Risk Factors Associated with Childhood Asthma - A Case Control Study

Dongol Singh S, Shrestha A

Department of Pediatrics

Kathmandu University School of Medical Sciences

Dhulikhel, Kavre, Nepal.

Corresponding Author

Srijana Dongol Singh

Department of Pediatrics

Kathmandu University School of Medical Sciences

Dhulikhel, Kavre, Nepal.

E-mail: docsrijana@yahoo.com

Citation

Dongol Singh S, Shrestha A. Risk Factors Associated with Childhood Asthma - A Case Control Study. *Kathmandu Univ Med J.* 2018;64(4):290-5.

ABSTRACT

Background

Asthma is one of the most common chronic childhood illnesses with rapidly increasing prevalence in low income countries. For planning effective intervention to reverse this condition we need a better understanding of the risk factors for asthma in early life.

Objective

To identify the risk factors associated with childhood asthma and its morbidity patterns.

Method

The case control study was conducted in the pediatric department of Dhulikhel hospital, Kathmandu University hospital, Dhulikhel from March 2016 to March 2017. The control group was composed of 175 age matched children attending the outpatient clinic with non pulmonary health problem. Data was collected through Performa and analyzed using SPSS version 23. The association of asthma with genetic and environmental risk factors was evaluated by univariant (chi-square or Fisher's exact test) and binomial logistic regression.

Result

Childhood asthma was more common in male children between 1-5 years. Majority of children 77(44%) were graded as mild persistent asthma. Risk factor associated with asthma include family history of asthma (OR0.06; 95%CI .005-0.94, p=0.04), nonexclusive breast feeding (OR18.42; 95% CI 2.56-132.3, p=0.004), allergic disorder in children (OR0.003; 95%CI 0.000-0.037, p=0.0001).

Conclusion

Family history of asthma, allergic history in the patient and nonexclusive breast feeding were significantly associated with asthma. There is no significant association of asthma with exposure to allergic food, exposure to smoke and domestic animals.

KEY WORDS

Breastfeeding, Childhood asthma, Risk factor

INTRODUCTION

Childhood Asthma is one of the most common chronic pulmonary diseases of children. The prevalence of asthma and allergies in general has considerably increased over the last two decades, particularly among children.[1] Worldwide, an estimated 300 million people are affected by asthma. It appears that the global prevalence of asthma ranges from 1-18% of the population in different countries.[2]

The risk for developing asthma depends on a complex interaction of hereditary and environmental factor. Risk factors are: genetic predisposition (family history of atopy or asthma); perinatal factors (low birth weight and prematurity); environmental factor (nonexclusive breast feeding, early weaning with allergic food, smoke- tobacco or stove exposure, pets at home, dampness, allergic diseases).[3] Breast feeding has been advocated for the prevention of asthma, although the result of individual studies are conflicting.[4-6] Furthermore, reviews concluded that the protective effect of breast feeding on asthma in children were stronger in children with an allergic heredity, It has a potential adverse effect on society in terms of morbidity of life (physical activity, education, socialization and self-esteem) and heath care cost.[5,6]

Although, precise reasons for this increase in incidence of asthma are unknown, it is likely that a number of environmental factors are at least partly responsible. There are very few studies that attempted to explore the role of risk factors for asthma in population of children in Nepal.[7] The identification of risk factors is essential for the adaptation of preventive measures and optimization of asthma patient management. This study aimed to identify the risk factors associated with asthma and its morbidity patterns in children recruited from pediatrics department of Dhulikhel hospital.

METHODS

This case-control study included 350 age matched children who attended the pediatrics department of Dhulikhel hospital, Kathmandu University Hospital, Nepal between March 2016 to March 2017. The patient group comprised 175 asthmatic children and the control group, 175 non asthmatic children.

