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ORIGINAL RESEARCH

Risk Assessment of Allergic Diseases Among Preschool Children in Guangzhou, China: A Cross-Sectional Study

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Purpose: To investigate the lifestyle and stress of mothers during pregnancy to analyze the risk factors for the disease in early childhood.

Patients and Methods: A cross-sectional survey was conducted from January 2022 to June 2022 in a sub-district in Guangzhou, China. A total of 3437 valid questionnaires were eventually collected. The questionnaire consisted of 56 questions in three sections included questions on child's birth conditions and early life environment, questions on mother's lifestyle during pregnancy, and questions about father.

Results: 49.75% of the children were likely to have allergic diseases (suspected allergy group). There were more boys in the suspected allergy group (58% vs 50%), and the percentage of children born at first birth was also higher in the suspected allergy group (61% vs 51%). 67% to 69% of children had suspicious allergies when one parent claimed an allergy, and 80.1% when both parents reported an allergy. The results of the multifactorial logistic model showed that male had 1.49 (1.28 to 1.73) times the risk of allergic diseases than female, and preterm births increased the risk of allergic diseases by 1.53 (1.13–2.07) times compared to full-term births. Both unplanned pregnancies and pregnancy complications increased the risk of allergic diseases in children before school age [1.34 (1.15–1.55) and 1.82 (1.46–2.26)]. Among pregnant women who reported regular passive smoking, the risk of the disease was increased 2.43 (1.71 to 3.50) times in preschool children. Reported allergies in all family members were significant risk factors for allergic diseases in children, especially mother [2.88 (2.41~3.46)]. In the prenatal period, maternal negative emotions are more common in children with suspected allergies.

Conclusion: Nearly half of the children in the region suffer from allergic diseases. Sex, birth order and full-term delivery all contributed to early childhood allergy. Family history of allergy, especially maternal, was the most important risk factor, and the number of family members with allergy was significantly associated with the allergy in children. Maternal effects are also reflected in prenatal conditions such as unplanned pregnancy, smoke exposure, pregnancy complications, and prenatal stress.

Keywords: cross-sectional, heritability, risk factor, questionnaire, allergic rhinitis

Introduction

Allergy is one of the most common and serious diseases affecting children's health. It has a significant negative impact on the quality of life and learning status of affected children, as well as a significant medical burden on society. Allergic diseases primarily include allergic rhinitis (AR), allergic conjunctivitis (AC), allergic asthma (AA), urticaria, eczema, as

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well as food allergy (FA) and drug allergy (DA). Anaphylaxis can occur in severe cases which is life-threatening. Numerous studies have shown that different types of allergic diseases are related to each other and affect each other,[1–3] For example, a typical progression of allergic diseases includes pediatric FA eczema, and asthma before a child reaches school age and later. Allergic rhinitis (AR) is associated with many cognitive and psychiatric problems in children, including lack of attention, hyperactivity disorder, poor concentration, and reduced motor skills.[4–6] Severe neonatal eczema is an important risk factor for the development of allergic rhinitis and asthma. In addition, AR is an independent risk factor for the development of AA.[7,8]

The prevalence of allergic diseases has continued to rise in recent decades, affecting about 20% population worldwide, mostly children.[9] A study conducted in 2009 showed that in Wuhan, children aged 3–6 years old had a prevalence of questionnaire-based AR of 27.1%, and a prevalence of allergen skin prick test confirmed AR of 10.8%.[10] The prevalence of AA in children also increased from 0.9% in 1990 to 3.0% in 2010.[11] The first few years of life are when atopic dermatitis (AD) mostly manifests. According to some epidemiological studies, 45% of affected children are affected by 6 months of age, 60% by 1 year of age, and up to 85% by 5 years of age.[12–14] Food allergy (FA) primarily occurs in the first or second year of life, with the prevalence of 11% diagnosed by oral food challenge (OFC).[15–17] The prevalence decreases gradually thereafter and stabilizes at 3%-4% in late childhood.[18,19]

Genes and environment are the main factors in disease development. Allergic diseases have a clear family aggregation characteristic. Children are at higher risk of developing allergic rhinitis when their parents have a history of AA, or hives, or asthma. In China, a genetic epidemiologic study involving 23,825 families from Jiangsu province reported that the average AR heritability of the first, the second, and third generations was 81.86%.[20] In addition, studies have shown that prenatal nutrients, metabolites and environmental pollutants can have a direct impact on the fetus through placental transfer.[21] More and more studies point that maternal diet during pregnancy and breastfeeding can have a lasting effect on the infant's immune system and even on future health.[22–24] The study of the Isle of Wight Birth Cohort showed that children whose mother or grandmother smoked during pregnancy had a higher chance of wheezing in early childhood.[25]

Analysis of known or suspected causes of allergy in pregnant women and infants can help to further identify factors that contribute to allergic diseases occurring in early life. In this study, a standardized questionnaire was used to assess the current status and family distribution of allergic diseases in preschool children in an area of Guangzhou. A standardized questionnaire was also used to investigate the lifestyle and stress of mothers during pregnancy to analyze the risk factors for the disease in early childhood.

Materials and Methods

Subjects

It is a cross-sectional study, conducted from January 2022 to June 2022 in a sub-district in Guangzhou, China. All preschool children in the sub-district (3–6 years, 4661 children in total) were included in the study and were issued a questionnaire. All conditions are unrestricted except for age and residence, and no selection will be made. Finally, a total of 3437 valid questionnaires were eventually collected, with a response rate of 73.74%. The reasons for non-enrolled included (1) Failure to submit the questionnaire within the deadline, (2) Missing contents in the submitted questionnaire, (3) Refuse to sign an informed consent form.

