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FAMILY HISTORY OF ATOPY AS A RISK FACTOR FOR CHILDHOOD ASTHMA AND ALLERGIC DISORDERS IN SAUDI ARABIA

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AUTHORS' CONTRIBUTIONS
This work was carried out in collaboration between all authors. Author AAF contributed the idea, concept, discussion and references. Author ZS contributed data analysis and writing. Author SMH as the corresponding author contributed the rewriting, discussion, references and overall completion of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To analyze risk conferred by family history of asthma, rhinitis and eczema for the development of childhood asthma.
Study Design: Survey of school children in 3 cities of Saudi Arabia using a questionnaire.
Place and Duration of Study: Department of Pediatrics and Pathology, King Saud University, Riyadh and Department of Biological and Medical Research, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. January 2008 to December 2010.
Methodology: A cross-sectional, population based study was carried out in 1601 school children, in 3 cities of Saudi Arabia. A questionnaire comprising 35 questions were used for this study. Risk for developing asthma was estimated in terms of odds ratio by bivariate analysis using the chi-squared test with $P < 0.05$ being considered significant.
Results: While 18.0% and 20.6% of asthmatics, respectively, did not have a positive history of asthma in the immediate family and in relatives, 48.1% and 46.1% had immediate family and relatives with a positive history. History of asthma in the immediate family (parents, siblings) conferred a 4.2-fold and in relatives (aunts, uncles) a 3.3-fold risk ($P < 0.0001$) increased risk. The risk with a history of rhinitis or eczema in the immediate family was increased ≥ 3 times ($P < 0.0001$) and for rhinitis in the relatives ($P < 0.0001$). Exposure to cigarette smoke conferred a 2-fold increased risk ($P < 0.0001$). Neither exposure to household pets (cats and birds) nor the history of eczema in relatives was significant risk factors.
Conclusion: The findings suggest that the presence of strong familial aggregation and atopy in the immediate family and relatives can be a considerable increased risk factor for the development of childhood asthma.

Keywords: Atopy; risk factor; childhood asthma; allergic diseases.

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1. INTRODUCTION

Bronchial asthma is known to be one of the most common diseases in the world, and its prevalence is known to be increasing, particularly among children [1,2]. Interactions between hereditary and changing environmental factors may be responsible for the increased prevalence of asthma. Atopy is a genetic predisposition to immediate hypersensitivity reactions. Children of atopic parents (i.e. those who suffer from asthma, allergic rhinitis or eczema) are at greater risk for atopy and asthma than are children of non-atopic parents. However, the mode of inheritance of asthma and allergic diseases has not been fully elucidated. It appears that the inheritance of these disorders does not follow classic Mendelian patterns characteristic of single-gene disorders; rather, there may be a number of genes that predispose to the development of these complex traits [3].

A strong familial aggregation of asthma and allergic disease has already been established [3,4]. Familial aggregation and segregation analysis of physician-diagnosed asthma has shown a significant correlation between parents and offspring and between siblings [5]. Studies of twins and of families of asthmatic individuals have shown that asthma occurs in a pattern consistent with heritable factors. There are clearly components of the asthma phenotype that appear strongly heritable, although these inherited components do not follow the simple Mendelian pattern that is seen in monogenic disorders such as cystic fibrosis [6]. The contribution of genetic control in susceptibility to multifactorial diseases can be estimated only by comparing the morbidity in 2 groups of patients where the genomes are known and identical by descent. Genetic modelling has shown that the differences in morbidity among the twin pairs suggest that asthma accumulates in families more likely because of shared genes than shared environmental risk factors [7].

It is generally believed that genetic predisposition is important in asthma, whereas environmental factors are assumed to trigger and modify the expression of the disease. The rapid increase of asthma in developed and urban environments is most likely explained by changes in environment and lifestyle rather than by changes in the gene pool [8]. We have previously reported a 3-fold increase in the prevalence of childhood asthma in Saudi Arabia over a period of 9 years which was mainly believed to be related to environmental factors and the rapid urbanization of Saudi society in the recent past [9].

As an extension of the same questionnaire-based cross-sectional study, we examined the family history of asthma as a risk factor for childhood asthma in 3 cities of Saudi Arabia.