The inclusion criteria for the patients were potentially eligible if they had an International Classification of Diseases, Ninth Revision k code of asthma (493XX) at a hospitalization, emergency department visit or outpatients visit plus any of the following during the previous 12 months: (1) Four or more prescriptions for any asthma medication, (2) one or more asthma related hospitalization or emergency department visit, or (3) Three or more asthma related outpatient visits and 2 or more prescription for asthma medications.[8]

The controls were children of same age, who attended the pediatric department of the hospital immediately after selection of the index case. The inclusion criteria for the controls were (1) having the same age (± 3 months) as the corresponding patient, (2) absence of respiratory disease, (3) no previous episode of wheezing.

Participants were informed about the study and those who agreed to participate in the study. Informed written consent was taken. Once they had given consent for participation in the study, the patients were asked the questionnaire and Performa was filled.

A preliminary questionnaire was hence developed consisting of items focusing detailed information about morbidity, past medical history (hospital admission, emergency department visit, school day missed, and history of nebulization, night disturbance, exercise limitation and prolonged cough). The questionnaire included information relevant to asthma risk factor including socioeconomic status (age, gender and education level), genetic predisposition (family history of atopy and asthma); perinatal factors (low birth weight and prematurity); allergen exposure or environmental air pollution (smoke exposure, domestic animals or pets). The duration of nonexclusive breast feeding and early weaning with allergic food were also noted.

For the purpose of study, breast feeding was defined as nonexclusive breast feeding up to 6 month of age; smoking was considered positive if there was history of smoking by father, mother, grandfather or grandmother, any one or two of them and if they used smoke stove. Family history was considered positive if there was history of asthma in either mother or father or both; family history of allergy was considered positive if there was either father or mother or both of them was allergic to dust or foods. Low birth weight was defined as birth weight less than 2500 gm and preterm was defined as delivery before 37 completed weeks of gestation.

The grading and management of asthma of the patient were done according to National Asthma Education and Prevention Program.[9]

The chest radiography was done in all cases and was interpreted by two independent radiologists. Total counts, differential counts, CRP and blood culture were done only in suspected cases of secondary bacterial infection to asthma. Peak flow of children aged 15 years and more was measured and Vitalograph Peak Flow Meter and result interpreted by using Peck Flow Chart.[10] The spirometry was done in only selected cases who were more than 5 years and difficult to diagnose as asthma with history and chest X-ray. Skin prick test was done in children more than 3 years, with history of allergy or atopy to food and dust.

Children enrolled in the study were scheduled for regular follow up visit in asthma clinic in every 2 week to 12 weeks interval depending on asthma control test and distance from where they come from. In each visit detail history regarding asthma day and night symptom, signs of exacerbation, needing emergency room visit,

bronchodilator requirement, frequency of school missing, drug compliance and side effect of drugs were noted. In all cases full physical examination were done. Those cases that had frequent prolonged cough and cold also received influenza vaccination during their follow up visit in asthma clinic.

The collected data was analyzed using SPSS 23 version. Pearson's chi square test or Fisher's exact test was used to compare qualitative variables. Differences was considered to be significant at p value < or = to 0.05. The strength of the relationship between risk factor and asthma was evaluated by calculating Odds Ratios (OR) and their Confidence Intervals (CI) for all the factors tested.

Ethical approval for the studies was obtained from the Institutional Review Committee, Kathmandu University School of Medical Science.

RESULTS

We studied a total of 350 patients: 175 asthmatic children and 175 non asthmatic children matched with age. The children were aged between 1 year to 16 years. Table 1 shown the baseline characteristics of the cases and controls. One hundred and twenty nine (73.71%) had asthma in between 1-5 years. Male to Female ration was almost 2:1 in both asthmatic and non-asthmatic children. Among the different ethnicity there was Tamang ethnic group (28.6%) more in asthmatic children and Brahmin (32%) in non-asthmatic children. Most of the asthmatic children lived in urban areas. The asthmatic children (66.3%) were hospitalized more frequently than the non-asthmatic children (17.7%). The asthmatic children were 13 times more frequent visit to emergency department in comparison with the control group.