Questionnaire

The standardized questionnaire used in this survey was designed by allergists from the First Hospital of Guangzhou Medical University and the National Center for Respiratory Medicine for a cross-sectional survey of allergic diseases in the Chinese population. And it was reviewed and evaluated for quality by several experts in the field. Since the questions for children were answered through their guardians instead, the questionnaire was expressed in the form of questions for adults rather than children. Therefore, we invited only allergists for validation and not pedagogues. The electronic questionnaires were collected with the help of a widely used online questionnaire collection system (WenJuanXing, Changsha Ranxing Information Technology Co., Ltd. China, https://www.wjx.cn/). A statement of informed consent was included at the beginning of the questionnaire. The link to the electronic questionnaire was accurately distributed to the

smartphones of all guardians with the assistance of the local government. The questionnaire consisted of 56 questions in three sections questions on child's birth conditions and early life environment (filled by the guardians), questions on mother's lifestyle and emotional state during pregnancy (filled by mothers), and questions on information about fathers (filled by fathers).

The questionnaire system is an intelligent online questionnaire collection system. It allows setting various logical formula. When any of the logical rules are violated, it will result in failure to submit, including the number box not being filled with text, and missing or conflicting answers. Take a question "Whether keeping pets in home" for example, if you answer "yes", you will be asked to further answer the type of pet and the time of keeping it, if "No", it will skip automatically. In summary, the electronic questionnaire uses various strategies, from question setting, questionnaire design and collecting, to ensure the validity and accuracy of the information.

Definition

We collected the subject's information of allergic diseases through a questionnaire (Considering the cognitive imperfection of preschool children, the guardians were required to fill in according to the actual situation). For the diagnosis of allergic diseases in preschool children we refer to the study of García-Marcos L et al[26] method. For example, allergic rhinitis and conjunctivitis were defined by positive answers to two questions: "In the past 12 months, has this child had a problem with sneezing, or a runny or blocked nose when he/she did not have a cold or the flu?" and "In the past 12 months, has this (child's) nose problem been accompanied with itchy-watery eyes?". "Severe rhino conjunctivitis symptoms" was defined by the response "a lot" to the question "In the past 12 months, how much did this (child's) nose problem interfere with your (his/her) daily activities? (Not at all, a little, a moderate amount, a lot)" "Asthma symptoms" was defined as any positive answer to the two questions "Have you (has your child) had wheezing or whistling in the chest in the past 12 months?" or "Has your child ever had asthma?" "Eczema symptoms" was defined as positive answers to the two questions: "Have you (has this child) had this itchy rash 'defined in a previous question' at any time in the past 12 months?" and "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?" "Drug allergy" was defined as a positive answer to the question: whether an allergic reaction occurred as a result of taking or injecting any drug in the past". Otherwise, were defined as "Excluded allergy". We collected the information on allergy of family members (parents and grandparents) in the same way.

The maternal prenatal stress scores included 5 positive and 2 negative questions: (1 During pregnancy, you are interested and passionate about yourself about what is happening around you. (2 During pregnancy, you are anticipating the imminent arrival of a child. (3 You often feel disappointed during pregnancy. (4 During pregnancy, you often have very complicated and mixed feelings and thoughts. (5 During pregnancy, you can get satisfactory help from your family when you are in trouble. (6 I was happy with the way my family spent time with me during my pregnancy. (7 During pregnancy, when I was down or full of stress, I could often handle it very well. Mothers were asked to choose one of the options "never, seldom, sometimes, not clear, often, usually, always", these 7 options corresponded to scores 1 to 7 respectively.

Premature birth was defined as a gestation period of less than 37 weeks. Breastfeeding for at least 5 months was defined as exclusive breastfeeding. With the use of hydrolyzed or amino acid formulas was defined as hydrolyzed formulas. Other factors evaluated included the age of the parents at delivery, the mother's active (yes or no) versus passive smoking during pregnancy (hardly ever, rarely, usually, or frequently), the father's smoking history prior to conception (yes or no), the birth order of the child (first, second, or third and above), the mother's access to knowledge about the science of pregnancy, the parents' educational level, and the family's monthly disposable amount.

Questionnaire Information Processing

Destroy data stored in the cloud immediately after completing online collection of questionnaire information, and encrypt all form files offline. The survey information was consolidated using Excel 2019 (Microsoft® Excel® 2019) for data consolidation, and used GraphPad Prism 8.0.2 (© 1992–2019 GraphPad Software, Inc.), R Studio 2022.07.2 Build 576

(© 2009–2022 RStudio, PBC) for data analysis. Adobe Illustrator CC 2015.0.0 (Adobe Inc.) was applied for image retouching and integration.

Statistical Analysis

Categorical data are reported as frequency (percentage). Chi-square test ($\chi 2$) was used to compare the distribution differences among groups (when the theoretical frequency was less than 5, fisher exact probability method was used to calibrate), and Bonferroni method was used to correct the pairwise comparison of significance level. Parametric quantitative data are presented as the mean ± standard deviation, and nonparametric quantitative data are presented as the median (interquartile range). The *t* test or Mann–Whitney *U*-test was used to compare the distribution differences between the two groups, and a one-way ANOVA or Kruskal–Wallis *H*-test was used to compare the distribution differences between multiple groups. Bar charts were used to show percentages. Venn plots (UpsetR package) were visualized collections for different disease types as well as co-morbidities among family members. Violin plots were used to compare differences in mood scores across groups. Finally, binary logistic regression was used to analyze risk factors for developing allergic diseases (forest plots were used to show ratios). The relationships between all independent and dependent variables were examined in advance by univariate analysis (*t*-test, chi-square test, etc.) before conducting binary multivariate logistic regression analysis, and apparently nonsignificant variables were kicked out. The risk ratio ratios of the variables that are eventually included in the model are adjusted. All p values were based on two-sided tests and were considered statistically significant at $P < 0.05$.

