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Risk Factors for Wheeze in the Last 12 Months in Preschool Children

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SUMMARY **Most children with asthma develop their symptoms before the age of 5 years and many preschool wheezers continue to wheeze in the early school years. It is thus important to investigate the factors that predispose young children to wheeze. The objective of this study was to investigate the relevant environmental and family influences on recent wheeze (wheeze within the last 12 months) in preschool children. A cross-sectional study was conducted in five primary health clinics in the district of Kota Bharu from April to October 1998. Nurses from these clinics distributed Bahasa Malaysia questionnaires containing questions on asthma symptoms, environmental risk factors, family's social status and family history of atopy and wheeze to preschool children aged 1-5 years during their home visits. The respondents were parent(s) or carer(s) of the children.**

A total of 2,524 (87.7%) complete questionnaires were available for analysis of risk factors. One hundred and fifty six (6.2%) children had current wheeze. Significant risk factors associated with current wheeze were a family history of asthma (O.R. = 6.36, 95% C.I. = 4.45-9.09), neonatal hospital admission (O.R. = 2.38, 95% C.I. = 1.51 - 3.75), and a maternal (O.R. = 2.12, 95% C.I. = 1.31-3.41) or paternal (O.R. = 1.52, 95% C.I. = 0.95-2.43) history of allergic rhinitis. Among environmental factors examined, namely, household pets, carpeting in bedroom, use of fumigation mats, mosquito coils and aerosol insect repellents, maternal and paternal smoking, and air conditioning, none were associated with an increased risk of wheeze. In conclusion, the strongest association with current wheeze was a family history of asthma. Also significant were neonatal hospital admission and a history of allergic rhinitis in either the mother or father. None of the environmental factors studied were related to current wheeze in preschool children.

Epidemiological surveys have indicated that the prevalence of asthma has increased significantly.[1,2] In Aberdeen schoolchildren, the prevalence of wheeze increased from 10.4% in 1964 to 19.8% in 1989.[1] Increased prevalence is thought to reflect more than increased awareness and diagnostic transfer as there is a concomitant increase in the prevalence of other allergic disorders such as eczema and hay fever. The increased prevalence of asthma is also reflected in increased rates of hospital admissions.[3] Furthermore, objective measures of bronchial responsiveness to inhaled histamine have increased over time.[2] Available data from Asian countries, though less comprehensive, suggest similar trends in prevalences for these conditions.[4] Differences in the prevalence of asthma between industrialised and developing countries, and urban-rural differences within developing countries,[5] suggest that urbanisation and industrialisation may play an important part in the changing prevalence. Environmental factors, including exposures in the home environment, outdoor pollution, and diet may have a role in this condition.

As the genetic pool is unlikely to have changed substantially over the past decade[6,7] the explanation is more probably related to

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changes in environment or lifestyle. The genetic contribution to asthma is considerable. The proportion of variance due to genetic factors has been estimated to be 0.77 for males and 0.68 for females.[8] A strong genetic component is reflected by the increased prevalence of atopic disease in children of atopic parents, and higher concordance rates of atopic sensitization and symptoms in monozygotic compared with dizygotic twins.[8] The significant increase in asthma and wheezing illness in industrialised countries over the past 30 years points to a significant environmental contribution. Recent concern about environmental influences on childhood asthma has focused on the possible hazards of outdoor pollutants, particularly those derived from vehicle exhausts, such as nitrogen dioxide and ozone.[9] Less attention has been directed towards the indoor environment, although many people, especially young children, spend up to 90% of their time indoors.[10] Increasing affluence, high levels of house dust mite and the mould *Alternaria*,[11,12] increased exposure to passive tobacco smoke, reduced family size[13] and fewer respiratory infections[14] have been shown to increase the risk of wheezing illness. The only Malaysian study investigating the effects of indoor environmental factors on respiratory illness was in primary schoolchildren in Kuala Lumpur.[15] These authors found that exposure to mosquito coil smoke and passive smoking were independently associated with respiratory symptoms.

It is important to investigate more fully the factors that predispose young children to wheeze as wheezing in children usually begins in preschool years.[16] The indoor environment, to which they have the greatest exposure, should be intensively investigated. To the best of our knowledge no such study in this age group has been carried out in Malaysia. Our aim, therefore, was to investigate the relevant family and environmental influences on current wheeze (wheeze within the last 12 months) in preschool children.

