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Risk Factors Associated with Atopic Asthma among Yemeni Children in Sana'a city: A Case-Control Study

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Abstract

Background: Asthma is the most common chronic respiratory disease, affecting millions of people of all ages worldwide. The average global prevalence ranges from 5 to 10%. Asthma is influenced by complex interactions between particular external factors such as pollution, viral and bacterial infections, allergens, and tobacco smoke, as well as an individual's genetic makeup. This study aimed to determine the risk factors associated with atopic asthma in children in Sana'a City, Yemen.

Methods: This case-control study included 75 Yemeni children diagnosed with bronchial asthma and 75 healthy control children, matched for age and sex. Data were collected from each participant using a pre-designed questionnaire. Clinical assessments by a pulmonologist confirmed the definitive diagnosis of bronchial asthma in children. Laboratory confirmation was performed by measuring both serum Interleukin-13 (IL-13) levels using enzyme-linked immunosorbent assay (ELISA) and serum Immunoglobulin E (IgE) levels using the electrochemiluminescence technique.

Results: Living in urban areas served as a protective factor and was associated with a lower likelihood of atopic asthma in children than in those living in rural areas (χ^2 =5.4, OR = 0.3, CI = 0.08-0.9, p = 0.03). Similarly, the use of gas only in the kitchen serves as a protective factor and is linked to a reduced likelihood of atopic asthma in children compared to using a mixture of gas and wood (χ^2 =7.9, OR = 0.08, CI = 0.01 - 0.7, p = 0.02). Although family history and the presence of other allergic disease factors were associated with atopic asthma in the univariate analysis, their significance was not maintained in the multivariate logistic regression model.

Conclusion: The findings suggest that living in urban areas and using gas as the sole fuel source in the kitchen are associated with a lower risk of atopic asthma. The authors also highlighted the significant role of environmental factors in atopic asthma.

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1. INTRODUCTION

Bronchial asthma is a type I hypersensitivity disorder characterized by a Th2-driven immune response. Exposure to diverse allergens, particularly airborne substances such as dust mites and pollen, triggers the production of IL-4, IL-5, and IL-13, leading to immunoglobulin E (IgE) antibody class switching [1]. Globally, asthma ranks among the top 20 chronic illnesses in terms of disability-adjusted life-years in children, particularly within the mid-childhood age group of 5–14 years. The

impact of asthma on patients, families, and society is substantial in low- and middle-income countries, where adequate treatment accessibility is limited [2]. Clinical symptoms of asthma include wheezing, coughing, chest tightness, and shortness of breath [3]. The asthma predictive index is considered positive if a child has more than three episodes of wheezing within the first three years of life, accompanied by at least one major or two minor criteria. The major criteria included physician-diagnosed atopic dermatitis, a family history of asthma, and sensitivity to an aeroallergen, whereas the minor criteria included peripheral eosinophils greater than 4%, wheezing not caused by a common cold, and sensitization to a food allergen. Allergic asthma typically persists and often continues to adulthood [4]. Asthma is influenced by complex interactions between particular external factors such as pollution, viral and bacterial infections, allergens, and tobacco smoke, as well as an individual's genetic makeup [5, 6]. Socioenvironmental and housing variables, which operate at both the individual and community levels, significantly contribute to the risk of childhood asthma and asthma exacerbation, and thus serve as the main determinants of health inequalities [7]. The conventional gene-environment interaction theory holds that a given gene variation predicts the chance of acquiring a disease after exposure to environmental stimuli. Particularly, an individual's environmental exposure may impact the magnitude of the effect of genetic determinants [8]. The complex interplay between infections, atopy, genetic susceptibility, and environmental factors such as farm environment, air pollution, and tobacco smoke exposure contributes to the observed heterogeneity in childhood asthma [9]. This study aimed to identify risk factors associated with asthma in children recruited from the Pediatric Department of Al-Sabeen Hospital in Sana'a City.

2. MATERIALS AND METHODS

2.1. Study sample

In this case-control study, 75 Yemeni children diagnosed with atopic asthma were compared to 75 healthy controls matched for age and sex. Asthmatic children were selected from hospitalized patients in the pediatric department of Al-Sabeen Hospital for Women and Children in Sana'a City, with confirmation of asthma diagnosis by a pulmonologist based on the criteria of the Global Initiative for Asthma (GINA) guidelines from 2022 to 2024. All participants underwent comprehensive medical assessments including complete medical histories, physical examinations, pulmonary function tests, and laboratory investigations. Children with non-atopic asthma or other respiratory or chronic illnesses were excluded from this study. The median age of the participants in both the case and control groups was 8 years, with an age range of 1–14 years. The sex distribution was nearly similar between the two groups, with the asthma group comprising 53% males and 47% females, while the control group included 49% males and 51% females. A designed questionnaire was employed in this study to gather data on demographic information and asthma risk factors, including, symptoms, medical history, genetic predisposition, environmental exposure.