Results

Characteristics of the Study Subjects

A total of 3437 children were enrolled in the study, with a slightly higher of male than female children (54% vs 46%). The age of the children was 4.75 (4.08, 5.50) years. 49.75% (1710/3437) of the children were likely to have allergic diseases (suspected allergy group) and we compared the differences in demographic information between groups of suspected allergy and excluded allergy (Table 1). According to the data, there were more boys in the suspected allergy

Table 1 Basic Information of Preschool Children Included in the Study

Variable	Total cohort	Suspected Allergy N = 1710[a]	Excluded Allergy N = 1727[a]	p-value[b]
Sex				**<0.001**
Male	1863 (54%)	996 (58%)	867 (50%)	
Female	1574 (46%)	714 (42%)	860 (50%)	
Age				
Months	57 (49, 66)	58 (49, 66)	57 (48, 65)	0.069
Years	4.75 (4.08, 5.50)	4.83 (4.08, 5.50)	4.75 (4.00, 5.42)	0.069
Ethic				**0.007**
Han	3306 (96%)	1660 (97%)	1646 (95%)	
Others	131 (3.8%)	50 (2.9%)	81 (4.7%)	
Mode of delivery				0.300
Premature cesarean delivery	112 (3.3%)	58 (3.4%)	54 (3.1%)	
Full-term cesarean delivery	1058 (31%)	535 (31%)	523 (30%)	
Premature natural delivery	107 (3.1%)	62 (3.6%)	45 (2.6%)	
Full-term natural delivery	2160 (63%)	1055 (62%)	1105 (64%)	

(*Continued*)

Table 1 (Continued).

Variable	Total cohort	Suspected Allergy N = 1710[a]	Excluded Allergy N = 1727[a]	p-value[b]
Birth order				**<0.001**
First child	1937 (56%)	1048 (61%)	889 (51%)	
Second child	1323 (39%)	596 (35%)	727 (42%)	
Third child and above	176 (5.1%)	65 (3.8%)	111 (6.4%)	
Neonatal eczema				**<0.001**
Mild to moderate	1072 (31%)	770 (45%)	302 (17%)	
Severe	51 (1.5%)	47 (2.7%)	4 (0.2%)	
Newborn breastfeeding[c]				**<0.001**
Exclusive breastfeeding	1697 (49%)	833 (49%)[d]	864 (50%)[d]	
Cow's milk	435 (13%)	194 (11%)[d]	241 (14%)[e]	
Mixed feeding	1257 (37%)	644 (38%)[d]	613 (35%)[d]	
Hydrolyzed formulas	48 (1.4%)	39 (2.3%)[d]	9 (0.5%)[e]	
Complementary feeding time				**0.013**
< 4 months	116 (3.4%)	47 (2.7%)[d]	69 (4.0%)[e]	
4~6 months	1061 (31%)	545 (32%)[d]	516 (30%)[d]	
6~12 months	2119 (62%)	1062 (62%)[d]	1057 (61%)[d]	
≥12 months	141 (4.1%)	56 (3.3%)[d]	85 (4.9%)[e]	
Living Environment				0.200
Urban Village	2092 (61%)	1043 (61.0%)	1049 (60.7%)	
Rural self-built houses	106 (3.1%)	43 (2.5%)	63 (3.6%)	
Community	1239 (36%)	624 (36.5%)	615 (35.6%)	
Living floors				**0.048**
Ground floor (1–3 floors)	1026 (30%)	478 (28%)[d]	548 (32%)[e]	
Mid-floor (4–6 floors)	1221 (36%)	618 (36%)[d]	603 (35%)[d]	
High floor (≥ 6 floors)	1190 (35%)	614 (36%)[d]	576 (33%)[d]	
Exposure to pets	311 (9.0%)	170 (9.9%)	141 (8.2%)	0.069

Notes: [a]n (%); Median (IQR). [b]Pearson's Chi-squared test, Wilcoxon rank sum test and Fisher's exact test were used to compare the difference between the two groups. [c]Feeding for infants during the first 6 months of life. [d,e]Pairwise comparison of the chi-square test, if the same letter is included between two groups, indicate no significant difference, and vice versa.

group than excluded allergy group (58% vs 50%, P <0.001). The percentage of children born at first birth was also higher in the suspected allergy group (61% vs 51%, P <0.001). Regardless of severity, the proportion of children with neonatal eczema (having eczema within one year of birth) was significantly higher in the suspected allergy group than in the excluded allergy group (all with $P < 0.001$). The percentage of children who require special formulas within six months of birth in the suspected allergy was higher (2.3% vs 0.5%), The suspected allergy group had a lower proportion of children who were introduced to complementary foods earlier (<4 months) or later (>12 months) compared with the excluded group (P =0.013). In addition, the proportion of children living on ground floor in the suspected allergy group slightly higher than that in the excluded allergy group (32% vs 28%, P =0.048).

Analysis of Differences in Allergy Prevalence Among Family Members

We simultaneously surveyed all of the children's parents and grandparents for allergies. Overall, 35.7% (748/2090) of the 2090 children whose parents denied having any allergic condition had suspicious allergies. 67% to 69% of children