Table 1. Baseline characteristics of the study group

Characteristics		Cases	Control
Age	1-5 years	129(73.7%)	129(73.7%)
	6-10 years	32(18.3%)	32(18.3%)
	11-16 years	14(8.0%)	14(8.0%)
	Mean age		-
Sex	Male	119(68.0%)	114(65.1%)
	Female	52 (32.0%)	61(34.9%)
Ethnicity	Brahmin	57 (32.6%)	45 (25.7%)
	Chettri	28(16.0%)	12 (6.9%)
	Newar	40 (22.9%)	48(27.9%)
	Tamang	22 (12.6%)	50 (28.6%)
	Madhesi	7 (4.0%)	3 (1.7%)
	Dalit	21 (12.0%)	17 (9.7%)
Residence	Urban	75 (42.9%)	85(48.6%)
	Semi-urban	46 (26.3%)	25 (15.4%)
	Rural	54 (30.9%)	63 (36.0%)
Hospital admission		116 (66.3%)	31 (17.7%)
Emergency visit at least one time		9 (5.14%)	121 (69.1%)
Educational status	University	2 (1.1%)	13 (6.9%)
	Secondary	19 (10.3%)	9 (5.1%)
	Periphery	67 (38.3%)	14 (8%)
	Primary	53(33.1%)	43(24%)
	Illiterate	30 (17.1%)	98 (56%)

Factor associated with asthma

The risk factors associated with bronchial asthma was described in Table 2.

Genetic factors

Family history of asthma (OR0.069; 95% CI0.005-0.94, p=0.045) was associated with asthma while family history of allergic disorders (OR 0.87, 95% CI 0.045-16.58, p=0.0925) were not associated with asthma.

Perinatal factor

We found a statistically insignificant association between asthma with prematurity (OR 0.08, 95% CI 0.02-35.11, p=0.92) and low birth weight (OR 0.33, 95% CI 0.039-2.84, p=0.31)

Environmental factors

Nonexclusive breast feeding

There was a statistically significant relationship between asthma and nonexclusive breast feeding (OR 18.42, 95% CI 2.56-132.3, p=0.004), history of allergic disorder in children (OR 0.003, CI 0.001-0.037, p=0.001). Although exposure to dampness, smoke and pet has been previously associated with asthma, we did not find any significant association with them in this study. Similarly there were no association between asthma and early exposure to allergic food. (OR 0.116, 95% CI 0.013-1.043, p=.05). Allergic good are those food which when eat in tiny amount also can cause sign and symptom of allergy such as digestion and respiratory problem. American Academy of allergy, asthma and immunology has given 8 kinds of food causes allergies. They are cow's milk, egg, peanuts, wheat, soy, fish, shellfish and free nuts.

The morbidity pattern of bronchial asthma is described in Table 3. Forty four children (25.14%) had mild intermittent asthma, 77(44%) were graded as having mild persistent asthma, 41(23.42 %) had moderate persistent asthma and 13(7.42%) had severe persist asthma. Forty eight (27.4%) children were missing school 1-5 days in a month. We found an obvious decrease in frequency of night symptom after treatment. Among all asthmatic cases, 165 patients were symptom free at night after treatment while only 55 were symptom free at night before treatment. Sixty patient (34.28%) of asthma got influenza vaccine as a part of treatment. Among them only 1(1.66%) had acute exacerbation of asthma.