MATERIAL AND METHODS

A cross sectional study of preschool children was conducted in the district of Kota Bharu from April to October 1998. Five primary health clinics under the Ministry of Health, Malaysia, in the district of Kota Bharu were selected for the study: Kota Bharu; Pengkalan Chepa; Kubang Kerian; Wakaf Che Yeh; and Ketereh. All primary health clinics have trained nurses who conduct home deliveries and examine newborns, and who trace children in default of their immunization schedules. Their activities at health clinics include routine antenatal care, and vaccination procedures. Nurses were recruited from individual health clinics to distribute questionnaires related to wheezing and cough in the community. The subjects were preschool children, age 1-5 years, living in the areas served by the individual health clinics. The children were divided into five age groups: 1 to <2 years; 2 to <3 years; 3 to <4 years; 4 to <5 years; 5 to <6 years. Households where a home visit was necessary were selected at random from each area. One child aged 1-5 years was selected from each household without knowledge of his/her symptoms. In each health clinic, approximately equal numbers of children in each age group were then selected. The questionnaires were then completed by the parent(s) or carer(s) following explanation of their nature and purpose. Each questionnaire contained an introductory paragraph explaining the nature of the study, and instructions on how to complete the questionnaire. The carer(s) were assured that their participation in the study was voluntary and that the information provided would be kept confidential. Completed questionnaires were collected by the same nurse two days later. Non-respondents were reminded by the nurse to complete the questionnaires.

Questionnaire

The questionnaire was adapted in part from an English questionnaire developed by Luyt[17] for preschool children and translated into Bahasa Malaysia, the national language. Questions relating to wheezing and night cough had previously been translated into Bahasa Malaysia from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.[18] The first section of the questionnaire dealt with respiratory history and symptoms such as wheeze, night cough and doctor diagnosed asthma. The second examined environmental risk factors, social status and family history of atopy and wheeze. A history of allergic rhinitis was positive if there was a history of sneezing, or a runny, or blocked nose when they did not have a cold or flu. A history of eczema was positive if there was a history of an itchy rash which was coming and going for at least six months. Admission to the neonatal care nursery during the neonatal period was also noted. A positive history in any family member refers to a history of the condition (asthma, allergic rhinitis or eczema) in

either the mother, father or sibling. Parents' smoking habit in the house was also inquired. Low education was defined as an education level of primary school or less. Wheeze in the last 12 months (current wheeze) was the outcome measure used as it had least recalled bias. The presence of wheeze in the last 12 months was elicited by the question "Has your child had wheezing or whistling in the chest in the last 12 months?"

All data were analyzed using SPSS for windows for personal computers. Differences between groups were compared using the Chi-square test. Two tailed *P* values of less than 0.05 were considered statistical significance. The relationship between current wheeze and categorical independent variables were examined using 2 x 2 contingency tables. Both univariate and multivariate analyses including the 95% confidence intervals were calculated. All significant independent variables were included in the backward stepwise logistic regression to examine for confounders.

RESULTS

All 2,882 parent(s) included in the study responded. Four questionnaires were not analyzed because the children were less than one or more than six years of age. A total of 2,524 (87.7%) complete questionnaires were available for analysis of putative risk factors. There were 1,292 (51.2%) males and 1,232 (48.8%) females. The number of children in each age category were as follows: 1-<2 years, 473 (18.7%); 2-<3 years, 540 (21.4%); 3-<4, 524 (20.8%); 4-<5 years, 530 (21%); 5-<6 years and 457 (18.1%). The mean birth weight was 3.1 kg (S.D. = 0.5). One hundred and fifty-six (6.2%) children had wheezing in the past 12 months (current wheeze).

Table 1 shows the univariate analysis for genetic factors. There was no gender difference in current wheeze prevalence. Although a family history of asthma, allergic rhinitis or eczema were all significantly associated with current wheeze, the association was greatest for a family history of asthma. A history of asthma in the mother (O.R. = 6.82) or among siblings (O.R. = 6.88) was associated with a higher risk of current wheeze than a history of asthma in the father (O.R. = 4.04).

