

GENETICS AND ENVIRONMENTAL RISK FACTORS ASSOCIATED WITH ASTHMA IN SCHOOLCHILDREN

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SUMMARY:

Objectives: *The objective of this study was to investigate the genetic and environmental risk factors associated with asthma among Qatari school children aged 6-12 years.*

Design: A cross-sectional study was performed. The International study of asthma and allergies in childhood (ISAAC) and some additional questionnaires were used to collect the data of the school children between Feb 2003 and Feb 2004.

Setting: Government primary schools in the State of Qatar.

Subjects: A multistage sampling design was used and a representative sample of 3500 children were targeted for this study. Of these, 3204 parents (91.6%) of the children agreed to participate in this study.

Results: Of the total study sample 3204 school children living in urban and semi urban areas, 51.9% were boys and 48.1% girls. Their mean age was 8.92 ± 1.89 . The population sample had a high prevalence rate of asthma (19.8%) and allergic rhinitis 30.3%. The frequency of asthma, allergic rhinitis and eczema among parents reflected the same pattern as that seen in the children. Environmental risk factors associated with asthma were pets at home, allergic to certain food or medicine, smoking history among parents or elder siblings ($p < 0.0001$). A stepwise logistic regression analysis results showed that allergic to food and medicine, history of asthma in father, mother, siblings and asthma in second degree relatives and smoking habit of father were significant predictors for asthma after adjusting age and sex and other confounding covariates in the model.

Conclusion: The present study revealed that the family history of asthma contributed more to childhood asthma than indoor and outdoor environmental factors. Boys were found more asthmatic than girls. The results of this study support the hypothesis that asthma is a multi-factorial disease related to both familial and environmental influences.

Key-words: Asthma - Allergic rhinitis - Parental asthma - Genetics, Environment. Children.

INTRODUCTION

Asthma is one of the most common disorders in childhood (1-2). Accumulating evidence indicates that asthma is becoming increasingly common (1-4) and is the most common chronic illness of childhood and there is a wide consensus that asthma and allergies have become more prevalent among children, especially in developed societies 1-6. The prevalence of asthma and allergies in some western countries has reached alarming proportions, affecting more than one-third of children within the general population 1-9. A child's chance of

developing asthma increases steadily if the child is atopic, 6,8,10-11, if the child is exposed to specific allergens in the environment (8, 12-15). and if the child has parents with asthma or atopy (6, 8, 16-19).

The environmental factors responsible for asthma are not well understood, but changes in lifestyle leading to changes in immediate environment may have an adverse effect on the prevalence of asthma (10). Opinions differ as to the extent of which environmental factors affect the prevalence and out-come of asthma. Increased sensitization to inhaled allergens present in house dust, car fur, and grass pollen has been cited as the reason for the increased prevalence of asthma (12-15, 20). An important goal of asthma research is to understand the genetic and environmental triggers for asthma and the factors that lead to variations in its natural history.

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The objective of this study was to investigate the familial and environmental risk factors associated with asthma among Qatari school children aged 6-12 years.

SUBJECTS AND METHODS

The school children studied were the subjects of a cross-sectional population study conducted in both urban and semi urban areas of the State of Qatar. The study was performed between February 2003 and February 2004. The period included the time taken to recruit students and interview their parents at a convenient timing.

The methods included a self-administered questionnaire to parents. We have opted and used the International study of asthma and allergies in childhood (ISAAC) questionnaires and other (10, 17) standardised questionnaire to determine the prevalence of asthma. The questionnaire was translated in Arabic by a professional translator. A translated Arabic version of the questionnaire was revised by a bilingual consultant, Allergist and a Pulmonary physician, and then back translated by a bilingual physician who was unfamiliar with the original English version. The survey instrument was tested on 100 randomly selected children studying in different schools and validated in this way. Both translators made necessary corrections after considering the minor differences that had occurred.

