

THE PATTERN AND GENETICS OF PEDIATRIC EXTRINSIC ASTHMA RISK FACTORS IN POLLUTED ENVIRONMENT

Abdulbari Bener, PhD MFPHM FRSS (1, 2),
Mohammed Ehlayel FAAP FAAAAI, FACAAI (3), Alfred Sabbah MD (4)

SUMMARY

■ **Aim:** The aim of the present study is to determine the effect of polluted environment on extrinsic of asthma and allergic diseases among school children.

■ **Design:** This is case and control study.

■ **Setting:** The study was carried out among school children living and attending the school in industrial and residential area during the period of October 2004 and June 2005.

■ **Subjects:** The study based on age, sex, and ethnicity of 716 cases (with asthma) and 716 controls (without asthma) school children living in both urban and in industrial polluted with oil refinery and chemical pollutant.

■ **Methods:** The International study of asthma and allergies in childhood (ISAAC) and some additional questionnaires were used to collect the data of the school children. The questionnaire included information about:

- socio-demographic characteristics;
- respiratory symptoms;
- associated respiratory illness;
- family history of allergic diseases among first-degree relatives of asthmatic children;
- behavioural factors which could be additive to asthma. Univariate and multivariate statistical analyses were performed.

■ **Results:** The proportion of children in the asthmatic group who reported symptoms was significantly higher than in non-asthmatic group (<0.0001). The asthmatic group reported that 47.5% morning time breathlessness, shortness of breath (61.4%), wheeze after exercise (65.4%), phlegm (45.3%) and chronic cough (42.2%). Male asthmatics had a average age at onset of symptoms of 6.9% (± 4.8) years compared with female asthmatics who had higher age at onset of symptoms, 7.6(± 5.9). Male asthmatics also had longer duration of symptoms (7.5 ± 4.9 in males and 6.4 ± 4.6 years in females). Significantly odds ratios were found higher in asthmatic compared to controls for pneumonia, bronchitis, atopy (allergic rhinitis and atopic dermatitis), sinusitis, croup, parental asthmas, parental atopy including parental allergic rhinitis, atopic dermatitis and parental smoking ($p < 0.0001$). The logistic regression model showed that shortness of breath, bronchitis, pneumonia, sinusitis, parental asthma, allergic rhinitis, atopic dermatitis, croup, pets ownership and parental smoking were significant risk factors for asthma

■ **Conclusion:** The present study provides some evidence that exposure to outdoor air pollutants increases the risk of childhood asthma and allergic diseases in school children. The results are consistent with the hypothesis that long term exposure to NOx and CO levels suggests that emissions from photochemical air pollution and oil refinery contributes to adverse health effects in Qatar.

Key-Words: Asthma - Allergic rhinitis - Eczema - Risk factors - Pollution - Environment - Genetics - School children.

INTRODUCTION

Asthma is the single most common chronic childhood disease in developed nations (1-3) and its prevalence and severity have been reported as increasing in many countries (1-10). 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 (4-6). The pre-

valence rate of childhood asthma, allergic rhinitis and eczema showed geographical variation, but generally an increase worldwide through the latter half of the 20th Century (7-10). The changing pattern of the disease has not been fully explained, in part because of an incomplete understanding of its pathogenesis. Also, both genetic and environmental factors play important role in the aetiology of childhood asthma, and there is probably also genetic susceptibility to effects of air pollution (6, 11). Apart from a recent study done in Scotland (10), which showed flattening off the trend, there is general agreement on the increasing prevalence of asthma and allergies in western countries²⁻⁴, those trends might reflect changes in severity, changes in medical care practices, and change of diagnostic labelling of these disorders, as well as a true increase in prevalence (1-10).

(1) Department of Medical Statistics and Epidemiology, Hamad Medical Corporation.

(2) Dept. Evidence for Population Health Unit, School of Epidemiology and Health Sciences, The University of Manchester, Manchester (UK).

(3) Department of Pediatrics Allergy and Immunology, Hamad Medical Corporation (Qatar).

(4) 25, avenue Jeanne d'Arc - 49100 Angers (France).

The aim The aim of the present study is to determine the effect of polluted environment on extrinsic of asthma and allergic diseases among school children in the State of Qatar.