Among environmental factors examined (Table 2), i.e. household pets, carpeting in bedroom, use of fumigation mats, mosquito

Table 1 Univariate analysis of genetic factors for current wheeze

Risk Factor	No. & frequency exposed		No. & frequency not exposed		Crude odds ratio	95% Confidence interval	*P* value
	n	%	n	%			
Male sex	85	6.6	71	5.8	1.15	0.83 - 1.59	0.40
History of asthma in							
Father	18	19.6	138	5.7	4.04	2.35 - 6.96	< 0.001
Mother	34	26.8	122	5.1	6.82	4.42 - 10.51	< 0.001
Siblings	50	24.8	106	4.6	6.88	4.73 - 10.0	< 0.001
Any family member	78	22.9	78	3.6	8.00	5.70 - 11.23	< 0.001
History of allergic rhinitis in							
Father	31	13.8	125	5.4	2.80	1.84 - 4.25	< 0.001
Mother	33	19.8	123	5.2	4.47	2.93 - 6.82	< 0.001
Siblings	22	16.7	134	5.6	3.37	2.07 - 5.50	< 0.001
Any family member	91	7.4	65	5.0	1.51	1.09 - 2.10	0.013
History of eczema in							
Father	9	12.3	147	6.0	2.20	1.08 - 4.52	0.027
Mother	9	12.7	147	6.0	2.28	1.11 - 4.67	0.021
Siblings	7	11.6	149	6.0	2.05	0.92 - 4.60	0.074
Any family member	19	12.1	137	5.8	2.24	1.35 - 3.73	0.001

Table 2 Univariate analysis of environmental and miscellaneous factors for current wheeze

Risk Factor	No. & frequency exposed		No. & frequency not exposed		Crude odds ratio	95% Confidence interval	*P* value
	n	%	n	%			
Pets in the house	68	7.1	88	5.6	1.29	0.93 - 1.79	0.13
Carpet in the bedroom	27	7.5	129	6.0	1.27	0.83 - 1.95	0.28
Use of fumigation mat	36	7.2	120	5.9	1.22	0.83 - 1.80	0.30
Use of mosquito coil	69	6.1	87	6.3	0.96	0.69 - 1.33	0.81
Use of aerosol insect repellent	28	7.4	128	6.0	1.25	0.82 - 1.92	0.30
Use of any insect repellents	117	6.4	39	5.5	1.17	0.81 - 1.70	0.41
Air condition in bedroom	1	1.8	155	6.3	0.28	0.038 - 2.01	0.26
Paternal smoking	97	6.6	59	5.6	1.20	0.86 - 1.67	0.29
Maternal smoking	0	0	156	6.2	1.00	1.00 - 1.01	0.44
Low birth weight (≤ 2 kg)	6	14	150	6.0	2.52	1.05 - 6.07	0.033
Attendance at nursery ever	22	6.0	134	6.2	0.97	0.61 - 1.54	0.90
No breast feeding at any time	13	9.7	143	6.0	1.69	0.93 - 3.07	0.082
Neonatal hospital admission	30	13.8	126	5.5	2.76	1.81 - 4.22	< 0.001
Low paternal education	30	6.7	126	6.1	1.11	0.73 - 1.67	0.63
Low maternal education	26	6.1	130	6.2	0.98	0.64 - 1.52	0.93
High birth order (≥ 5th in family)	39	5.1	117	6.7	0.74	0.51 - 1.08	0.12

coils and aerosol insect repellents, maternal and paternal smoking, and air conditioning, none were associated with an increased risk of wheeze. Univariate analysis of miscellaneous factors (Table 2) showed that birth weight ≤ 2 kg [O.R. = 2.52] and hospital admission during the neonatal period [O.R. = 2.76]) were significantly associated with current wheeze. Nursery attendance, breast feeding (ever), low paternal education and high birth order (≥ 5th in the family) were not significant. Infants who were admitted to hospital after birth (n = 24, 11% [≤ 2 kg]) had significantly (p = < 0.001) lower birth weight than those not admitted (n = 19, 0.8% [> 2 kg]).

