionally, it is unknown whether these chemicals have direct effects on IgE or B cells, and it is important to clarify these possible effects.

Interestingly, the chemicals correlated with IgE in Group 2 and Group 3 differed from those in Group 1. Specifically, heavy metals, cotinine, phthalates, THMs, phenols and other VOCs showed a positive correlation with IgE, which aligns with a previous study indicating that more environmental chemicals are correlated with IgE in adulthood AA.[20] Furthermore, there was a partial overlap between the chemicals in Group 1 and Group 3, including phthalates, THMs and phenols, although the reasons for this similarity remain unclear. The consistent concentrations of most chemicals among the groups suggest that the differences in correlated chemicals may be attributed to varying levels of tolerance to chemical exposure. While this partially explains the complexity of asthma, it also emphasizes the challenge of elucidating the relationship between these factors and allergies. As in this study, no definitive findings were obtained when attempting to analyze the relationship among environmental factors, IgE, and asthma-related issues. To overcome this challenge, traditional research and analysis methods may not be sufficient, and new methods such as omics and artificial intelligence may be necessary in the future.[48]

Finally, this study found that tIgE was positively correlated with asthma control and functional impairment in Group 1 but not in Group 2 and was even negatively correlated in Group 3. The broad correlation between sIgE and asthma-related issues as well as significantly higher coefficients further confirmed that IgE had greater clinical relevance in childhood AA than in adulthood AA, which may provide an explanation for the different benefits of omalizumab in childhood (those who experienced exacerbations have higher concentrations of IgE) and adulthood AA,[6] as well as the higher control rate in children after discontinuing omalizumab.[7] In addition, these findings are consistent with previous studies that have shown a correlation between tIgE and childhood asthma control, but they mainly focused on asthma control or disease severity based on lung function tests.[10,11] However, missed school and limited activities are both important issues in childhood AA that affect the quality of life of both patients and parents.[49,50] On the other hand, the correlation between tIgE and adulthood asthma control has been reported to decrease,[9,10] which aligns with our finding that there is less correlation between IgE and asthma-related issues in adulthood AA. Therefore, it is valuable to understand the differences in the clinical relevance of IgE between childhood and adulthood asthma, which provides guidance for clinical practice or suggests new associations.

Strengths and limitations

The strengths of this study are worth mentioning. In summary, the NHANES 2005–2006 dataset includes comprehensive data, including a significant number of sIgEs, allergens in household dust and various chemicals and their metabolites. Despite its strengths, it is important to acknowledge its limitations. The survey was carried out at an early stage, which resulted in some important variables, such as sIgE from other microorganisms, not being fully considered. In addition, some asthma-related data, such as lung function, exhaled nitric oxide, and asthma control score, were not collected.

CONCLUSIONS

In summary, there are notable differences in the characteristics and environmental factors of IgE among childhood AA, childhood-onset adult AA and adulthood-onset AA. Additionally, IgE plays a more significant role in childhood AA due to its higher concentration, fewer relevant environmental chemicals and greater clinical relevance. This may partially explain the age-related features of asthma. By analyzing asthma from the pers-

pective of IgE, valuable insights can be gained to better comprehend the differences in the clinical features of asthma. To further elucidate the role of IgE in AA, new methods such as omics and artificial intelligence may be necessary in the future.

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Availability of data
The datasets analyzed during the current study are available in the NHANES repository at www.cdc.gov/nchs/nhanes/index.htm.

Abbreviations
AA: allergic asthma; IgE: immunoglobulin E; sIgE: allergen-specific IgE; tIgE: total IgE; NHANES: National Health and Nutrition Examination Survey; PAH: polyaromatic hydrocarbon; THM: trihalomethane; VOC: volatile organic compound

Authors' contributions
Heping Fang: Conceptualization, Formal analysis, Methodology, Writing - Original Draft.
Juan Li: Conceptualization, Software, Visualization, Writing - Original Draft.
Luo Ren: Conceptualization, Writing - Review & Editing, Supervision.
Enmei Liu: Writing - Review & Editing, Project administration, Funding acquisition.

Ethics approval
The program (NHANES 2005–2006) was approved by NCHS Ethics Review Board (Protocol #2005–06).

Authors' consent for publication
The authors confirmed that neither the entire paper nor its content has been submitted, accepted, or published elsewhere. All authors have approved the manuscript and agree with the submission.

Declaration of competing interest
The authors declare that they have no competing interests.

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Appendix A. Supplementary data
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