

BIOMARKERS

Fractional Exhaled Nitric Oxide in Relation to Asthma, Allergic Rhinitis, and Atopic Dermatitis in Chinese Children

FENG XU, M.D.,¹ ZHIJUN ZOU, B.E.,² SHUXIAN YAN, M.D.,¹ FEI LI, M.D.,¹ HAIDONG KAN, PH.D.,³
DAN NORBACK, PH.D.,⁴ GUNILLA WIESLANDER, PH.D.,⁴ JINHUA XU, PH.D.,¹ AND ZHUOHUI ZHAO, PH.D.^{3,*}

¹Department of Dermatology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, PR China.

²Department of Building Environment and Equipment Engineering, School of Environment and Architecture, University of Shanghai for Science and Technology, Shanghai, PR China

³Department of Environmental Health, School of Public Health, Key Laboratory of Public Health Safety, Ministry of Education, Fudan University, Shanghai, PR China.

⁴Department of Occupational and Environmental Medicine, University Hospital, Uppsala University, Uppsala, Sweden.

Objective. Fractional exhaled nitric oxide (FeNO) is a non-invasive biomarker of airway inflammation. Our aim was to analyze the interrelationship and differentiate the predicting effects of asthma, allergic rhinitis (AR), and atopic dermatitis (AD) on the FeNO levels in children from mainland China. **Methods.** A case-control study with age- and gender matched 1:1 was designed based on a larger cross-sectional survey on asthma, AR, and AD in Shanghai. A self-administered questionnaire was used to collect information on children's health information. Children with positive reports on physician-diagnosed asthma and/or AR and/or AD were recruited as cases, and children with no report of any of the diseases were designated as controls. The FeNO measurement was performed online, using the NIOX MINO[®] instrument (Aerocrine AB, Solna, Sweden) at 50 ml/min. **Results.** A total of 130 subjects (65 cases and 65 controls, average age = 10 years) were recruited in this study. The average FeNO level was significantly higher in the cases (29.8 ± 1.9 ppb) than that in the controls (13.3 ± 1.7 ppb) ($p < .001$). Using multiple linear regression analysis controlling for confounding factors, including parental asthma/allergic diseases and home exposure, asthma ($\beta = 0.330$, $p < .001$) and AR ($\beta = 0.157$, $p = .006$) showed significant predicting effects for high FeNO levels, whereas AD was not related to the FeNO levels. **Conclusions.** Both asthma and AR could independently increase the FeNO levels in Chinese schoolchildren. Other diseases besides asthma should be considered when applying FeNO as a screening tool for asthma in Chinese children.

Keywords airway inflammation, Chinese, fractional exhaled nitric oxide

INTRODUCTION

There is still an increasing prevalence of asthma in children in the mainland China, and among other cities Shanghai ranked the highest in the prevalence of physician-diagnosed asthma (1). A key characteristic in the pathogenesis of asthma is chronic airway inflammation (2). Fractional exhaled nitric oxide (FeNO) has been shown as a non-invasive surrogate marker of airway inflammation (3, 4). An appropriate application of FeNO measurements is expected to help identify children with or at risk for developing asthma; this would be beneficial in improving the control of asthma in clinics and the community.

FeNO measurements, however, need to be interpreted with caution in relation to childhood asthma, from several points of view. Determinant factors that contribute to FeNO levels have been widely investigated in western populations, including disease-related factors, such as asthma, allergic diseases, cystic fibrosis, primary ciliary

dyskinesia, and so on (5–8), and non-disease-related factors including age, gender, height, tobacco smoking, and so on (9–11). Asthma, as the most directly disease-related factor, has been the main field of interest. In the case of equal levels of positive skin prick tests, asthmatic children had higher FeNO than non-asthmatic ones (7). Atopy or allergic diseases [such as allergic rhinitis (AR) or atopic dermatitis (AD)] have been reported as potential factors confounding the relationship between FeNO and asthma (7, 12, 13). Atopic asthmatics had higher FeNO levels than non-atopic asthmatics, and no difference was detected between non-atopic asthmatics and non-asthmatics, whether atopic or not (5). Other studies concluded that AR should be taken into consideration in the evaluation of FeNO (7), and higher FeNO levels were found in AR subjects without asthmatic symptoms (14). Moreover, there were studies stating that the asthma and AD group recorded significantly higher FeNO levels than the asthma-only group (13). High FeNO levels in the AD subjects indicated the presence of potential airway inflammation, which could be a risk factor for developing AR and asthma later in life based on the concept of atopic march (15). However, there were also studies demonstrating that atopy and airway inflammation were separate dimensions in the assessment of childhood asthma (16).