SUBJECTS AND METHODS

■ **Study Design:** This case-control study, conducted among school children aged 6-13 years old, attending school during the period of October 2004 and June 2005 in State of Qatar. They were 716 cases (with asthma) and 50 km away to polluted environment and 716 controls (without asthma) school children living in both urban [Residential area] and semi-urban with 60 km distances to industrial oil refinery and chemical pollutants. The school children were selected randomly from 8 both residential and polluted areas and 8 randomly selected school as a proportionally males and females. The sample size was estimated as the number of cases needed to detect an odds ratio of 3.5, assumed to be the lowest odds ratio among risk factors, with power 0.80 and two-sided type I error probability $\alpha = 0.05$.

Approval for the study was obtained from the Medical Ethics Committee of Hamad General Hospital, Hamad Medical Corporation. A written consent form was obtained from the parents of each child after the explanation of aims and the nature of the study.

The inclusion criteria for **cases** comprised physician-diagnosed, confirmed and treated for asthma. Children who were not regularly receiving medication for asthma or who occasionally receive medicine for their symptoms were excluded in this study. **Non-asthmatic controls** were randomly selected from the residential school areas and matched by age, gender and nationality with the cases. Controls were subjected to medical examination by school health physicians.

■ **Questionnaires, sampling and data collection:** A composite questionnaire was prepared from the ISAAC questionnaire (7-9) and with an addition of Bener's questionnaire (13 for the survey. The questionnaire was translated in Arabic by a professional translator. The survey instrument was tested on 50 randomly selected children studying in different schools and validated in this way.

The questionnaires with a letter of explanation were distributed to the parents of these children, who were Qatari nationals, and lived in either residential or oil and chemical pollutant areas of Qatar. The questionnaire was completed by the parents of each child and returned to the school. In case of illiterate parents, a qualified trained Nurse interviewed both parents and completed the questionnaire. All were biological parents. All questionnaires with missing data were omitted from the study (7.5%).

The questionnaire included information about:

- socio-demographic characteristics: age, gender, education and occupation of parents;
- respiratory symptoms: morning breathlessness, shortness of breath based on the rest of day, wheeze after exercise, phlegm, chronic cough, age at onset of symptoms, duration of symptoms and number of asthmatic attacks during the last 12 months;
- associated respiratory illness: pneumonia, bronchitis, sinusitis, and croup;
- associated allergic diseases: allergic rhinitis and atopic dermatitis;
- family history of allergic diseases among first-degree relatives of children such as asthma, atopic dermatitis and allergic rhinitis;
- behavioural factors which could be additive to asthma: parental smoking habit.

The questions concerning the diagnosis of asthma were "Has the child ever been diagnosed as having asthma by a doctor?", and "has the child ever needed treatment or hospital admission due to asthma?" The diagnosis of Allergic rhinitis was based on questions. Has your child ever had a problem with frequent sneezing or prolonged blocked nose during the last six months? When he/she did not have a cold or flu? The questions concerning the diagnosis of persistent eczema were as follows: has your child ever had a dry and itchy red rash for at least 6 months? The questionnaire also included the diagnosis of similar conditions among parents and first degree relatives.

Student's t-test (two tailed) was used to determine the significance of any difference between two continuous variables. Chi-square and Fisher exact test were performed to ascertain the association between two or more categorical variables. The Mantel-Haenszel procedure was used to calculate odds ratios and their Confidence Interval (CI). Stepwise logistic regression was used to adjust for potential confounders and to rank factors (determinants) for asthma in order of importance. The level $p < 0.05$ was considered as cut-off value for significance.

RESULTS

Table 1 depicts the frequency distribution of respiratory symptoms in asthmatic and non-asthmatic children. The proportion of children in the asthmatic group who reported symptoms was significantly higher than in non-asthmatic group (< 0.0001). In the asthmatic group, 47.5% reported morning timing breathlessness, breathlessness rest of the day (61.4%), wheeze after exercise (65.4%), phlegm (45.3%) and extrinsic dry chronic cough (42.2%). Figure 1 shows monthly average of SO_2 , NO , NO_2 , and O_3 in the polluted areas, State of Qatar during the period from January 2004 to

December 2005. As can be observed from this figure the peak of pollutants raised during academic year from September to May.