The study sample included children aged 6-12 years using a multistage cluster sampling technique. There are 104 schools in 21 districts with 56 schools for boys and 48 for girls. Out of these, 30 schools were selected which have majority of Qatari national students. Again, we have divided these schools in equal proportion for boys and girls. Similarly, the classrooms and school children were selected in the second and third stages using the same simple random sampling procedure that resulted in the selection of students. The questionnaire with a letter of explanation was distributed to parents of 3500 Qatari school children living in either urban or semi urban areas of the State of Qatar. Information was obtained on individual school children and also on their related sibling and first degree relatives. Both or either of the parents of each child were interviewed by trained nurses or physician. Out of parents of 3500 children, only 3204 (91.5%) gave their consent for the study.

The questions concerning the diagnosis of asthma were "Has the child ever been diagnosed as having asthma by a doctor?", "what was the age at which

asthma was first diagnosed?" and "has the child ever needed treatment or hospital admission due to asthma?". Asthma was defined as a positive answer to two out of the three questions related to doctor diagnosed asthma, asthma treatment and admission to hospital for asthma. The diagnosis of Allergic rhinitis was based on these questions. Has your child ever had a problem with sneezing or blocked nose during the last six months? When he/she did not have a cold or flu? Has your child ever had Hay fever? The questions concerning the diagnosis of eczema were as follows Has your child ever had an itchy rash that was coming and going for at least 6 months? Has your child ever had eczema? The questionnaire also included the diagnosis of similar conditions among parents and first degree relatives (2-5, 10).

Fisher exact and chi-square tests were performed to ascertain the association between two or more categorical variables. The relative risk and its confidence interval were obtained using Mantel-Haenszel test. Stepwise logistic regression was used to adjust for potential confounders and to rank factors (determinants) for asthma in order of importance. $P < 0.05$ was considered as the cut-off value for significance.

RESULTS

The study based on the sample parents of 3204 children with 51.9% males and 48.1% females. The age range of the children studied was 6-12 years with a mean and standard deviation of 8.92 ± 1.89 years. Of the studied subjects, 972 children had allergic rhinitis (30.3%) and 721 children with eczema (22.5%).

The results show that the population sample has a high prevalence rate of bronchial asthma (19.8%) 635/3204. Allergic rhinitis was more frequently seen in school children. The prevalence of asthma, allergic rhinitis and eczema among parents and siblings reflected the same pattern as seen in study group (table 1). Prevalence rate of asthma tended to be higher in siblings than in parents and the difference was statistically significant. ($p < 0.001$). There were statistical significant differences between asthmatic and non asthmatic in the family history of asthma in parents ($p < 0.001$); siblings ($p < 0.001$); and close relatives ($p < 0.001$).

Table 2. shows the environmental risk factors associated with asthma in Qatari school children. These factors are pets at home, allergic to food (banana, tomato, fish, egg, strawberry and egg), allergic to medicine (antibiotic or penicillin) and smoking habit of father. The relative risk and 95% confidence interval

Variables	Asthmatic n=635 n(%)	Non Asthmatic n=2569 n(%)	RR and 95% CI	P Value
Age group (Years)				
6-7	205(32.3)	715(27.8)	1.00	NS 0.001
8-9	209(32.9)	757(29.5)	1.0(0.8-1.2)	
10-12	221(34.8)	1097(42.7)	0.8(0.6-0.9)	
Gender				
Male	429(67.6)	1234(48.0)		<0.001
Female	206(32.4)	1335(52.0)	1.9(1.7-2.2)	
Parental history				
Father				
Asthma	117(18.4)	172(6.7)	2.3(1.9-2.7)	<0.001
Allergic rhinitis	161(25.4)	402(15.6)	1.6(1.4-1.9)	<0.001
Eczema	112(17.6)	324(12.6)	1.4(1.1-1.6)	<0.001
Mother				
Asthma	139(21.9)	240(9.3)	2.1(1.8-2.4)	<0.001
Allergic rhinitis	170(26.8)	426(16.6)	1.6(1.4-1.9)	<0.001
Eczema	122(19.2)	351(13.7)	1.4(1.2-1.6)	<0.001
Siblings history				
Asthma	403(63.5)	768(29.9)	3.0(2.6-3.5)	<0.001
Allergic rhinitis	164(25.8)	357(13.9)	1.8(1.5-2.1)	<0.001
Eczema	226(35.6)	711(27.7)	1.3(1.2-1.5)	<0.001
History among close relatives				
Asthma	385(60.6)	935(36.4)	2.2(1.9-2.5)	<0.001
Allergic rhinitis	189(29.8)	476(18.5)	1.6(1.4-1.9)	<0.001
Eczema	192(30.2)	662(25.8)	1.2(1.0-1.4)	0.023