Table 2. Risk factor associated with Asthma

	Risk factors	Children N(%)	Control group N(%)	Odds ratio OR	95% CI	P value
Genetic predisposition	Family history of asthma	49 (28)	3(1.7)	0.069	0.005-0.94	0.045
	Family history of atopy or allergy disorder	116 (66.3)	10(5.7)	0.87	0.045-16.58	0.92
Perinatal factors	Low birth weight	70 (40)	12 (6.9)	0.33	0.03-2.84	0.31
	Prematurity	38 (21.7)	5 (2.9)	0.84	0.02-35.11	0.92
Environmental risk factors	Exclusive breast feeding	44(25.1)	159 (90.9)	18.42	2.5-132	0.004
	Early weaning with allergic food	158 (90.3)	67 (38.3)	0.116	0.13-1.04	0.05
	Exposure to tobacco/smoke	110 (62.9)	32 (18.3)	0.358	0.057-2.23	0.27
	Exposure to pets or domestic animal	107 (61.1)	59 (33.7)	1.33	0.02-8.72	0.76
	H/O eczema	126 (72.0)	3 (1.7)	0.069	0.001-3.6	0.187
	Allergic disorder	156 (89.1)	3 (1.7)	0.003	0.00-0.37	0.0001

Table 3. Morbidity pattern of Bronchial Asthma

Age of First Attack	Number	Percentage
< 1 yrs		
1-5 yrs	129	73.7
6-10 yrs	32	18.3
10-16 yrs	14	8
Grading		
Mild Intermittent Asthma	44	25.1
Mild Persistent Asthma	77	44.0
Moderate Persistent Asthma	41	23.4
Severe Persistent Asthma	13	7.4
School Missing Before and after the Treatment		
Days of School Missing		
No school missing	123	70.24
1-5 days/month	48	27.4
5-10 days/month	4	2.3
10-15 days/month	0	0
Night Symptoms Before and after treatment		
Night Symptoms	6 months before Rx	6 months after Rx
No Night Symptoms	55	165
1-3 nights	80	8
4-5 nights	26	1
>5 nights	14	1

DISCUSSION

Bronchial asthma is an important cause of morbidity and mortality in children. This study shows that childhood bronchial asthma is more than twice more common in male (65.1%) than female. This result is compatible with another study done by Muhi et al. in 2010 where it was found that male formed 68% asthmatic children.[11] A similar result was reported by Awis et al. in Mosul in 2005.[12] In this study prevalence of asthma decreased with increasing age. Symptoms of bronchial asthma started before 5 years of age in 73.71% and this is in agreement with Muhi et al. and Jinan et al. studies done in Baghdad.[11,13]

Genetic factors

There was a significant association between a parental asthma and childhood asthma. This is in conformity with many previous studies that have demonstrated an association between parental asthma and development of childhood asthma and further emphasizes the important role of genetic susceptibility in development of asthma.[14,15] The precise mechanism for this is not clearly understood. But several studies have postulated that multiple genes are involved in pathogenesis of asthma such as: production of allergen-specific immunoglobin E (IgE), expression of bronchial hyper responsiveness, generation of inflammatory mediators such as cytokines and modulation of Th2 response to antigen.[16,17] However, this study did not confirm the results from previous studies which suggest that maternal allergic disease is a greater risk factor for childhood asthma.[18]

Environmental factors

Nonexclusive breast feeding

The protective role of nonexclusive breast feeding against asthma was demonstrated in this study population. Breast milk contains cytokines and growth factors that may play a role in modulating the development of asthma by preventing sensitization to environmental allergens, enhancing infant lung development and reducing susceptibility to respiratory infection.[19] The result of other publications are mixed, however, and another recent follow up study for 8 years in children showed mothers gave nonexclusive breast feeding and concluded that breast feeding is associated with a lower asthma risk in children until 8 years of age without evidence of attenuation of association and regardless of the family history of allergy.[20] The protective role of nonexclusive breast feeding against asthma mainly applies to children with genetic susceptibility to asthma such as those with asthmatic mother, rather than the general population.[19,20]

Early exposure to allergenic food

The other topic of importance in the development of childhood atopic disease, including asthma, is dietary

exposure in early life. Food allergen sensitization was 3.2 times more frequent (95% CI 1.5-6.9) when food was introduced at 4-6 months and 2.5 times more frequent when food introduction was delayed beyond 6 months (95% CI 1.03-6.30).[21,22] The reported results are in line with an American Academy of Pediatrics clinical report published in 2008, which also concluded that delayed introduction of foods beyond 4-6 months did not protect against atopic disease, including the introduction of very allergenic food such as fish, egg and peanuts.[23] This result was in consistent with our finding that there was no association between childhood asthma and early exposure to allergic food.