Controls were more physically active than asthmatics and were more prevalent in heavy and moderate physical activity categories ($p<0.0001$). The proportion of children who awoke at early morning due to respiratory illnesses was significantly higher in the asthmatic group (45.3%) than in the non-asthmatic group (12%), $p<0.0001$. Significantly higher proportion of asthmatic children (57.7%) found difficulty in maintaining sleep at night than the non-asthmatic children (8.2%), $p<0.0001$. Median absenteeism days from school was 12 days per academic year, hospital referrals and hospital admissions during the last 12 months preceding the study were significantly higher in the asthmatic group than in the non-asthmatic group, $p<0.001$. Male asthmatics had a average age at onset of symptoms of $6.9 (\pm 4.8)$ years compared with

female asthmatics who had higher age at onset of symptoms, $7.6 (\pm 5.9)$. Male asthmatics also had longer duration of symptoms (7.5 ± 4.9 in males and 6.4 ± 4.6 years in females).

Table 2 shows the univariate analysis of co-morbid factors to asthma. These factors include lower and upper respiratory illnesses co-morbid, atopy and familial factors. Significantly odds ratios were found higher in asthmatic compared to controls for pneumonia, bronchitis, atopy (allergic rhinitis and atopic dermatitis), sinusitis, croup, parental asthmas, parental atopy (including parental allergic rhinitis, atopic dermatitis) and parental smoking ($p<0.0001$).

A logistic regression model was constructed which included the asthma status (0 for control, 1 for case) as the dependent variable and the risk factors to asthma as seen in Table 3. The logistic regression model showed that morning timing shortness of breath, bronchitis, pneumonia, sinusitis, parental asthma, allergic rhinitis, atopic dermatitis, croup, pets ownership and parental smoking were significant risk factors for asthma (Table 3). The model correctly classified 608 children (84.9%) of cases and controls.

DISCUSSION

There have been many previous studies of the prevalence of asthma in children from around the world, with which these data can be compared (1-15). It is common to find that Asthma is always associated with other disorders like allergic rhinitis and persistent eczema. There is 5.1% of the children had all three disorders at the same time, Asthma with allergic rhinitis was 11.8% and asthma with eczema was 7.5%.

Childhood asthma may be uncommon in some developing countries (12-15, 17). The prevalence of asthma in Qatari school children is higher than in developing and developed countries such as

Symptom	Asthmatics † (N=716) N (%)	Non-Asthmatics ‡ (N=716) N (%)	P-Value
Age groups (in years)			
6-9 Yyears	329(45.9)	341(47.6)	P= 0.5.25
10-13 Years	387(54.1)	375(52.4)	
Gender			
Male	386(53.9)	392(58.7)	P=0.791
Female	330(46.1)	324(45.3)	
Respiratory symptoms			
Morning breathlessness	340(47.5)	49(49)	<0.0001
Shortness of breath	435(61.4)	17(2.9)	<0.0001
Wheeze after exercise	464(65.4)	48(6.7)	<0.0001
Phlegm	324(45.3)	76(10.6)	<0.0001
Chronic cough	302(42.2)	61(8.5)	<0.0001
Restricted physical activity			
None	62(8.7)	31(4.3)	0.0001
Mild	439(61.3)	373(52.1)	
Moderate	163(22.8)	246(34.4)	
Heavy	52(7.3)	66(9.2)	
Sleep interruption			
Awake at early morning	324(45.3)	86(12.0)	<0.0001
Difficulty in maintaining sleep at night	413(57.7)	59(8.2)	<0.0001
Parental smoking habit			
Yes	207(28.9)	104(14.5)	<0.0001
No	509(71.1)	612(85.5)	
Pet ownership			
Yes	183 (25.6)	122(17)	<0.0001
No	532(74.4)	594(83)	

Table 1: Respiratory symptoms, physical activity, sleep interruption and environmental risk factors of 1432 school children in asthma case-control study.
† Photochemical industrial and oil production areas.
‡ Residential area - central town.