*Corresponding author: Zhuohui Zhao, Ph.D., Department of Environmental Health, School of Public Health, Key Laboratory of Public Health Safety, Ministry of Education, Fudan University, Shanghai 200032, PR China; Tel: 00 86 21 54237343; Fax: 00 86 21 54237343; E-mail: zhzhao@fudan.edu.cn

Until now, there have been no publications on the interrelationship of asthma and allergic diseases (including AR and AD) in children from a community population in mainland China. In this study, a case-control study was designed based on a large cross-sectional survey on children's asthma, AR, and AD in Shanghai. Our hypothesis was that asthma and allergic disease including AR and AD might all be related to FeNO levels.

METHODS

Study Population

Children aged 9–11 years ($n = 579$, equivalent to 3rd–5th grade) in one random primary school were recruited as our potential participating subjects in this study. They were distributed in six classes in three grades. The schoolmaster was contacted and agreed to participate. Based on the questionnaire survey in the large cross-sectional study, there were a total of 145 subjects (25%, out of 579) giving positive reports on physician-diagnosed asthma ($n = 75$), and/or AR ($n = 84$), and/or AD ($n = 65$) (including the concomitant diseases in each group). A random 100 children (out of 145; 55 boys and 47 girls) were selected as potential cases and another 150 children (76 boys and 74 girls) as potential controls. Controls were selected among the same age range of children in the same school with no physician-diagnosed conditions (asthma, AR, or AD). Letters were sent to the parents or legal guardians of the children asking whether they agreed to their children taking the non-invasive FeNO test. Finally, 72 potential cases (out of 100; 42 boys plus 30 girls) and 104 potential controls (out of 120; 59 boys and 45 girls), whose parents agreed on the FeNO test (156/250, average 70.4% participating rate), were recruited for the study.

Before the FeNO measurement, a further face-to-face interview was performed applying a small questionnaire on the children's recent respiratory health, medication, and diet, both in the cases and the controls. Among the potential cases, children ($n = 3$) who had positive reports on recent cold, fever, or respiratory infection within 1 month, or current attacks or medication for asthma/AR/AD within 2 weeks ($n = 2$) or intake of food or beverage within 1 h before the FeNO measurement ($n = 1$) (food intake may influence the FeNO levels shortly), were excluded. In the end, there were 66 case children (40 boys and 26 girls) who performed the FeNO tests. Unfortunately, one girl could not complete the FeNO test successfully within the allowed maximum time and was excluded from this study. Thus, 65 cases (40 boys and 25 girls) were finally recruited for this study (32 AD, 38 AR, and 30 asthmatics, irrespective of concomitant diseases). At this time, controls (94 were available after the face-to-face interview, using the same selection principles) were selected and were matched 1:1 with respect to age and gender, and they were all asked to take the FeNO test. If any of the control children failed in the FeNO test ($n = 2$), he/she was replaced by another

child with the same age and gender. Finally, 65 cases and 65 matched controls successfully completed the FeNO tests. This study was approved by the Ethics Committee of Fudan University, Shanghai, PR China.

Questionnaire

In the larger community study, a questionnaire was distributed in classes and collected back by the trained school staff. It was taken home by the children and answered by the parents or legal guardians, with their names signed on the paper.

The questionnaire collected information on AD, AR, asthma symptoms in the children, as well as demographic data, parental asthma/allergic diseases, smoking, home environmental tobacco smoking (home ETS), and home living environment. Children with asthma were selected according to affirmative answers to the question "Have you ever been diagnosed with asthma by a physician in a hospital?" Children with AR were defined as answering affirmatively to "Have you ever been diagnosed with AR by a physician in a hospital?" These questions were cross confirmed by the question at the time of diagnosis. Children with AD were screened using the diagnostic criteria of the UK Working Party (UKWP), which showed a similar diagnostic efficiency to that of the gold standard, with the sensitivity, specificity, and k -value reaching 95.50%, 97.52%, and 0.93, respectively, in the Chinese population (17). The UKWP criteria include itchy skin (or parental report of scratching or rubbing by the child) plus three or more of the following: (1) history of involvement of the skin creases such as folds of elbows, behind the knees, front of ankles, or around the neck (including cheeks in those under 10 years); (2) a personal history of asthma or hay fever (or history of atopic disease in a first degree relative in those under 4 years); (3) a history of generally dry skin in the last year; (4) visible flexural dermatitis (or dermatitis involving the cheeks/forehead and outer limbs in children under 4 years); and (5) onset under the age of 2.