2.2. Sample Collection

Peripheral blood samples were obtained from all study participants. Blood (2.5 mL) was collected in two EDTA-containing tubes, and 5 ml was collected in a plain gel tube. EDTA blood samples were used for hematological assays. Serum was separated from the gel plain tube after blood clotting and stored for immunological analyses.

2.3. Measurement of serum IgE Levels

Total IgE levels were quantified by electrochemiluminescence immunoassay (ECLIA) using a Cobas e 411 analyzer (Roche Diagnostics, Switzerland). This assay was performed in a sandwich immunoassay format (Roche Diagnostics, Switzerland). The assay was performed by mixing 10 μL of the antigen with biotinylated and ruthenium-labeled monoclonal IgE-specific antibodies to form a sandwich complex. Streptavidin-coated microparticles were added to bind the complex to the solid phase. The reaction mixture was transferred to a measuring cell where microparticles were magnetically captured on the electrode surface. Unbound substances were removed using ProCell/ProCell M. Applying voltage to the electrode triggered chemiluminescence, which was measured by a photomultiplier. The results were obtained through a 2-point calibration method using a calibration curve and master curve from the reagent barcode.

2.4. Measurement of Interleukin 13 (IL-13)

IL-13 levels were measured using enzyme-linked immunosorbent assay (ELISA) (Meril, India). This assay employed a sandwich ELISA technique (Elabscience). The samples were bound using a micro-ELISA plate precoated with an antibody specific to IL-13. Biotinylated detection antibody and avidin-horseradish peroxidase conjugate was sequentially added and incubated. Unbound components were washed away and a substrate solution was added, resulting in a blue color in the presence of IL-13. The reaction was stopped, causing the color to change to yellow. The optical density was measured at 450 nm, with higher values indicating higher levels of human IL-13. The IL-13 concentrations in the samples were determined using a standard curve.

2.5. Blood cell analysis

Complete blood count (CBC) was performed using a Sysmex-XT-2000i auto analyzer (Sysmex, Japan), an automated 5-part system that measures and calculates various blood cell parameters. The evaluation included the determination of the total number of white blood cells (WBCs) in the collected blood samples.

2.6. Data analysis

Data were analyzed using mean and standard deviation, median, range, or frequency and percentage, as appropriate. Chi-square or Fisher's exact tests were used to compare the data. To compare means between groups, an independent t-test or one-way ANOVA was applied for normally distributed data, while Mann-Whitney U and Kruskal-Wallis H tests were used for non-parametric data. The strength and direction of the relationships between continuous variables were assessed using Pearson's correlation, depending on the data distribution. Statistical significance was defined as a p-value less than 0.05. All analyses were conducted using the IBM SPSS Statistics version 22.

2.7. Ethical approval

The study protocol was approved by the postgraduate studies and the Scientific Research Council of Sana'a University. Informed consent was obtained from all participants after explaining the purpose and nature of the study. Participants and their parents were informed that their participation was voluntary and that they could refuse to participate without stating any reason.

3. RESULTS

Demographic characteristics of patients and control subjects Table 1 demonstrated that the age groups were classified into three groups: 1-5 years, 6-10 years, and 11-14 years. The age distribution was relatively matched between the cases and controls, with minor differences in each age category. The 6-10 years age group had the highest proportion in both groups, which included 31 children with atopic asthma (41%), and the control group included 33 healthy children (44%). While the 11-14 years age group was the smallest in both patients and controls, with 21 (28%) and 18 (24%), respectively. The gender distribution within each group showed a relatively matched proportion. In the case group, 40 (53%) were male and 35 (47%) were female, while in the control group, 37 (49.3%) were male and 38 (50.7%) were female. A higher proportion of atopic asthmatic children lived in urban areas 62 (82.7%) than in rural areas 13 (17.3%).