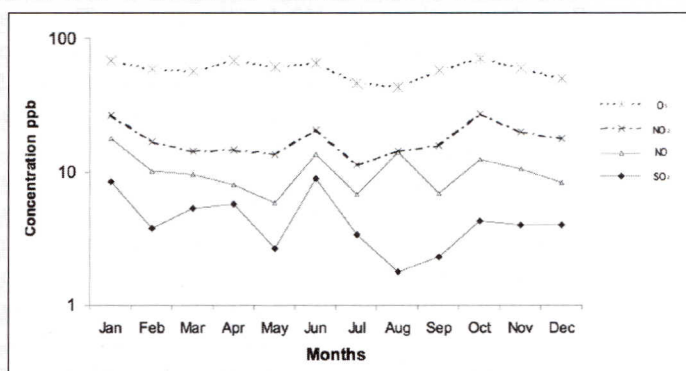


Figure 1: Monthly average of SO_2 , NO , NO_2 , and O_3 in the polluted areas, State of Qatar during the period of years from January 2004 to 2005.

inDublin (16) (15.2%), and Germany (2) (8.8%) and it is considerably higher when compared to the prevalence rates in the Asia-Pacific areas (11) countries and in Bangladesh (15). The prevalence rate of asthma among school children in Qatar (7, 9) is very close to study conducted in the United Arab Emirates (13), in Saudi Arabia (17), and in Oman (14). This study focused on the quantitative effects of a number of factors associated with as well as those that may be causally related to the occurrence of

asthmas in children. Male asthmatics were diagnosed at younger ages than females with more extreme cases in terms of duration of symptom. This could be attributed to many factors such as genetics, environment, cultural, socio-demographic and economic factors.

Our results support the hypothesis that asthma is a multi-factorial disease related to both familial and environmental influences (6-12). Our data showed that bronchitis, atopy (allergic rhinitis and atopic

Symptom	Asthmatics † (N=716)	Non-Asthmatics ‡ (N=716)	Odds ratio	95% Confidence Interval	P-value
Lower respiratory illness					
Pneumonia Yes	53	15	3.73	2.08-6.92	<0.001
No	663	701			
Bronchitis Yes	350	52	12.21	8.85-16.78	<0.0001
No	366	664			
Upper respiratory illness					
Sinusitis Yes	169	58	3.50	2.54-4.82	<0.0001
No	547	658			
Allergic Yes	131	44	3.42	2.38-4.97	<0.0001
No	585	672			
Atopy co-morbid					
Allergic rhinitis Yes	413	59	15.17	11.19-20.58	<0.0001
No	303	657			
Atopic dermatitis Yes	147	50	3.44	2.45-4.83	<0.0001
No	569	666			
Parental atopy co-morbid					
Asthma Yes	238	65	4.99	3.66-6.80	<0.0001
No	478	651			
Allergic rhinitis Yes	156	80	2.21	1.65-2.96	<0.0001
No	560	636			
Atopic dermatitis Yes	58	33	1.82	1.17-2.83	<0.0001
No	658	683			

Table 2: Some risk factors for asthma in a case-control study of 1432 school children.

† Photochemical industrial and oil production areas.

‡ Residential area - central town.

Steps	Factors	Odds ratio	95% Confidence Interval	P-value
1	Allergic rhinitis	9.84	4.88-17.52	<0.0001
2	Shortness of breath	7.9	3.83-14.42	<0.0001
3	Pneumonia	5.95	2.32-16.31	<0.0001
4	Parental asthma	4.49	1.90-20.07	<0.0001
5	Atopic dermatitis	3.65	2.58-5.15	<0.0001
6	Bronchitis	3.28	1.31-6.03	<0.0001
7	Sinusitis	3.02	1.09-22.91	<0.001
8	Croup	2.75	1.31-5.48	<0.001
9	Pets	2.61	1.07-4.06	<0.001
10	Parental Tobacco smoke	2.53	1.93-3.30	<0.001

Table 3: Significant environmental and familial risk factors to asthma, as estimated by the stepwise logistic regression analysis, in a case-control study of 1432 school children, State of Qatar.

dermatitis), croup, parental asthma and parental atopic dermatitis were significant comorbid factors for asthma in children. Bronchitis was the most dominant risk factor followed by parental asthma, allergic rhinitis, croup, parental atopic dermatitis and children atopic dermatitis.

That parental asthma and parental atopic dermatitis were significant predictors for childhood asthma affirms the observation that asthma clusters in families and can be inherited (1-9, 11, 17). Our finding that parental asthma was a strong predictor than parental atopic dermatitis agrees with previous studies that have shown that parental asthma (including atopic dermatitis) may increase the likelihood for the expression of asthma (1, 9, 11, 17-18). Other studies (1, 17-18) showed that children which one have parent with asthma have approximately a 25% chance of developing asthma compared to those more than two parents whom the mother and father both have asthma have 50% chance to develop asthma. In families with one allergic parent the risk of the child developing asthma was increased by parental asthma but not by parental allergic rhinitis or atopic dermatitis (1, 9, 17-18).