Smoke exposure (tobacco and an open fire for cooking)

A survey of smoking habits in the rural area of Nepal showed that the prevalence of daily tobacco smoking for men and women was 85% and 62% respectively.[24] Most Nepalese families use unprocessed biomass fuel such as wood, grass and crop residue for heating and cooking. In the present study, cigarette consumption in families and open fire stove at home showed negative effect to the occurrence of childhood asthma, which was consistent with some other recent international studies.[25,26] The possible explanation could be the cigarette smoking and stove use might be reduced by families with children with atopic disease. In contrast to our study another study done in Nepal by Melson et al. shown the risk for asthma was higher among children exposed to smoky fuels (OR 1.8, 95% CI 1.0-4.5, p=0.04).[27]

Pets

In Nepal a large proportion of the population are peasants and, as in many developing countries, there is a tradition of keeping cattle inside the house. Similar to our study another study done in Nepal by Melson et al. in western Nepal also shown keeping cattle inside the house was inversely related to the risk of having asthma.[27] Another PIAMA birth cohort study done in 2009 also shown a protective effect on asthma of early presence of pets at home.[28]

Allergic disease (history of allergic rhinitis, eczema and conjunctivitis)

Occurrence of atopic conditions was significantly higher in asthmatic population. The most common are allergic rhinitis followed by allergic conjunctivitis and atopic dermatitis. Similar to our study other studies also reported atopic conditions like atopic dermatitis, allergic rhinitis and allergic conjunctivitis to be associated with asthma.[29,30]

Dampness

The presence of dampness on walls at home (OR=0.22; 95% CI: .028-1.79, p=0.16) is not associated with asthma. In another case control study, done in Kenyan school children also showed no significant differences were seen in relation to damage due to dampness being present in home of cases compared with controls was 6.8(95% CI 2.6-17.7%) in the school that were blinded and 4.6(95% CI 1.5-15.1) in school that were not.[31] However, there is also abundant evidence that exposure in dampness in the home may lead to the development of asthma.[32,33]

Perinatal factor

Perinatal factor, including gestational age and birth weight, influence the development of atopy in early life increase the risk of developing lower respiratory tract infection and play a possible role in development of asthma in later life.[3,34] In the present study as well, the incidence of asthma was several fold increased in preterm and LBW babies, however it is not statistically significant.

Morbidity pattern of asthma

According to day and night symptom, asthma has been classified as shown in Table 3. Among all cases of asthma nearly 50% were mild persistent and 23% were moderate persistent, which are consistent with other study done in Kathmandu in the year 2006.[35]

Asthma is given as the reason for a school absence in high percentage in children.[36] These authors also confirmed that asthma was most frequent reason for children missing school for > 5 days. In our study most of the children are preschool group, so only 27% of children were missing school for 1-5 days and 2.3% were missing > 5 days. In our study we found an obvious improvement in patient wellbeing and night symptoms after starting the treatment and dietary advice. Similar finding was also found in another study done in Nepal in 2006.[35]

The limitation of this study is the small sample size which might be the reason that result was different as compared with other studies which are based on large number of patients. In the current study asthma was diagnosed based on International classification of disease which was based on clinical observation and history but not based on infant spirometry.

CONCLUSION

The present study concludes certain risk factors being associated with childhood asthma namely parental asthma, nonexclusive breast feeding and allergic disease in children. No significant association was found with early weaning with allergic food, exposure to smoke and domestic animals with asthma. Further large scale studies are recommended in Nepal to define risk factors associate with childhood asthma more precisely.

ACKNOWLEDGEMENT

The authors are grateful to Mr. Sehananda Sanjel from Department of Community Medicine for helping in statistical analysis.