Table 2 illustrates the risk factors observed among atopic asthmatic children compared to healthy children,

Table 1. Demographic characteristics

Variable		Cases (n=75)		Controls (n=75)	
		No.	%	No.	%
Age	1-5 years	23	31%	24	32%
	6-10 years	31	41%	33	44%
	11-14 years	21	28%	18	24%
Gender	Male	40	53%	37	49.3%
	Female	35	47%	38	50.7%
Residence	Urban	62	82.7%	71	94.7%
	Rural	13	17.3%	4	5.3%

as follows: Family history analysis revealed that nearly two-thirds 46 (61%) of the children with asthma had a family history, while 29 of the asthmatic children (39%) did not. In contrast, none of the healthy children 75 (100%) had a family history. The difference between groups was statistically significant (χ^2 =3.8, OR = 239, CI = 14-3989, p < 0.001). However, when the multivariate logistic regression model was used to determine the significant factors, family history was not considered a significant predictor. This suggests that their effect may not be independent or strong when other variables are considered. Exposure to secondhand smoke was similar between the two groups, with 27 children with atopic asthma (36%) and 28 healthy children (37%) reporting exposure to passive smoking. In contrast, 48 children with asthma (64%) and 47 healthy children (63%) were not exposed to passive smoking. The difference between the two groups was not statistically significant (χ^2 =0.3, OR = 0.9, CI = 0.5-1.8, p = 0.9). The majority of patients and controls were from urban areas, with 62 patients (83%) and 71 controls (95%) residing in urban areas. However, a higher proportion of patients were from rural 13 (17%) compared to the control group 4 (5%). The difference between the groups was statistically significant (χ^2 =5.4, OR = 0.3, CI = 0.08-0.9, p = 0.03). Urban residence has been shown to be a protective factor, contributing to a lower risk of developing atopic asthma compared to rural areas. Most kitchens in both study groups relied exclusively on gas stoves as fuel source for cooking. However, the proportion of asthmatic children showed a decrease of 65 (87%) compared to healthy children 74 (99%). In contrast, a significantly higher proportion of homes with atopic asthmatic children used both wood and gas stove 10 (13%) than one healthy child (1%). The difference between the groups was statistically significant (χ^2 =7.9, OR = 0.08, CI = 0.01 – 0.7, p = 0.02). Using gas as the primary fuel source in the kitchen service is a protective factor and is associated with a significantly lower risk of atopic asthma than using a mix of gas and wood. Children with asthma had a higher proportion of contact with pet animals in their homes 11 (15%) compared to healthy children 6 (8%). However, the majority of both groups did not have pets, with 64 children with asthma (85%) and 69 healthy children (92%) reporting no pet ownership. The difference

Table 2. Risk factors among atopic asthmatic children and healthy children

Risk factor	Options	Patient (n=75)		Control (n=75)		OR	95% CI	χ^2	P
		No.	%	No.	%				
Family history of asthma	No	29	39%	75	100%	239.0	14 - 3989	38.0	<0.001
	Yes	46	61%	0	0%				
Passive smoking	No	48	64%	67	89%	0.9	0.5 - 1.8	3.0	0.09
	Yes	27	36%	8	11%				
Residence	Urban	62	83%	71	95%	0.3	0.08 - 9.4	1.8	0.01
	Rural	13	17%	4	5%				
Fuel used in the kitchen	Gas	65	87%	74	99%	0.08	0.01 - 0.7	7.9	0.02
	Mix (Gas & Wood)	10	13%	1	1%				
Pet animals	No	64	85%	69	92%	1.9	0.7 - 5.7	1.7	0.08
	Yes	11	15%	6	8%				
Access to sunlight	Bad	22	29%	54	72%	0.5	0.3 - 0.9	6.8	0.01
	Good	53	71%	21	28%				
Room ventilation	Poor	59	79%	65	87%	85.6	1.5 - 60.7	0.8	0.002
	Good	16	21%	10	13%				
Other allergic diseases	No	48	64%	70	93%	854.6	5.1 - 1436	3.1	0.002
	Yes	27	36%	5	7%				

between the two groups was not statistically significant (χ^2=1.7, OR= 1.9, CI= 0.7-5.7, p = 0.2). Our study analyzed the home environment of both groups, focusing on access to sunlight. Sunlight exposure in the rooms was similar between the two groups, with 53 children with asthma (71%) and 54 healthy children (72%) with good access to sunlight. In contrast, 22 children with asthma (29%) and 21 healthy children (28%) had poor sunlight exposure in their rooms. The difference was not statistically significant (χ^2 = 0.03, OR = 0.6, CI = 0.5-1.9, p = 0.9). Regarding room ventilation, 59 (79%) asthmatic children and 65 (87%) healthy children had good room ventilation. In contrast, 16 (21%) children with asthma and 10 (13%) healthy children had poor ventilation. This difference was not statistically significant (χ^2 = 1.7, OR = 0.6, CI = 0.2-1.3, p = 0.2). The present study examined the distribution of allergic diseases, including eczema and rhinitis, in both study populations. Among asthmatic children, 27 (36%) had at least one additional allergic condition, whereas none of the children in the control group had such conditions. However, 48 (64%) children had asthma and 75 (100%) had no additional allergic conditions. The difference between the groups was statistically significant (χ^2 =3.1, OR = 85.6, CI = 5.1-1436, p = 0.02). However, when the multivariate logistic regression model was used to determine significant factors, the presence of other allergic diseases was not considered a significant predictor.