2. MATERIALS AND METHODS

We conducted a cross-sectional, population-based study in 3 cities in Saudi Arabia (Hail, Taif and Jizan). Hail is an agricultural region surrounded by desert, Taif is a Mountainous region, located over 1000 metres above sea level while Jizan is a coastal area with high humidity. Each city was divided into 4 zones and 1 school from each zone (boys and girls) was randomly selected with a total of 16 schools. A total of 2000 children aged 6–16 years, were targeted by distribution of 500 forms at each zone.

Questionnaires [9] were distributed for parents of the selected children to complete. Parents were given the option to come to the school where the regional medical co-investigators were available to answer queries while completing the questionnaire. Alternatively the questionnaire could be completed at home and returned via the child. The questionnaire comprised 35 questions and was designed originally by our team in Saudi Arabia which included Professor J.D. Wilson, the then Professor of Immunology at King Saud University in consultation with late Professor Anne Woolcock of the University of Sydney, Australia. Apart from demographic data, the questionnaire included questions regarding symptoms and physician-diagnosis of asthma, allergic rhinitis, eczema, and family history of these conditions. Family members were grouped as immediate family (biological mother, father and siblings) or relatives (cousins, aunts and uncles). Asthma and atopy were defined as ever having had a physician-diagnosis of such conditions. Information was also requested about exposure to cigarette smoke (at least 1 family member was a regular smoker in the household) and having a pet in the house.

The data were analyzed using *SPSS* analytical software. Risk for developing asthma was estimated in terms of odds ratio by bivariate analysis using the chi-squared test. $P < 0.05$ was considered significant.

3. RESULTS AND DISCUSSION

Out of the 2000 questionnaires distributed, a total number of 1601 (80.05%) were appropriately completed and accepted for inclusion. The number of fully completed questionnaires for each category, however, varied (Table 1). There were 865 (54.0%) male and 736 (46.0%) female children. The majority (72.2%) were 7–12 years of age.

The data revealed overall prevalence of physician-diagnosed asthma as 22.3%, rhinitis 24.1% and

eczema 11.5%. The prevalence of asthma, allergic rhinitis and eczema in the immediate family members of all 1601 children was consistently higher than in the relatives (Fig. 1).

Table 1. Frequency and percentage of family history amongst the participants (n =1601, data were missing on some categories)

History	Frequency	%
Asthma (immediate family)	411	25.8
Asthma (relatives)	316	19.8
Rhinitis (immediate family)	501	31.4
Rhinitis (relatives)	247	15.5
Eczema (immediate family)	290	18.1
Eczema (relatives)	139	8.8
Exposure to cigarette smoke	549	34.4
Exposure to pets	408	25.5

Data regarding the estimates of relative risk of asthma for some demographic and clinical variables are presented in Table 2. Prevalence of asthma was highest in children 15–16 years of age followed by those aged 6 years. Gender did not confer a significant risk.

In children with allergic rhinitis, the risk of having asthma increased almost 8-fold (Table 2). Similarly, children with eczema were 3.1 times more likely to have asthma.

History of asthma in the immediate family and relatives also increased the risk of the child developing asthma. Only 18.0% of children with asthma did not have a positive history of asthma in the immediate family and 20.6% did not have a history of asthma in relatives. In contrast, 48.1% of children with asthma had immediate family members with a history of asthma and 46.1% of those had relatives with history of asthma (Table 2).

History of rhinitis in the immediate family was associated with a 3-fold increased risk of having childhood asthma and history of eczema in the immediate family a 3.4-fold increased risk. History of eczema in relatives was not associated with any increased risk.

Exposure to cigarette smoke was associated with a 2.6-fold increased risk of having asthma. Exposure to pets (cats and birds) in the household was not a significant risk factor.

The overall prevalence rates of childhood asthma, rhinitis and eczema have already been reported as a part of nationwide survey [9]. In a recent study in Saudi Arabia, investigating the association between obesity and asthma in pre-pubertal children concluded an association between BMI and allergic sensitization in girls [10]. The 4.2-fold increase in the risk for childhood asthma reported in the current study in those with a history of asthma in the immediate family is twice as great as that reported in a community-based study done in Boston, Massachusetts of 770 children 5–9 years of age where at least 1 parent had asthma [11]. Studies carried out in Germany [12] and the United Arab Emirates [13] have reported around a 2-fold increased risk of childhood asthma when 1 of the parents had asthma.