Table 1: Occurrence of asthma, allergic rhinitis and eczema among first-degree relatives of children who have asthma*.

* The Mantel-Haenszel test was performed to determine significance differences and to obtain relative risk (RR) and 95% confidence interval (CI).

NS=Not-significant.

Variables	Asthmatic n=635 n(%)	Non Asthmatic n=2569 n(%)	RR and 95% CI	P Value
Pets at home	215(33.9)	742(28.9)	1.3(1.0-1.5)	0.014
Allergic to				
Food	132(20.8)	216(8.4)	2.2(1.8-2.5)	<0.001
Medicine	39(6.1)	48(1.9)	2.3(1.8-3.0)	<0.001
Smoking history				
Father	224(35.3)	683(26.6)	1.3(1.2-1.6)	<0.001
Mother	23(3.6)	115(4.5)	0.8(0.6-1.2)	0.342†
Brother	19(3.0)	91(3.5)	0.9(0.6-1.3)	0.495†
Smoker in the same room	31(4.9)	80(3.1)	1.4(1.1-1.9)	0.029

Table 2: Environmental risk factors associated with asthma in school children*.

* The Mantel-Haenszel test was performed to determine significance differences and to obtain relative risk (RR) and 95% confidence interval (CI).

† Not significant.

of asthma with these exposures are also presented in table 2. Allergic to food and medicine was more common among asthmatic than non asthmatic subjects ($p<0.001$). Asthma was more common among subjects who had a smoker in the same room ($p=0.029$) and father of the child was smoking ($p<0.001$).

Families were divided according to the number of children in table 3. It was found that 42.4% (171/403) of either parent had asthma if more than one child was affected and 23.3% (54/232) of either parent had asthma in those families in which only one child was affected. This difference was statistically significant ($p<0.001$).

A stepwise logistic regression analysis results showed that allergic to food, allergic to medicine, history of asthma in father, mother, siblings, second degree

relatives and smoking habit of father were significant predictors for asthma after adjusting age and sex and other confounding covariates in the model (table 4).

DISCUSSION

Our findings support the hypothesis that asthma is a multi-factorial disease related to both environmental (12-15, 20) and familial influences (10-11, 16-19). The relative contribution of genetic and environmental factors are not yet clear. However, our results of higher prevalence of asthma among offspring of parents with allergic respirator diseases strongly support the hypothesis that asthma is inherited, as reported previously (16-19). The finding of the occurrence of asthma, allergic rhinitis and eczema in the parents and of asthma in their children suggest that these

Family size	No. of families with at least one affected child		No. of families with one affected child and status in parent		No. of families with more than one affected child and status in parent	
	Asthma	No Asthma	Child	Parent	Child	Parent
1	11	37	7	3	4	1
2	29	99	14	3	15	5
3	85	301	34	6	51	21
4	107	427	32	6	75	32
5	112	565	42	10	70	28
6	112	477	42	6	70	23
7	73	282	28	8	45	26
8	44	121	15	8	29	13
>=9	62	260	18	4	44	22
	635	2569	232	54	403	171

Table 3: Affected children according to the number of children in the family and children affected in the family.