Parental asthma/allergic diseases included physician-diagnosed asthma, AR, or AD in the children's parents. Home ETS was evaluated by current smoking at home by the mother, father, or other family members who live together. Other questions on the home living environment included "Has your mother ever lived in a newly decorated home (the first 6 months after decoration) during pregnancy?" and "Have you ever lived in a newly decorated home (the first 6 months after decoration) since birth?" Other questions included smoking and the self-evaluated social economic status (SES), which were categorized into five levels: low, middle-low, middle, middle-high, and high.

FeNO Test

FeNO tests were performed using the portable NIOX MINO[®] machine (Aerocrine AB, Solna, Sweden). Briefly, pupils were required to sit, rinse their mouths with potable, pure water, and then empty their lungs by thorough expiration. They deeply inhaled the NO-free

air through the disposable filter up to the lung capacity. Finally, they breathed out the air through the filter at an exhalation rate of 50 ± 5 ml/s.

The FeNO value was obtained by one single measurement for each participant. The standard mode for a 10 s exhalation time was used in all the tests. A maximum of five repeated tests, with 10 min rest between each test, were allowed for each child if he/she could not complete the test successfully with one try. No nose clip was used. The sensor in the device was replaced periodically according to the manufacturer's guide. The FeNO measurement was performed in the winter season.

Statistical Analysis

The FeNO values fit with a log-normal distribution; thus the geometric mean (GM) and the geometric standard deviation (GSD) ($GM \pm GSD$) were reported. Comparison of the demographic data and the living environment between cases and controls was run by Analysis of Variance (ANOVA) for continuous variables, and the χ^2 -test for binomial variables. Parametric paired *t*-test was applied in examining the difference in FeNO levels (log-transformed) between cases and controls. Within cases, independent sample *t*-test was applied for comparing the FeNO levels between groups stratified by different (or a combination of) diseases. Multivariate linear regression was applied to evaluate the predictive effects of AD, AR, and asthma on log-transformed FeNO values, combining cases and controls, and the anthropometric and living environment factors were analyzed separately in cases and controls. All tests were two-sided and the 5% level was applied to establish statistical significance. The SPSS 11.5 package was used for analysis (Spss Inc, Chicago, IL, U.S.A.).

RESULTS

FeNO Levels, Anthropometric Parameters, and Living Environment

The average FeNO level ($GM \pm GSD$) in the cases (29.8 ± 1.9 ppb) was significantly higher than that in the controls (13.3 ± 1.7 ppb) ($p < .001$) (Table 1). The average age of the subjects was 10.0 ± 0.5 (range 9–11) years, and girls accounted for 38.5%. No difference was found for body weight and body height between the cases and controls, as well as the positive reports on home ETS (average 74.6%). None of the recruited children were smokers. In comparison, the prevalence of the parents' asthma/allergic diseases ($p < .001$), exposure to new decoration by the mother during pregnancy ($p = .038$), and in children since birth ($p = .002$) was significantly higher in the cases than that in controls. These significant factors were controlled in the later multivariate linear regression on FeNO levels combining cases and controls.

In the cases separately, none of the above anthropometric and living environment factors was related to the FeNO level by multivariate linear regression; and in controls, body height was significantly ($p = 0.012$)

TABLE 1.—FeNO, anthropometric measurements, parental asthma/allergic diseases, and living environment in cases and controls.

	Cases (<i>n</i> = 65)	Controls (<i>n</i> = 65)	<i>P</i> -value
FeNO ($GM \pm GSD$; ppb)	29.8 ± 1.9	13.3 ± 1.7	<.001
Body height (arithmetic mean $\pm$ SD; cm)	147.6 ± 7.8	146.3 ± 7.6	.349
Body weight (arithmetic mean $\pm$ SD; kg)	42.5 ± 9.3	39.8 ± 10.9	.152
Parental asthma/allergic diseases (%)	53.8	6.2	.000
Mother's exposure to new decoration during pregnancy ^a (%)	15.6	4.6	.038
Children's exposure to new decoration since birth ^b (%)	35.4	12.3	.002
Home ETS ^c (%)	73.8	76.9	.684
SES (middle or higher level) ^d	50.9	49.1	.640

Notes: GM, geometric mean; GSD, geometric standard deviation; IQR, interquartile range; SES, social economic status; ETS, environmental tobacco smoking.

^aRefers to mother's ever living in the newly decorated home (the first 6 months after decoration) during pregnancy.

^bRefers to children ever living in the newly decorated home (the first 6 months after decoration) since birth.

^cHome ETS was defined as current smoking by father, mother, or any other persons living with the family.