History of asthma in the relatives conferred a 3.3-fold increased risk for childhood asthma in our study. The severity of risk conferred was also reflected by the higher proportion of children who had immediate family members with asthma compared with having relatives with asthma. The increased risk may be related to factors such as stronger tendency towards familial aggregation in Saudi Arabia, genetic heterogeneity of asthma, ethnic differences or variation in exposure to environmental factors such as air pollution, allergen load or viral epidemics, operating either individually or in combination.

The relative importance of history of maternal or paternal asthma in childhood asthma is yet to be established. Maternal asthma history was strongly associated with the onset of asthma in the second generation and children whose mother had an earlier age of onset had an increased risk of 3.71. For an approximately 10-year decrease in mother's age at onset of asthma, the risk of asthma for the offspring increased by 1.37-fold. Using our new risk scores led to smaller standard errors and thus more precise estimates than using a binary indicator [14]. There are reports, indicating both maternal [14] and paternal [12] history as individual risk factors. However, a study performed in the United Arab Emirates reported that the risk was about the same [13]. We did not attempt to quantify the separate contributions of maternal and paternal asthma to the risk for asthma in the child, but the 4.2-fold increased risk for asthma conferred by history of asthma in the immediate family appears to be quite important.

Apart from the immediate family, relatives also conferred a considerable risk for having asthma if they had a history of asthma or allergic rhinitis, whereas history of eczema in the relatives was not a risk factor. These findings suggest that familial aggregation could be an important risk factor for asthma. A number of studies on familial aggregation of chronic obstructive pulmonary disease have been conducted that have focused on lung function. Initial clinical reports documented the familial occurrence of

chronic obstructive pulmonary disease [15], and subsequent reports described the similarity of pulmonary function levels among first-degree relatives. In an another study, researcher found that parents of asthmatic adolescents had significantly lower values of the lung function than both parents together and mothers of non-asthmatics (84.6 vs. 97.6, $p<0.01$, for FEV and 84.3 vs. 97.9, $p<0.01$, for FVC, and 97.3 vs. 109.7, $p<0.01$, for FEV and 89.5 vs. 105.5, $p<0.01$, for FVC, respectively). Also, siblings of asthmatic adolescents had lower FEV (98.6 vs. 109.4, $p<0.01$) and FVC values (85.9 vs. 102.7, $p<0.01$). The healthy first-degree relatives of asthmatic adolescents have worse respiratory function than those of non-asthmatic adolescents [16].

In the analysis of risk for asthma in offspring of asthmatic mother vs father, no significant differences were observed between maternal and paternal odds ratios when analyzing the studies in which the patient population was 5 years or older (3.15 vs. 2.60, $p=0.14$) [17]. However, in all cases the trend remained the same, that maternal asthma was a greater risk factor for asthma than paternal [14]. Aggregating data from 33 studies, the odds ratio for asthma in children of asthmatic mothers compared with non-asthmatic mothers was significantly increased at 3.04 (95% confidence interval: 2.59–3.56). The corresponding odds ratio for asthma in children of asthmatic fathers was increased at 2.44 (2.14–2.79). When comparing the odds ratios, maternal asthma conferred greater risk of disease than did paternal asthma (3.04 vs. 2.44, $p=0.037$). When analyzing the studies in which asthma was diagnosed by a physician the odds ratios were attenuated [14]. These results suggest that inheritance of a tendency to develop high total serum IgE levels is the only factor related to the inheritance of asthma susceptibility and that, by itself, has limited ability to predict asthma inheritance.

Overall, history of atopy in the family was associated with a ≥ 3-fold increased risk of asthma in this study. Our results are in agreement with the previous reports from Boston, Massachusetts and the United Arab Emirates which also found the risk of childhood asthma was increased when 1 of the parents had atopy [12,14]. It is difficult to explain the discrepancy in these results on the basis of existing data. Many risk factors have been identified, but it is not clear how these factors act to produce disease in any given individual.

Exposure to environmental tobacco smoke is a risk factor for paediatric asthma [18] although many studies have not found any clear association between smoking and asthma [19–21]. A recent study, however, provides clear evidence linking parental smoking with childhood asthma [22]. This study shows a monotonic exposure–response relationship between paternal smoking and decline of pulmonary function. Maternal smoking has also been associated with reduced pulmonary function in children [23,24]. Some studies suggest that pulmonary function decrement in school-aged children is a result of combined early life (including in utero) and current exposure to maternal smoking [25,26]. Reports on the effect of paternal smoking on children's pulmonary function have yielded inconsistent results. Studies in the United States of America [27], Great Britain [28] and Australia [29] found that decreased $FEV_{25–75\%}$ in children was associated with maternal smoking, but not paternal smoking. In contrast, studies in China [30] and Turkey [31] found associations of paternal smoking with decrements in children's $FEV_{25–75\%}$.