Furthermore, pneumonia and sinusitis were significant risk factors in the univariate analysis, they confirmed by the logistic regression model after adjusting for other covariates. A possible explanation is that bronchitis and pneumonia as well as allergic rhinitis and sinusitis are often accurately indistinguishable from each other. Also, allergic was shown to be a significant factor to asthma, and this is consistent with another study (1, 9). Our study showed association between smoking and a child's asthma as other authors concluded (1, 7, 9, 13).

Environmental factors may also be of importance (1, 6, 7, 9, 13). A buoyant economy, rapid industrialization, oil refinery, gas, development of the agricultural sector, an increase in domestication of animals and dairy farms, environment may have contributed to the high prevalence rate in Qatar that we witness today (7, 9, 18). However, in an adult study there was no statistically significant difference in prevalence of asthma and allergic diseases between residential and polluted areas of Qatar (19). It is important to mention that in Qatar the farthest polluted areas are only over 60 Km away from the capital city (Doha). As a result, there has been an increase in diseases and in serious public health problems. This could be one of the main reason for increase in prevalence of respiratory diseases like Asthma in the chemical industrial and oil-production area.

CONCLUSION

The present study provides some evidence that exposure to outdoor air pollutants increases the risk

of childhood asthma, eczema and allergic rhinitis in school children. The observed relation between the risk of childhood asthma and NO_x and CO levels suggests that emissions from photochemical air pollution and oil refinery contributes to adverse health effects in Qatar.

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Press Releases

AAAAI NEWS RELEASE: SECONDHAND SMOKE PROVEN TO MAKE ALLERGIES WORSE, FROM THE JACI

MILWAUKEE — A new study offers concrete evidence that allergies are exacerbated by second-hand smoke.

The study, entitled "Challenge with environmental tobacco smoke exacerbates allergic airway disease in human beings" can be found in the articles in press area of the Journal of Allergy and Clinical Immunology (JACI) Web site located at www.jacionline.org. The JACI is the peer-reviewed journal of the American Academy of Allergy, Asthma & Immunology (AAAAI).

David Diaz-Sanchez, PhD, University of California - Los Angeles, and colleagues hypothesized secondhand smoke could interact with allergens and alter the immune system's response. In order to test the hypothesis, 19 nonsmokers with ragweed allergy were recruited for the study. Each of the individuals underwent a nasal lavage (rinse), and the lavage fluid was collected for testing. Immediately after the lavage, the study participants spent two hours in a chamber where they were either exposed to secondhand smoke or clean air. After another nasal lavage was performed and the fluid collected, each group was exposed to either ragweed or a placebo. Lavages were then performed at 10 minutes, 24 hours, and at 4 and 7 days afterward and analyzed for levels of IgE (the antibody produced in response to allergen exposure) and histamine (one of the substances responsible for the symptoms of inflammation).

Four days after exposure to ragweed/secondhand smoke, levels of IgE were 16.6 times higher in the nasal fluid than for study participants who were exposed to ragweed/clean air. Nasal histamine levels were also 3.3 times higher for those exposed to ragweed/secondhand smoke than those who were exposed to ragweed/clean air.

The authors noted the study provides the first experimental evidence that secondhand smoke can exacerbate allergic responses and also suggest patients with allergies should avoid tobacco smoke.

The AAAAI is the largest professional medical specialty organization in the United States representing allergists, asthma specialists, clinical immunologists, allied health professionals and others with a special interest in the research and treatment of allergic disease. Allergy/immunology specialists are pediatric or internal medicine physicians who have elected an additional two years of training to become specialized in the treatment of asthma, allergy and immunologic disease. Established in 1943, the AAAAI has more than 6,000 members in the United States, Canada and 60 other countries. The AAAAI serves as an advocate to the public by providing educational information through its Web site at www.aaaai.org.

EDITOR'S NOTE: To receive a copy of the study, contact Karen Janka (kjanka@aaaai.org) or Natalie Lemke (nlemke@aaaai.org) at (414) 272-6071. For more information and access to the archive of past JACI news releases, visit the Media Center of the AAAAI Web site, www.aaaai.org.