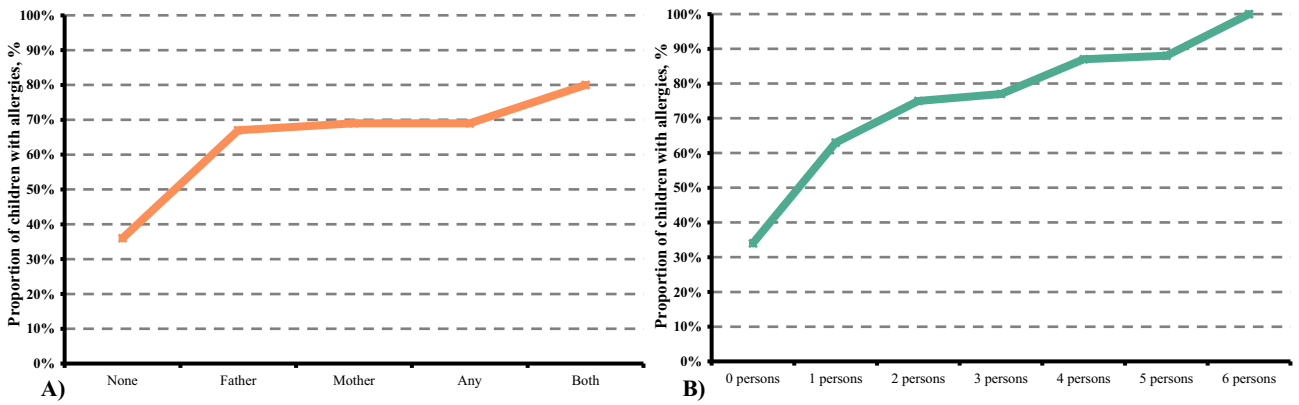

Figure 1 Differences in the percentage of preschoolers reporting allergies associated with (**A**) parental and (**B**) family member allergies.

had suspicious allergies when one parent claimed an allergy, and 80.1% (267/333) when both parents reported an allergy (Figure 1A). The rate of reported children's allergy significantly rose as the number of children's family members with allergy increased. When the number of family members with allergy exceeded 3, more than 80% of children were allergic, while when all 6 members of the family reported allergy, the suspected allergy in children was 100%. The likelihood of allergies in children was more than 80% when a household had more than three allergic members, and it increased to 100% when allergic members was six (Figure 1B). In addition, we further compared the differences in allergy reporting rates among family members in different child groups (Table 2). All family members' allergy reporting rates were significantly higher in the suspected allergy group than in the excluded allergy group (all P <0.001).

Analysis of Allergy Type Characteristics and Family Members' Co-Morbidity in Preschool Children

The predominant type of allergic disease in preschool children is AR, accounting for approximately 71.6% (1224/1710) of children with suspected allergies, followed by SA (38.0%, 650/1710). An analysis of the prevalence of different allergic disease types showed that preschool children had the highest proportion of rhinitis only (27.2%, 465/1710), followed by skin allergy only (10.6%, 181/1710). In addition, AR combined with AC, AR combined with SA, and AR combined with AA were the main co-morbid allergic diseases in preschool children (Figure 2A).

On the other hand, we also analyzed the allergic disease co-morbidity characteristics of family members (Figure 2B), with child allergy alone being the predominant type (38.3%, 655/1710), followed by child-mother co-morbidity (13.0%, 223/1710). Parent-child co-morbidity associations were stronger than grandfather-mother-child co-morbidity associations.

Table 2 Analysis of Family Members Reporting Allergies

Variable	N	Suspected Allergy N = 1710[a]	Excluded Allergy N = 1727[a]	p-value[b]
Mother	3437	645 (38%)	232 (13%)	**<0.001**
Father	3437	584 (34%)	219 (13%)	**<0.001**
Maternal grandfather	3437	233 (14%)	78 (4.5%)	**<0.001**
Maternal grandmother	3437	180 (11%)	56 (3.2%)	**<0.001**
Paternal grandfather	3437	153 (8.9%)	55 (3.2%)	**<0.001**
Paternal grandmother	3437	145 (8.5%)	47 (2.7%)	**<0.001**

Notes: [a]n (%); Median (IQR). [b]Pearson's Chi-squared test was used to compare the difference between the two groups. If the difference between groups is statistically significant, use bold fonts.

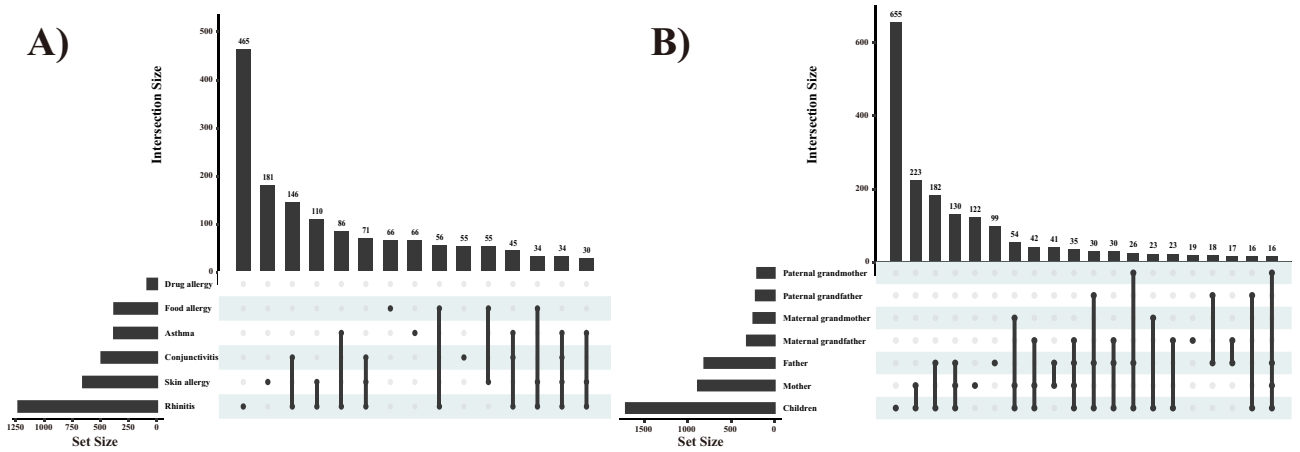

Figure 2 Analysis of (**A**) cross-over and (**B**) family member co-morbidity characteristics of allergic diseases in preschool children.
Notes: Each plot consists of three subplots, an intersection-size bar chart (top), a set-size bar chart (bottom left), and an intersection matrix between sets (bottom right). The columns of the matrix represent each intersection combination and correspond to the horizontal coordinates of the bar chart; the rows of the matrix represent the sets and correspond to the vertical coordinates of the bar chart.