Table (3) presents the median levels of IgE, IL-13, and eosinophils in the patient and control groups. The median IgE level was significantly higher in the patient group (413 IU/ml) compared to the control group (50 IU/ml), with a statistically significant difference (Mann-Whitney = 99, p < 0.001). Similarly, the median IL-13 level was elevated in the patient group (72 pg/ml) compared to the control group (44 pg/ml), with a significant difference (Mann-Whitney = 849, p < 0.001). The median eosinophil percentage was also higher in the patient group (8%) than in the control group (4%), with this difference being statistically significant (Mann-Whitney = 999, p < 0.001).

Table 3. Comparison of median values of IgE, IL-13 and eosinophil level on the patient and control groups.

Test	Case (n=75)	Control (n=75)	Mann-Whitney test	p-value
IgE level (IU/ml)	413 (28-812)	50 (13-197)	99	< 0.001
IL-13 level (pg/ml)	72 (35-211)	44 (18-112)	849	< 0.001
Eosinophil %	8 (2-13)	4 (1-10)	999	< 0.001

4. DISCUSSION

Asthma is mainly caused by interactions between genetic and environmental variables, with immunological mediators and cells playing critical roles [10]. In our results, family history factor initially appeared as a risk factor associated with childhood asthma in univariate analysis; however, its significance diminished when logistic regression analysis was conducted. This suggests that the effect of family history may not be independent or substantial when other variables are considered. The absence of significance in the multivariate analysis underscores the complexity of asthma as a multifactorial disease influenced by a combination of genetic, environmental, and other contributing factors. This underscores the importance of considering a broad range of potential contributing factors, including genetic predispositions, environmental exposures, and lifestyle choices when studying asthma etiology. Our findings align with those of previous studies suggesting that asthma is not caused by a single genetic mutation [11]. Our results contrast with those of previous studies that reported a higher risk when parents have asthma [10, 12, 13, 14,