Independent Variables	Relative Risk	95% Confidence Interval	p - value significance
Allergic to food	2.161	(1.641-2.846)	0.0001
Allergic to medicine	2.905	(1.736-4.861)	0.0001
Father asthmatic	2.332	(1.763-3.085)	0.0001
Mother asthmatic	1.786	(1.383-2.305)	0.0001
Sibling asthmatic	2.921	(2.368-3.603)	0.0001
Asthma in second degree relative	1.623	(1.318-1.999)	0.0001
Father smoking	1.402	(1.145-1.717)	0.001

Table 4: Genetic and environmental risk factors associated with asthma as estimated by stepwise logistic regression analysis.

diseases share a common genetic defect. The association of asthma, allergic rhinitis, in the same patient has been reported in other studies (6, 8, 10-11, 16-19).

The exact mode of genetic inheritance or transmission for asthma is still unknown. A study (10, 17) showed that children who have one parent with asthma have about a 25% chance of developing asthma and that a child whose mother and father have asthma have a 50% chance of developing asthma. The genetics of basal total serum IgE levels was investigated in 278 individuals by Meyers (21). Their result suggest that a major gene for IgE levels appears to be independent of any similar locus controlling atopy. Cookson (6) showed that sibling pairs affected by atopy shared the maternal 11q13 allele in 62% of the cases, whereas only 46% of the paternally derived alleles were shared. The shared maternal allele differed significantly ($p=0.001$) from the expected distribution, whereas paternally derived alleles were not significantly different from the expected ratio. Marsh (22) revealed evidence for linkage of five markers in chromosomes 5q31.1 with a gene controlling total serum immunoglobulin concentration. Their analyses suggested that the interleukin-4 gene (IL4) or a nearby gene in 5q31.1 regulates IgE production in a nonantigen-specific (non-cognate fashion).

Many theories exist about how atopy is inherited, among which are that it is inherited as a simple Mendelian dominant character (23), as a simple recessive trait (22), as a single autosomal dominant gene with a reduced penetrance (10, 16) and as result of multi-factorial inheritance (10-11, 16-17).

Logistic regression analysis of factors involved in the etiology of asthma in the present study showed parental asthmatic to be the significant factor after adjusting for confounding factors (table 4). Our results showed that father smoking was a significant risk factor for asthma among children, which is consistent with previous reported studies 10,11. Smoking among women is not acceptable in Qatari society on cultural, religious and traditional grounds.

This analysis of a large population survey has provided precise estimates of environmental risk factors of childhood. These findings are consistent with other reported studies (1-6, 11-14). These factors include pets, foods, medicine, parental smoking. Relative risk and its 95% confidence interval of asthma with these exposure are also presented. Significant relative risk estimates were found for pets, drugs, food and parental smoking which showed apparent relation to the development of asthma. Environmental pollution resulting from the increased ozone and aerosols, par-

ticular matter, nitrogen oxides, and sulphur dioxide are known to cause a slight fall in lung function in asthmatics and in some non-asthmatics (13-15, 24-25). The effect of repeated exposure on asthmatics is not yet known.

In most parts of the Qatar city respirable particles, which are mostly inorganic, such as salt and sand, exceed accepted air-quality standards from May to December. In fact, admissions to hospitals of asthmatic children in these months increases. The increase in the prevalence of asthma could therefore be mainly due to environmental factors; genetic factors would be expected to contribute to a similar extent, even though genetic studies were performed separately from the environmental studies. Similar to the effects of increased risk of both sensitization to inhaled allergens and airway responsiveness to environmental pollutants (19-20, 24), such as ozone, sulphur dioxide and particulate matter, the effect of smoking has also been shown to increase sensitization to inhaled agents, including proteins (25).

In conclusion, the present study revealed that the family history of asthma contributed more to childhood asthma than indoor and outdoor environmental factors. Boys were found more asthmatic than girls. The results of this study support the hypothesis that asthma is a multi-factorial disease related to both familial and environmental influences.

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