All significant genetic, environmental and miscellaneous factors were included in a multivariate analysis for current wheeze. A history of asthma in any family member (O.R. 6.36, 95% C.I. = 4.45-9.09, p < 0.001), neonatal hospital admission (O.R. = 2.38, 95% C.I. = 1.51-3.75, p < 0.001) and allergic rhinitis in mother (O.R. = 2.12, 95% C.I. = 1.31-3.41, p = 0.002), or father (O.R. = 1.52, 95% C.I. 0.95-2.43, p = 0.08), remained significant, but low birth weight, not significant, after controlling for confounders.

The analysis was repeated for children aged 1-3, and 4-5, and the two age groups compared. There were 1,537 children in the 1-3 year age group and 987 children in the 4 - 5 year age group. Table 3 shows the significant risk factors for current wheeze in each age group. Genetic factors for current wheeze were similar in both age groups except for a history of paternal eczema (O.R. = 2.37) which was significant only in the 1-3 year age group and a history of eczema in siblings (O.R. = 3.54) which was significant only in the 4-5 year age group. All children in the 4-5 year age group had a history of allergic rhinitis in any family member.

Among environmental and miscellaneous factors, failure to breast feed (O.R. = 2.10) was associated with current wheeze only in the 1-3 year age group, and use of aerosol insect repellents (O.R. = 2.01) and low birth weight (O.R. = 5.03) were associated with current wheeze only in the 4- 5 year age group. Neonatal hospital admission

Table 3 Significant risk factors for current wheeze by age group

Risk Factors	Age group 1- 3 years n = 1,537			Age group 4 - 5 years n = 987		
	Crude odds ratio	95% Confidence interval	*P* value	Crude odds ratio	95% Confidence interval	*P* value
History of asthma in						
Father	4.51	2.28 - 8.89	< 0.001	3.60	1.44 - 9.02	0.004
Mother	7.34	4.37 - 12.36	< 0.001	5.64	2.54 - 12.50	< 0.001
Siblings	7.97	5.00 - 12.70	< 0.001	5.75	3.02 - 10.93	< 0.001
Any family member	8.96	5.92 - 13.57	< 0.001	6.52	3.60 - 11.83	< 0.001
History of allergic rhinitis						
Father	2.56	1.52 - 4.31	< 0.001	3.33	1.64 - 6.78	< 0.001
Mother	5.08	3.10 - 8.32	< 0.001	3.02	1.29 - 7.08	0.008
Siblings	3.32	1.79 - 6.16	< 0.001	3.62	1.61 - 8.14	0.001
Any family member	3.95	2.61 – 5.99	< 0.001	-	-	-
History of eczema in						
Father	2.37	1.04 - 5.42	0.04	1.69	0..39 - 7.40	0.36
Mother	2.12	0.88 - 5.12	0.09	2.60	0.75 - 8.96	0.13
Siblings	1.35	0.40 - 4.49	0.50	3.54	1.17 - 10.66	0.04
Any family member	2.16	1.16 - 4.02	0.01	2.38	0.97 - 5.84	0.052
Use of aerosol insect repellent	0.97	0.56 - 1.65	0.90	2.01	1.00 - 4.04	0.05
Low birth weight (≤2 kg)	1.62	0.48 - 5.46	0.44	5.03	1.37 - 18.45	0.03
No breast feeding	2.10	1.05 - 4.21	0.03	1.07	0.32 - 3.54	0.76
Neonatal hospital admission	2.62	1.54 - 4.46	< 0.001	3.15	1.55 - 6.40	0.001

was associated with current wheeze in both age groups. Keeping pets in the house, use of carpets in the bedroom, fumigation mats, mosquito coils, air-conditioning, passive smoking, attendance at nursery, paternal or maternal education and birth order were not significantly associated with current wheeze in both age groups. In multivariate analysis, factors which remained significant in the 1-3 year age group were family history of asthma (O.R. = 7.18, p <0.001), neonatal hospital admission (O.R. = 2.05, p = 0.02), maternal history of allergic rhinitis (O.R. = 2.56, p <0.001) and failure to breast feed (O.R. = 2.51, p = 0.02); and in the 4-5 year age group family history of asthma (O.R. = 6.09, $p < 0.001$), neonatal hospital admission (O.R. = 2.56, p = 0.02), paternal history of allergic rhinitis (O.R. = 2.42, p = 0.02) and low birth weight (O.R. = 5.32, p = 0.02).