Analysis of the Association Between Prenatal Lifestyle and Stress and Allergy in Preschool-Aged Children

Maternal gestational age was statistically different between the suspected allergy group and the excluded allergy group ($P = 0.009$), but the median value for both was 28.0 (25.0, 31.0) [mean 28.21 (4.55) vs 26.61 (4.77)]. While there was no difference in fathers' age at the time of maternal pregnancy. The ratio of planned pregnancy was higher in the excluded allergy group (68% vs 62%, $P < 0.001$). Passive smoking during pregnancy was significantly associated with allergies in preschool children, with the higher percentage of mothers reporting often or general had passive smoking during pregnancy in the suspected allergy group (6.2% vs 3.1% and 14% vs 9.6%, $P < 0.05$). On the other hand, father's history of smoking prior to successful conception was also statistically different, with more smoking in the suspected allergy group [2 (0, 44) vs 2 (0, 38)]. Mothers receiving more scientific knowledge about pregnancy during pregnancy and parents with a high level of education were both more prevalent in the group of children with suspected allergies (all $P < 0.01$), while there was no statistical difference in family economy (monthly disposable amount). The percentage of mothers with pregnancy complications was higher in the suspected allergy group (15% vs 8.9%, $P < 0.001$) (Table 3).

In addition, we investigated the emotional state of mothers during pregnancy, including positive and negative emotions (Figure 3). The questionnaire addressed five positive questions, including enthusiasm for life in pregnancy,

Table 3 Differences in Prenatal Information for Preschool-Age Children with Allergies

Variable	Overall, N = 3437[a]	Suspected Allergy N = 1710[a]	Excluded Allergy N = 1727[a]	p-value[b]
Pregnancy age				
Mother	28.0 (25.0, 31.0)	28.0 (25.0, 31.0)	28.0 (25.0, 31.0)	**0.009**
Father	30.0 (27.0, 33.0)	29.0 (27.0, 33.0)	30.0 (27.0, 34.0)	0.068
Planned pregnancy	2242 (65%)	1062 (62%)	1180 (68%)	**<0.001**
Scientific pregnancy[c]				**0.005**
Take a training	521 (15%)	255 (15%)[h]	266 (15%)[h]	
Self-study online	2056 (60%)	1070 (63%)[h]	986 (57%)[i]	
Others' experiences	634 (18%)	285 (17%)[h]	349 (20%)[i]	
Almost no active learning	226 (6.6%)	100 (5.8%)[h]	126 (7.3%)[h]	

(*Continued*)

Table 3 (Continued).

Variable	Overall, N = 3437[a]	Suspected Allergy N = 1710[a]	Excluded Allergy N = 1727[a]	p-value[b]
Mother's education				**<0.001**
Undergraduates and above	1679 (49%)	951 (56%)[h]	728 (42%)[i]	
Secondary	872 (25%)	388 (23%)[h]	484 (28%)[i]	
Junior secondary and below	886 (26%)	371 (22%)[h]	515 (30%)[i]	
Father's education				**<0.001**
Undergraduates and above	1602 (47%)	872 (51%)[h]	730 (42%)[i]	
Secondary	947 (28%)	452 (26%)[h]	495 (29%)[h]	
Junior secondary and below	888 (26%)	386 (23%)[h]	502 (29%)[i]	
Family economy[d]				0.300
Less than 5000	1310 (38%)	635 (37%)	675 (39%)	
5000~8000	1132 (33%)	560 (33%)	572 (33%)	
8000 or more	995 (29%)	515 (30%)	480 (28%)	
Passive smoking[e]				**<0.001**
Often	160 (4.7%)	106 (6.2%)[h]	54 (3.1%)[i]	
General	407 (12%)	242 (14%)[h]	165 (9.6%)[i]	
Less	1039 (30%)	530 (31%)[h]	509 (29%)[h]	
Almost none.	1831 (53%)	832 (49%)[h]	999 (58%)[i]	
Pregnancy complications History of paternal smoking[f]	412 (12%)	259 (15%)	153 (8.9%)	**<0.001**
Years	1.0 (0.0, 9.0)	1.0 (0.0, 9.0)	1.0 (0.0, 9.0)	0.067
Tobacco consumption[g]	2 (0, 38)	2 (0, 44)	2 (0, 38)	**0.021**

Notes: [a]n (%); Median (IQR). [b]Pearson's Chi-squared test, Wilcoxon rank sum test and Fisher's exact test were used to compare the difference between the two groups. [c]The access to scientific knowledge during pregnancy reflects, in a sense, the level of motivation and attention of the pregnant woman. [d]The household economy is determined by surveying the average amount of discretionary money available to the household each month (in RMB). [e]Specifically refers to a woman's exposure to smoke during pregnancy. [f]Specifically refers to father's history of smoking prior to successful conception. [g]Tobacco consumption = year*average cigarettes/day. [h,i]Pairwise comparison of the chi-square test, if the same letter is included between two groups, indicate no significant difference, and vice versa. If the difference between groups is statistically significant, use bold fonts.