REFERENCES

1. Morgan WJ, Crain EF, Gruchalla RS, Oconnor GT, Kattan M. Result of a home – based environmental intervention among urban children with asthma. *N Engl J Med*. 2004; 351:1068-80.
2. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen Jm, FitzGerald MM et al. Global Strategy for asthma management and prevention: GINA executive summary. *Eur Respir J.* 2008 Jan; 31(1):143-78.
3. Brakcken MB, Belanger K, Cookson WO, Triche E, Christiani DC, Leaserer BP. Genetic and perinatal risk factors for asthma onset and severity: a re-view and theoretical analysis. *Epidemeiol Rev.* 2002; 24:176-89.
4. Van Odijk J, Kull I, Borres MP. Breastfeeding and allergic disease: a multidisciplinary review of the literature (1996-2001) on the mode of early feeding in infancy and its impact on later atopic manifestation. *Allergy.* 2003; 58:833-43.
5. Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta analysis of prospective studies. *J Pediatr.* 2001; 139:261-6.
6. Fuhlbrigge AL, Adam RJ, Guilbert TW, Grant E, Lozano P, Jonson LS et al. The burden of asthma in United States: level and distribution are dependent on interpretation of National Asthma Education and Prevention Program Guidelines. *Am J Respir Cri Care Med.* 2002; 166: 1044-49.
7. Melson T, Brinch L, Hessen JO, Schei MA, Kolstup N, Jacobsen BK, et al. Asthma and indoor environment in Nepal. *Thorax.* 2001; 56(6):447-281
8. Fassl AB, Nkoy LF, Stone LB, Srivastava, Simon DT, Uchida AD. The Joint commission children's Asthma Care Quality Measures and Asthma Readmission. *Pediatrics.* 2012 Sep; 130(3):482-91.
9. National Heart Lung and Blood Institute. NAEPP Expert Panel Report. Guidelines for the Diagnosis and Management of Asthma – Update on Selected Topics 2002, downloaded from www.nhlbi.nih.gov/guidelines/asthma/execumm
10. Aljanabi KM, Alhammash JS, Waill N, Shebab M, Nasir AN. Risk factor of bronchial asthma in children. A Hospital based Study. The Iraqi postgraduate medical journal 2010; 9(1):6-9.
11. Muhi KA, Sadiq JA, Nabil W, Mahmoud S, Nadia An. Risk factor of Bronchial Asthma in Children. A Hospital based study. *The Iraqi postgraduate medical journal.* 2010; 9(1):6-9.
12. Aws H. Risk factors for the occurrence of childhood asthma. A thesis submitted to Iraqi Broad for Medical Specialization as partial fulfillment of the degree of fellowship of the Iraqi Board of Medical Specialization in Pediatrics 2005.
13. Jihan S. Growth assessment in asthmatic patients and the response to bronchodilators. A thesis submitted to the Iraqi Board for Medical Specialization as partial fulfillment of the degree of fellowship of the Iraqui Board for Medical Specialization in Pediatrics 2001.
14. Mavale-Manuel S, Alexandre F, Duarte N, Albuquerque O, Scheinmann P, Poisson-Salomon AS et al. Risk factors for asthma among children in Maputo (Mozambique). *Allergy.* 2004, 59 (4): 388-93.
15. Global Initiative for Asthma: Pocket guide for asthma management and prevention in children. 2005 http://www.ginasthma.org.
16. Ober C: Perspectives on the past decade of asthma genetics. *J Allergy Clin Immunol.* 2005, 116 (2): 274-8.
17. Joubert BR, Reif DM, Edwards SW, Leiner KA, Hudgens EE, Egeghy P, et al. Evaluation of genetic susceptibility to childhood allergy and asthma in an African American urban population. *BMC Med Genet.* 2011;12: 25.
18. Moffatt MF. Cookson WOCM. Maternal effects in atopic disease. *Clin Exp Allergy.* 1998; 28(Suppl1):56-61.