This study, like many other questionnaire-based studies, had methodological limitations. Parental smoking was measured by self-report. We did not attempt to examine the effect of maternal or paternal smoking individually; exposure to cigarette smoke in the household was, however, associated with a > 2-fold increased risk for childhood asthma. The cross-sectional analysis did not permit investigation of cumulative exposure to paternal smoking in relation to children's pulmonary function. Our data also did not permit investigation of the relative effects of prenatal versus postnatal exposure to parental smoking.

Environmental factors play an important role in the sensitization and elicitation of symptoms in genetically predisposed or susceptible individuals. However, these factors do not become part of the family history but certainly an environmental risk factor. Therefore, in addition to the family history and atopy as a risk factor for childhood asthma, this study also included the effect of exposure to pets in childhood as a risk of childhood asthma. The various environmental factors have already been determined and published [32,33]. However, as majority of children play in indoor environment with domestic pets and thus pet exposure was included in the survey. Concentrations of house dust mites, Dermatophagoides pteronyssinus (Der p I – Der p II), D. farinae (Der f I and Der f II) as well as material originating from household pets, e.g. cat saliva and dander (Fel d I), cockroach faecal particles (Per a I), and a number of fungal spores, particularly Alternaria (Alt a I) and Aspergillus (Asp f I) species, can contribute to the development of bronchial asthma in both children and adults. The impact of the indoor environment on human health constitutes a serious health risk and needs more attention to both short-and long-term health effects. Indoor environmental factors, particularly house dust mite and other

allergens of pet origin, are very common in sensitization and the development of bronchial asthma in Saudi Arabia [32]. Environmental studies from Europe and North America have proved that levels of mite exposure of 2 µg or 10µg of group I allergens per gram (equivalent to 100 or 500 per gram) of dust are relevant to bronchial asthma mites or mite allergens provide a valid "index of exposure," which can be used for risk evaluation in the above patients. Studies have also confirmed that appropriate mite avoidance measures in the bedroom decreases symptoms in mite-sensitive asthmatic patients, and secondly, mite immunotherapy appears to be helpful in some of these patients. It is evident from our data that the two

Table 2. Estimates of relatives risk of asthma and rhinitis, for some demographic and clinical variables in Hail, Taif and Jizan (*n* = 1601)

Variable	SS[a]		With asthma		OR (95% CI)	*P* value
	No.	%	No.	%		
Age (years)						
6	214	13.4	78	36.5	1.0	
7–8	447	27.9	83	18.5	0.4 (0.4–0.7)	0.0002
9–10	354	22.1	97	27.4	0.7 (0.5–1.0)	0.03
11–12	355	22.2	69	19.4	0.4 (0.3–0.6)	0.0001
13–14	169	10.6	52	30.8	0.8 (0.5–1.2)	0.7
15–16	62	3.9	25	40.3	1.1 (0.6–2.2)	0.6
Sex						
Male	865	54.0	203	23.5	1.0	
Female	736	46.0	205	27.8	1.3 (0.8–1.1)	0.397
Rhinitis						
No	1213	75.9	181	14.9	1.0	
Yes	386	24.1	224	58.0	7.9 (6.0–10.3)	0.00001
Eczema						
No	1414	88.5	318	22.5	1.0	
Yes	184	11.5	87	47.2	3.1 (2.2–4.3)	0.00001
History of asthma[b]						
No	1150	74.2	207	18	1.0	
Yes	411	25.8	192	48.1	4.2 (3.3–5.5)	0.00001
History of asthma[c]						
No	1249	80.2	257	20.6	1.0	
Yes	316	19.8	142	46.1	3.3 (2.5–4.3)	0.00001
History of rhinitis[b]						
No	1062	68.6	200	18.8	1.0	
Yes	501	31.4	198	40.8	3.0 (2.0–3.8)	0.00001
History of rhinitis[c]						
No	1307	84.5	288	22.0	1.0	
Yes	247	15.5	109	45.6	3.0 (2.2–4.0)	0.0001
History of eczema[b]						
No	1268	81.9	306	24.1	1.0	
Yes	290	18.1	93	33.2	3.4 (2.4–4.7)	0.00001
History of eczema[c]						
No	1418	91.2	370	26.1	1.0	
Yes	139	8.8	30	22.1	0.8 (0.5–1.2)	0.11
Exposure to cigarette smoke						
No	1049	65.6	197	18.8	1.0	
Yes	549	34.4	208	37.8	2.6 (2.0–3.3)	0.0001
Pets in the household						
No	1188	74.5	290	24.4	1.0	
Yes	408	25.5	113	27.8	1.2 (0.9–1.6)	0.18