anticipation of new life, satisfaction with solving any difficulties, happiness with family, and satisfaction with dealing with negative emotions. Although some of the questions did not show statistical differences (Figure 3A, B and E), we still observed that the questions of happiness with family [Median (IQR): 6.00 (5.00, 6.00) vs 6.00 (5.00, 6.00). Mean (SD): 5.42 (1.36) vs 5.59 (1.39)] and satisfaction with dealing with negative emotions [Median (IQR): 6.00 (5.00, 6.00) vs 5.00 (4.00, 6.00). Mean (SD): 5.07 (1.48) vs 4.97 (1.46)] scored lower in the suspected allergy group than in the excluded allergy group (Figure 3F and G). However, the scores of two negative questions in the questionnaire (feeling depressed at times and having bad moods at times) were both higher in the suspected allergy group than in the excluded allergy group (Figure 3C and D) (Both P <0.001). The overall maternal well-being in pregnancy scores were higher in the excluded allergy group (Figure 3H). Further, to minimize the interference arising from multiple allergic diseases. We selected children who reported having AR or rhinitis-related symptoms as the rhinitis group (suspected rhinitis), and analyzed the differences in maternal prenatal stress scores between the suspected rhinitis group and the excluded allergy group. The results were consistent with those described above (Table S1).

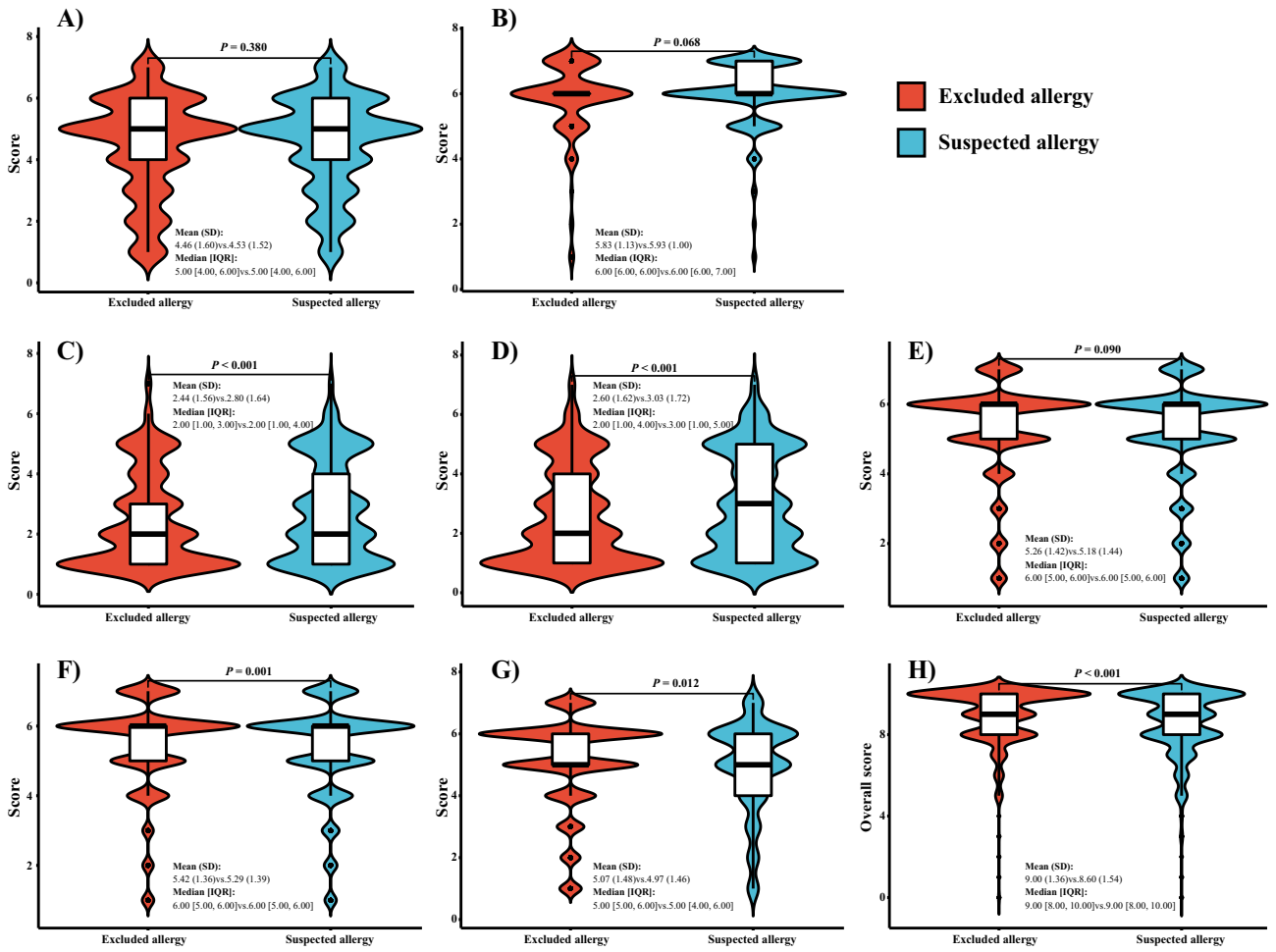

Figure 3 Differences in maternal prenatal stress scores for preschool-age children with allergies.
Notes: (**A**) During pregnancy, you are interested and passionate about yourself about what is happening around you. (**B**) During pregnancy, you are anticipating the imminent arrival of a child. (**C**) You often feel disappointed during pregnancy. (**D**) During pregnancy, you often have very complicated and mixed feelings and thoughts. (**E**) During pregnancy, you can get satisfactory help from your family when you are in trouble. (**F**) I was happy with the way my family spent time with me during my pregnancy. (**G**) During pregnancy, when I was down or full of stress, I could often handle it very well. (**H**) Satisfaction scores during pregnancy overall.