DISCUSSION

In this cross-sectional survey of preschool children, the main risk factors of current wheeze were a family history of asthma, neonatal hospital admission and a history of allergic rhinitis in the mother or father. Risk factors in the 1-3 year age group were similar to those in the 4-5 years age group, except for failure to breast feed (significant only in the 1-3 years age group), and use of any insect repellent and low birth weight (significant only in the 4-5 years age group).

The environmental factors examined in this study included household pets, carpeting in bedroom, use of fumigation mats, mosquito coils, and aerosol insect repellents, maternal and paternal smoking and air conditioning; none were associated with an increased risk of wheeze. However parental smoking was significantly associated with wheeze in preschool children in Leicester, United Kingdom.[17] Similarly Azizi and Henry[15] found that school children exposed to mosquito coil or passive smoking had more respiratory symptoms and

persistent wheeze. Differences between these and our findings might be due to different definitions of exposure. In this study it was defined as "any parent who smoked in the house", by Azizi & Henry[15] "sharing a bedroom with an adult smoker", and Luyt[17] "any parent who smoked". Maternal smoking during pregnancy and infancy has been shown to be a risk factor of early childhood wheezing[19] and could reflect the closeness of contact between mothers and their children. Wheeze is also more strongly associated with maternal smoking during pregnancy than maternal smoking during childhood. Although a positive association between wheezing illness and maternal smoking has been reported in several studies,[10,15,17,19] it did not contribute to an increase in the prevalence of asthma symptoms.[20] In a recent review, parental smoking, especially maternal smoking was significantly associated with asthma, wheeze, cough, phlegm and breathlessness.[21] The essential difference between the present study and other reports is that none of the mothers smoked either during or after pregnancy.

The sample size in this study was insufficient (O.R. = 0.51-1.08) to show a significant association between high birth order and current wheeze. Family size has been shown to be inversely related to the risk of atopic diseases[13,22,23] and asthma.[24] This might be due to the increased number and severity of infections in larger families as reduced number of infections has been suggested as a possible explanation for the higher prevalence of atopic diseases in small families.[25] Children who had measles were also less likely than those who did not to develop skin sensitivity to mites.[26] It is possible that early infections switch the development of T cell clones in the Th1 direction and inhibit the proliferation of Th2 cell clones, which predisposes to atopy, and therefore prevent allergies.[25] While family size was inversely related to atopy, attendance at preschool nursery[27] or infections in the first year of life[28] were not.

Neonatal hospital admission was found to be an independent risk factor for current wheeze in this population of preschool children (O.R. = 2.38) and also in both the 1-3 (O.R. = 2.05) and the 4-5 (O.R. = 2.56) year age groups. The effect of gestation could not be examined because of incomplete questionnaires. Babies admitted to neonatal intensive care units are by and large lighter and more premature, and thus more likely to develop chronic lung problems, manifest as wheezing illnesses. Even those preterm babies who do not develop bronchopulmonary dysplasia are at risk of developing wheeze.[29] In the 4-5 year age group, both neonatal hospital admission and low birth weight were independent risk factors, suggesting other reasons responsible for neonatal admission to hospital associated with wheeze were not identified.

As in other studies,[8] a family history of asthma (O.R. = 6.65) remained the strongest risk factor of asthma. Even though the prevalence of current wheeze in Leicester (12.4%)[17] was twice that in Kota Bharu (6.2%), a history of asthma was less often reported by parents in Leicester (16% of fathers and 18.1% of mothers)[17] than in Kota Bharu (19.6% of fathers and 26.8% of mothers). This suggests that genetic factors were mainly responsible for preschool wheeze in Kota Bharu and the excess number of children with current wheeze in Leicester could be due to environmental influences not yet operative in the present study population. It will be of interest to know whether this will change with time as economic development progresses.

In conclusion, this cross-sectional study identified a family history of asthma as the strongest association with current wheeze, followed by neonatal hospital admission and a history of allergic rhinitis in the mother or father. None of the environmental factors studied were associated with current wheeze in preschool children. With the exception of failure to breast feed in younger children, and low birth weight in older children which were significantly associated with current wheeze, differences between 1-3 and 4-5 year olds were unremarkable.

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