OR = Odds Ratio; CI = Confidence Interval

Note: SS = Sample size

a = Data were missing for some categories

b= Immediate family

c= Relatives

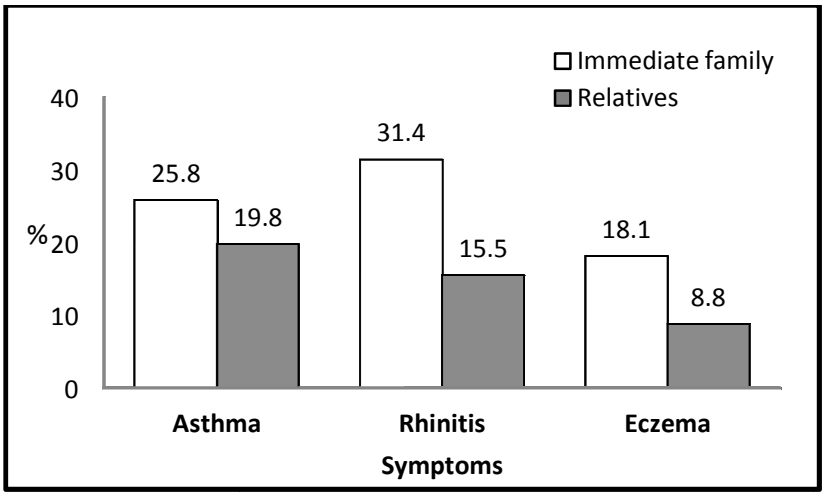

Fig. 1. Family history of asthma, allergic rhinitis and eczema in children in 3 Saudi Arabian cities (*n* = 1601)

clinically important HDM species, Dermatophagoides pteronyssinus and D. farinae are present with regional diversity in Saudi homes in levels l exceeding threshold values for sensitization and for acute attacks of bronchial asthma. The data also revealed that more than 25% of samples in the mountainous regions of Abha contained above the threshold level of Der p I, with a maximum level of 84,000 ng/g dust. Contrary to that, Der f I contents in the same samples remained far too low and did not reach even one-tenth of the sensitization level. Comparison of the data from Qassim agricultural region (Q) reveals neither any significant presence or major differences in Der p I and Der f I contents. In fact, there were n=more samples from this region analyzed to see any variation. A number of samples from the dry region, Riyadh (R), and coastal region, Jeddah (J), were also analyzed. Saudi Arabia is a large country with considerable variation in geography, climate and lifestyle. Thus, the variations in the contents of dust mite species in different geographical regions can be attributed to climate and geography of the regions which, in turn, increases the risk factor for sensitive individuals in the indoor environment. In addition, in Saudi Arabia's traditional society, where people prefer to stay more indoors that outdoors (this is also because of the hot weather of the region), the impact of indoor allergens and their sensitization effects are increased [33]. A sizeable proportion of the children we studied were exposed to pets but it did not seem to be a significant risk factor for childhood asthma. In another cross-sectional study 82% of children with allergic asthma were found to have pets [34]. When examined for effects on bronchial hyper-reactivity, no difference was found between children with and those without pets. In order to establish whether having pets at home is a risk factor for having childhood asthma, further investigations are required and assessment of sensitization status of the children exposed to pets may provide useful information.

4. CONCLUSION

Although asthma and other allergic conditions often go together, children are more likely to suffer from atopic diseases similar to those of their parents. It may be that inheritance patterns for asthma and the other atopic diseases differ. Presence of asthma and atopy in the immediate family and relatives is a considerable risk factor for having childhood asthma. These findings suggest that strong familial aggregation along with environmental influences may be linked to increased risk for childhood asthma in Saudi Arabia and elsewhere.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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