Multidimensional Analysis of Allergy Risk Factors in Preschool Children

Logistic regression analyses were conducted to explore the effects of early childhood life situation, maternal lifestyle during pregnancy, and family members' allergies on preschool children's allergy (Figure 4 and Table S2). Logistic model results for early childhood living conditions showed statistically significant on gender, premature delivery, neonatal eczema, and parental allergies (Figure 4A). The risk of allergic diseases is 1.49 (1.28 to 1.73) times higher in boys than in girls. Premature delivery increased the risk of allergic disease by 1.53 (1.13–2.07) times compared to full-term delivery. Neonatal eczema also meant a higher risk of developing allergic diseases in preschool children, with a 3.22 (2.72–3.81) and 12.49 (4.89–42.33) times increase in mild-moderate and severe eczema, respectively. Children whose parents reported allergic diseases had 3.31 (2.79–3.92) and 5.57 (4.30–7.80) times higher risk of allergic diseases (any and both). Logistic model results for mothers' lifestyle during pregnancy showed that birth order, planned pregnancy, passive smoking during pregnancy, and pregnancy comorbidities were statistically significant (Figure 4B). Birth order of second, third or later were protective factors for early childhood allergic disease, 0.67 and 0.52 times higher than first birth, respectively. Unplanned pregnancy and pregnancy complications significantly increase the risk of allergic diseases in preschool children [1.34 (1.15~1.55) and 1.82 (1.46~2.26)]. Preschoolers whose mother reported often passive smoking during pregnancy had 2.43 (1.71–3.50) times higher risk of disease. Logistic models of family members' allergies showed that all family members' reported allergies were significant risk factors for developing allergic diseases in children. And the closer the kinship, the stronger the effect, such that the influence of parents

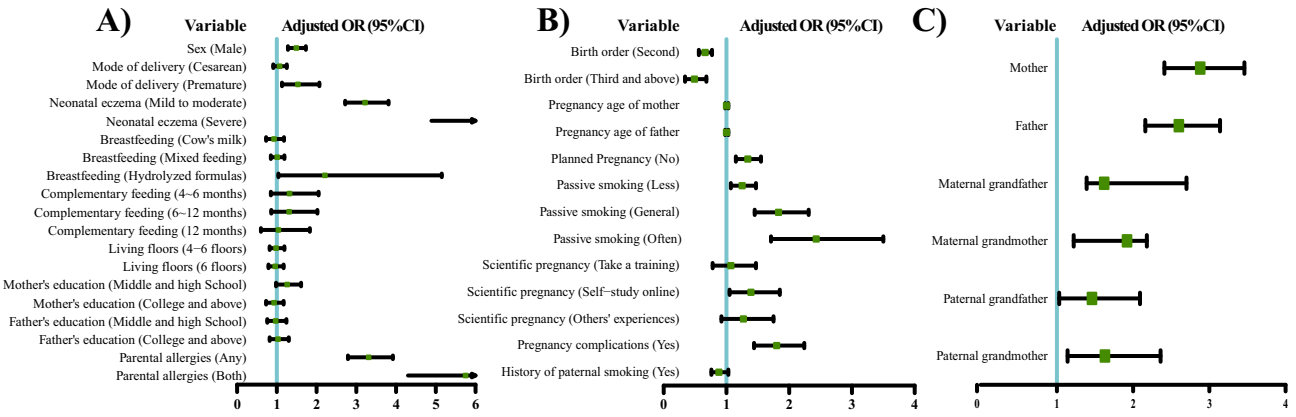

Figure 4 A forest plot of the effects of early childhood life conditions, maternal lifestyle during pregnancy, and family member allergies on child allergy.
Notes: In early childhood life conditions (**A**), gender, mode of delivery, neonatal eczema, breastfeeding, complementary feeding, living environment and floor, parental education level and parental allergy were included for multifactorial logistic regression analysis, and these possible risk factors were adjusted. In maternal lifestyle during pregnancy (**B**), birth order, parental age, passive smoking, learning of scientific pregnancy, pregnancy complications and paternal smoking history were included for multifactorial logistic regression analysis and these possible risk factors were adjusted. In family member allergies (**C**), all family members were included independently for multifactorial logistic regression analysis with adjustment.

was greater than that of grandparents. What's more, maternal influence is greater than paternal influence in the same generation, eg, mother is greater than father, maternal grandparents are greater than paternal grandparents (Figure 4C). Similarly, identical results were observed when comparing the suspected rhinitis group to the excluded allergy group (Table S3).

Discussion

The Helong Street area in Baiyun District, Guangzhou City, China, is a combination of urban and rural area, with a total resident population of about 140,000 people and a total of 4661 children aged 3–6 years old in 15 preschools. In this study, a questionnaire was administered to all preschool children in Helong Street. A total of 3437 valid questionnaires were eventually collected, with a return rate of 73.74%. Approximately 50% of children were determined to have potential allergic illnesses based on questionnaire responses, with rhinitis (allergic and non-allergic) reported at 35.6% and skin allergy at 18.9%. In a recent questionnaire survey, people aged 3 to 16 in Wuhan, China, self-reported having allergic rhinitis at a rate of 27.6%,[27] and in Changsha, also in southern China, 44.6% of primary and secondary school students self-reported having the condition. However, after further definitive diagnosis of the sample, the diagnosed prevalence of allergic rhinitis was calibrated at 19.4%.[28] Another study using the International Study of Asthma and Allergies in Childhood (ISSAC) in Shanghai, China, noted that the current prevalence of asthma in children was 11.2%, which is consistent with our results: 10.9% of children reported asthma or wheezing symptoms.[29] On the other hand, the associativity between different types of allergic diseases has been confirmed in several studies.[30,31] Nearly half of the children with suspected allergy in this study reported 2 or more types of allergic diseases. AR combined with AC, AR combined with SA, and AR combined with AA were the main co-morbid allergic diseases in preschool children in this region. Our results further showed significant association and co-morbidity between different allergic disease types.