15]. Our study found no statistically significant difference between children exposed to household smoking in both the patient and control groups, which is consistent with the findings of previous study [13]. However, this result contrasts with those of other studies [16, 17, 18, 19]. This suggests that, while passive smoking is known to be a risk factor for asthma, it may not be the sole or primary factor in determining asthma development. Other genetic, environmental, and immunological factors may play decisive roles in the onset of asthma. Our results revealed a statistically significant difference between children living in urban and those in rural areas. The Urban residence factor serves as a protective factor. Children living in urban areas have a significantly lower risk of developing atopic asthma than those living in rural areas do. This is indicated by the low Odds Ratio (OR) of 0.3 and a statistically significant p-value of 0.03. This result may be because urban environments have lower exposure to allergens such as pollen, mold, dust mites, and animals, which are commonly found in rural areas. Additionally, urban areas may have better access to healthcare and early interventions for respiratory conditions. Our findings do not align with those of previous studies that reported a higher prevalence of asthma and allergic conditions among urban residents than among rural residents [20, 21]. This study shows that using gas as the sole fuel source in the kitchen is associated with a significantly lower risk of atopic asthma than the use of a mixture of gas and wood. The low OR of 0.08 and the significant p-value of 0.02 support this suggestion. This result is consistent with a study that found that exposure to solid fuels, such as wood, for cooking or heating is associated with an increased risk of asthma and episodes of wheezing in children [22]. However, another study did not align with our findings as it revealed no association between indoor wood burning exposure and the risk of wheezing and asthma [23]. A meta-analysis revealed a significant association, showing that children living in homes with gas stoves have an increased risk of developing asthma [24]. A possible explanation for the association between fuel use and childhood asthma is that particulate matter (PM) emitted from wood combustion penetrates deeply into the lungs, increasing the frequency and severity of asthma attacks and exacerbating bronchitis and other lung diseases [25]. Poor ventilation in the home may also trap these pollutants, worsen air quality, and strengthen the association between fuel use and asthma [26]. This study investigated the association between pet ownership and atopic asthma in children. The analysis revealed an odds ratio (OR) of 1.9, suggesting that children living with pets may be 1.9 times more likely to develop atopic asthma than those without pets. However, this association was not statistically significant. This finding could be attributed to early exposure to pets in childhood, which may promote immune tolerance to airborne allergens rather than sensitivity and allergy [27, 28]. Our findings indicated no statistically significant differences in room ventilation or sunlight access between the patient and control groups. A chinses study demonstrated that adequate ventilation is crucial for reducing indoor air pollutants, mitigating the growth of allergens such as mold and dust mites, and consequently lowering the risk of asthma, allergic rhinitis, and other respiratory diseases [29]. Poor ventilation in homes leads to increased concentrations of indoor air pollutants and prolonged exposure, which contributes to respiratory problems [30]. Specifically, inadequate bedroom ventilation at night is significantly associated with a higher incidence of rhinitis in children with asthma [31]. Furthermore, poor ventilation can facilitate the growth of indoor fungi, which has been associated with respiratory diseases, such as asthma, allergic rhinitis, and worsening of existing respiratory conditions [32]. Additionally, humid housing conditions encourage the infestation of house dust mites, increasing the risk of sensitization and development of allergic diseases. The primary allergenic component of house dust is domestic mites, the density of which is influenced by various indoor environmental factors. Exposure to house dust allergens, primarily from domestic mites, is a significant cause of allergic reactions in sensitized asthmatic patients[33]. The current study indicated that the presence of other allergic diseases such as eczema and rhinitis, initially appeared to be risk factors for childhood asthma in the univariate analysis. However, this association was not statistically significant in the multivariate logistic regression analysis, suggesting that its influence may not be independent when accounting for other variables. These findings align with prospective longitudinal cohort studies, which revealed that approximately 50% of children with atopic dermatitis do not progress to atopic march. This contradicts the traditional linear model of allergic diseases, which suggests a straightforward progression from atopic dermatitis to food and respiratory allergies. Instead, the development of allergic phenotypes is influenced by a complex interplay between genetic, environmental, and psychosocial factors [34, 35]. Our results are in contrast with those of other studies [12, 36] that found a significant association between eczema and asthma. Additionally, a study from Latin America identified a strong association between rhinitis and asthma [37]. The present study demonstrated a highly statistically significant increase in the levels of IL-13, IgE, and Eosinophils among patients compared to control group. Our findings are consistent with a Pakistani study, which revealed that bronchial asthma patients had significantly increased levels of total serum IgE and IL-13 [38]. Similar results were found in many other studies, which reported significantly higher levels of IgE and IL-13, as well as eosinophil percentages, in allergic asthma patients compared to healthy individuals [10, 39, 40, 41, 42]. Early asthmatic responses are triggered by T cells, derived cytokines, IgE, mast cells, and recruitment

and activation of eosinophils, which appear to contribute to the persistent asthma phenotype with chronic airflow obstruction [10]. IgE is responsible for releasing several asthma-associated inflammatory mediators from mast cells, such as histamine and prostaglandins [43]. The function of specific cytokines in asthma became obvious; specifically, IL13 plays which is an important role in eosinophil accumulation and is considered a critical factor in IgE synthesis by B cells, differentiation of naïve T-cells into Th2 effector cells, airway hyperresponsiveness (AHR), and airway inflammation [10]. Furthermore, IL 13 contributes to regulating and driving Type-2 inflammation. It plays a key role in asthma by promoting airway hyperresponsiveness, mucus secretion, and airway remodeling [44]. Eosinophils exhibit elevated levels in both the bloodstream and airways of many asthma patients [45]. The influx of eosinophils and their activation in the bronchial mucosa are characteristic features of asthma [46]. Eosinophilic airway inflammation is observed in approximately 40-60% of individuals with severe asthma [47].

5. CONCLUSIONS

This study highlights the significant impact of environmental factors on atopic asthma development in children. Our findings showed that living in urban areas and using only gas for cooking were associated with a lower risk of atopic asthma in children. While family history and other allergies were initially considered as risk factors, their significance was not confirmed in the final analysis. This study suggests that environmental factors play a crucial role in atopic asthma development.

6. RECOMMENDATIONS

It is essential to support further research into the genetic and environmental factors that influence its development and progression. Promoting proper home ventilation plays a critical role in reducing indoor air pollutants and humidity, which can be achieved by encouraging practices, such as opening windows, using exhaust fans, and maintaining a smoke-free environment. In addition, minimizing indoor air pollution requires avoiding the use of wood as a fuel source for cooking. Raising awareness among parents of children with asthma about creating a cleaner and safer environment for their children is equally important, as it empowers families to adopt healthier practices that can mitigate asthma triggers. Future studies should incorporate quantitative environmental data, including air quality indices, levels of indoor and outdoor allergens, and exposure to environmental pollutants to provide more precise measurements of exposure levels.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest related to this study.

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