19. Bottcher MF, Jenmalm MC, Garofalo RP, Bjorksten B. Cytokinesh in breast milk from allergic and nonallergic mothers. *Pediatr Res.* 2000; 47:157-62.
20. Scholtens S, Wijga HA, Brunekreef B, Kerkhof M, Hoekstra OM, Gerritsen J et al. Breast feeding, parental allergy and asthma in children followed for 8 years. The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study. *Thorax.* 2009; 64:604-6-9.
21. Kewalramani A, Bollinger ME. The impact of food allergy on asthma. *J Asthma Allergy.* 2010;3:65–74.
22. Zutavern A, Brockow I, Schaaf B, Berg VA, Diez U, Borke M et al; for the LISA Study Group. Timing of solid food introduction in relation to eczema, asthma, allergic rhinitis, and food and inhalant sensitization at the age of 6 years: results from the prospective birth cohort study LISA. *Pediatrics.* 2008; 121:e44-e52.
23. Greer FR, Sicherer SH, Burks AW. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. American Academy of Pediatrics Committee on Nutrition. Pediatrics 2008; 121:183-91.
24. Soyseth V, Kongerud J, Boe J. Postnatal maternal smoking increases the prevalence of asthma but not of bronchial hyperesponsiveness or atopy in their children. *Chest.* 1995;107:389-394
25. Hjern A, Hedberg A, Haglund B, Rosen M. Does tobacco smoke prevent atopic disorders? A study of two generations of Swedish residents. *Clin Exp Allergy.* 2001; 31:908-14.
26. Basagana X, Sunyer J, Zock JP,Kogevinas M, Urrutia I, Maldonado Ja et al. Incidence of asthma and its determinants among adults in Spain. *Am J Respir Crit Care Med.* 2001; 164:1133-7.
27. Melson T, Brinch L, Hessen Jo, Schei MA, Kolstrup N, Jacobsen BK et al. Asthma and indoor environment in Nepal. *Thorax.* 2001; 56:477-81.
28. Kerkhof M, Wijga AH, Brunekreef B. Effects of pets on asthma development up to 8 years of age: the PIAMA study. *Allergy.* 2009; 64:1202-8.
29. Porsbjerg C, von Linstow ML, Ulrik CS, NepperChristensen S, Backer V. Risk factors for onset of asthma: a 12-year prospective follow-up study. *Chest.* 2006; 129: 309-16.
30. Kabir L, Rahman F, Hassan MQ, Ahmed F. Asthma, atopic eczema and allergic rhino-conjunctivitis in school children of Dhaka, Bangladesh using ISAAC protocol. Dhaka: Institute of Child and Mother Health; 2001.
31. Gent JF, Belanger K, Triche EW, Bracken MB, Beckett WS, Leaderer BP. Association of pediatric asthma severity with exposure to common household dust allergens. *Environ Res.* 2009; 109:768-74.
32. Mohamed N, Ng'ang'a L, Odhiambo J, Nyamwaya J, Menzies R. Home environment and asthma in Kenyan school children: a case control study. *Thorax.* 1995;50:74-8.
33. Dijkstra L, Houthuijs D, Brunekreef B, Akkerman I, Boleij J. Respiratory health effects of the indoor environment in a population of Dutch children. *Am Rev Respir Dis.* 1990; 142:1172.
34. Waegemaekers M, Wageningen N Van, Brunekreef B, Boleij JSM. Respiratory symptoms in damp homes. *Allergy.* 1989; 44:192-8.
35. Fergusson DM, Crane J, Beasley R, Horwood LJ. Peri-natal factors and atopic disease in childhood. *Clin Exp Allergy.* 1997; 27:1394-1401.
36. Manandhar K, Bajracharya BL, Dhakal S, Shrestha M. Morbidity pattern of children with asthma: A prospective study. *Kathmandu Univ Med J.* 2006; 4(15):324-8.
37. Doull I, Williams A, Freezer N, Holgate TS. Descriptive study of cough, wheeze and school absence in childhood. *Thorax.* 1996; 51:630-1.