Numerous studies have reported significant differences in allergic diseases by gender. The gender differences regarding AR are still uncertain, with some studies reporting a higher incidence of AR in women, while others have found a higher prevalence in men.[32,33] This may be related to geographic factors and ethnicity. According to the study's findings, males were shown to be more likely than girls to experience allergic disorders such as AR, AC, AA, SA, and FA. However, allergies to drugs did not differ by gender. Children with neonatal eczema are more likely to report allergic disease, a phenomenon consistent with the "atopic march" from AD and FA in infancy to AA and AR in childhood.[2] Children with eczema early in life often require special formulas. The two groups of children's living conditions did not differ, possibly because they shared the same neighborhood, but more of the excluded allergy children resided on lower floors (1 to 3 floors), which is thought to be related to a higher distribution of environmental allergens like pollen and urban dust in lower floors. The hygiene hypothesis proposes that a reduced exposure to allergens during early life results in allergy development.[34]

The heritability of allergic diseases has been discussed in several studies, and a history of allergic disease in the immediate family is one of the major risk factors for the disease in offspring.[25,35] In the current study, we simultaneously investigated allergies in children from one to two generations of close relatives. Our data show that nearly 40% of children with suspected allergy do not have any family history of allergies, even though children with a family history of allergies still predominate. Indicating that environmental factors are also significant contributors to childhood allergic diseases. The number of allergic family members is significantly and positively correlated with the probability of child allergy and when one elder immediate relative has a history of allergy, the probability of child allergy already exceeds 60%. In particular, the influence of parents on early childhood allergy is significant, with close to 70% of children reporting allergy when either parent reports allergy, and nearly 80% when both parents report allergy. A common perception is that mothers have a greater influence on allergic disease in their offspring.[36,37] Similar findings are found in this study: on the one hand, child-mother co-morbidity with allergic diseases is most prevalent, and on the other hand, logistic regression analysis reveals that mothers have the greatest weight of influence on the prevalence of allergic diseases in children, which is also reflected in multigenerational inheritance. Notably, children with allergic rhinitis experienced this behavior in a consistent manner.

Previous studies on maternal gestation and early childhood allergic disease have focused on the association between food intake during pregnancy and childhood food allergy.[24,38] Less attention has been paid to the impact of the child's birth situation and the mother's lifestyle during gestation. According to our statistics, the risk of allergic disease in early childhood is increased by several uncontrolled factors, including male gender, birth order, and preterm (less than 37 weeks of gestation). Joel J Liem[39] pointed out that prematurity and low birth weight are not associated with a change in risk for development of food allergy in childhood. This contradicts the results of the present study. Furthermore, in our study, the mode of delivery did not appear to be associated with allergic disease in children, whereas first-born children had a higher risk of developing the disease. This difference was also reflected in a metabolic study on the analysis of the association between birth order and allergy occurrence.[40] We hypothesize that the mothers' varied levels of psychological and physiological preparedness for childbirth may be the cause of the discrepancies, or that they may have had to care for another kid while pregnant, but this hypothesis must be confirmed. Another explanation is that it may be an extended phenomenon of the hygiene hypothesis, since the hygiene hypothesis suggests that reduced exposure to allergens early in life leads to allergy development.[41] In addition, we observed that unplanned pregnancy also could be risk factor, which had been mentioned in previous studies by Francisco Vázquez-Nava.[42] There is a general consensus that exposure to tobacco during pregnancy permanently deteriorates children's lungs and increases their risk of developing asthma, however fathers' preconception smoking history may not have an impact on childhood allergies.

Several studies have been conducted worldwide showing that prenatal psychological stress and stress-related factors (such as maternal anxiety or depression) increase the risk of new respiratory illnesses, including wheezing and asthma.[43–45] The Korean COCOA cohort study suggested that prenatal maternal depression and anxiety increased the risk of AD in offspring, and that this may be associated with a reduced placental glutathione to glutathione disulfide ratio, and placental 11β-hydroxysteroid dehydrogenase type 2 levels.[46] Based on data from a Chinese Han population, we also noticed that mothers of children with suspected allergy reported more negative emotions during pregnancy. Stressed mothers are more likely to smoke during pregnancy, and they would also be more likely to have preterm births and babies who are born underweight, both of which are risk factors for the early onset of asthma.

This research is a ground-breaking, multifaceted investigation of the potential factors associated with early onset of allergic diseases in local children aged 3–6 years. However, this study has some limitation. Firstly, we were unable to accurately diagnose all the children's allergic diseases due to a lack of laboratory testing, so we could only describe them as having a suspected allergy. Second, because the mother's lifestyle during pregnancy occurred at least three years ago, the investigation into her lifestyle, particularly her emotional status, may be biased by memory. We therefore designed the questionnaire in a more rigorous and understandable way. Finally, in this study we performed a preliminary analysis of the current status of childhood allergic diseases and associated risk factors in the region through an economic and rapid protocol, however, validation of the associated risk factors was lacking.

Conclusion

In conclusion, our study of preschoolers suggests that nearly half of the children in the region suffer from allergic diseases. Sex, birth order and full-term delivery all contributed to early childhood allergic disorders. Family history of

allergy, especially maternal, was the most important risk factor, and the number of family members with allergy was significantly associated with the probability of allergy in children. Maternal effects are also reflected in prenatal conditions such as unplanned pregnancy, smoke exposure, pregnancy complications, and prenatal stress.

Abbreviations

AR, Allergic rhinitis; AC, allergic conjunctivitis; AA, allergic asthma; FA, food allergy; DA, drug allergy; AD, atopic dermatitis; OFC, oral food challenge; SA, Skin allergy; IQR, interquartile; SD, standard Deviation.

Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (GYYY-2021-67). All subjects independently or through their parents (in the case of children), provided their written informed consent.

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Disclosure

The authors report no conflicts of interest in this work.

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