^dSES refers to self-reported family economic level (categorized into five levels: low, middle-low, middle, middle-high, and high).

positively associated with FeNO level with a β coefficient (95% CI (confidence interval)) of 0.014 (0.003–0.025).

FeNO Levels, AD, AR, and Asthma

Within the cases, we defined a total of seven groups of children stratified by the different diseases *only*, or a combination of diseases (Figure 1): AD *only* (with no AR, no asthma) ($n = 12$); AR *only* ($n = 13$); asthma *only* ($n = 11$); AD *and* AR (with no asthma) ($n = 8$); AD *and* asthma ($n = 4$); AR *and* asthma ($n = 11$); and AD *and* AR *and* asthma ($n = 6$). All had higher FeNO levels than the paired controls, except in the AD *only* group ($p = .157$), and the AD *and* AR groups ($p = .123$).

If stratified by physician-diagnosed AD ($n = 30$, $p = .001$), AR ($n = 38$, $p < .001$), or asthma ($n = 32$, $p < .001$), irrespective of the other concomitant diseases in each subgroup, children had higher FeNO levels in each group of cases than the paired controls (Table 2). Both the AD and AR groups were further divided into "with or without asthma" and the asthma group was further divided into "with AD and/or AR" and "without AD and AR". All the divided subgroups had significantly higher FeNO levels than the paired controls, except in the AD group without asthma ($n = 20$), where the statistical significance ($p = .074$) disappeared.

In the AD and AR groups, children with asthma in the AD group ($GM \pm GSD$, 45.3 ± 1.3 ppb vs. 20.9 ± 1.9 ppb) and in the AR group (40.1 ± 1.7 ppb vs. 25.8 ± 2.1 ppb) had higher FeNO levels than the children without asthma (Table 2), reaching statistical significance ($p = .001$ and $p = .05$, respectively). In the asthma

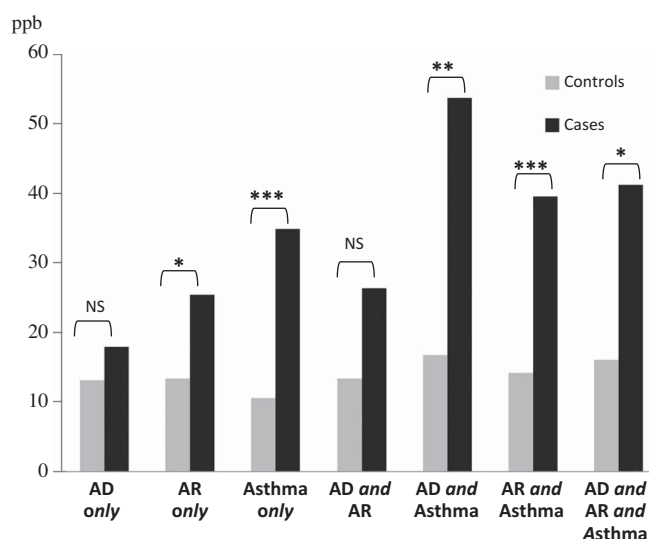


FIGURE 1.—FeNO levels [geometric mean (GM), ppb] in different (or combination of) diseases in cases and controls.

Notes: NS, no significance.

* $p < .05$; ** $p < .01$; *** $p < .001$.

TABLE 2.—Average FeNO levels (GM $\pm$ GSD, ppb) in cases and controls stratified by different diseases.

	Number of pairs (%)	FeNO level (ppb)		P-value (cases–controls comparison)
		Cases	Controls	
AD ^a	30 (46.2)	27.1 $\pm$ 1.9	14.1 $\pm$ 2.0	0.001
With asthma	10	45.8 $\pm$ 1.3	16.3 $\pm$ 2.1	<.001
Without asthma	20	20.9 $\pm$ 1.9	13.2 $\pm$ 1.9	.074
		$(p = .001)^*$		
AR ^a	38 (58.5)	31.4 $\pm$ 2.0	13.9 $\pm$ 1.7	<.001
With asthma	17	40.1 $\pm$ 1.7	14.8 $\pm$ 1.9	<.001
Without asthma	21	25.8 $\pm$ 2.1	13.3 $\pm$ 1.6	.008
		$(p = .05)^*$		
Asthma ^a	32 (49.2)	39.7 $\pm$ 1.6	13.3 $\pm$ 1.7	<.001
With AD and/or AR	21	42.4 $\pm$ 1.6	15.1 $\pm$ 1.8	<.001
Without AD and AR	11	34.9 $\pm$ 1.7	10.5 $\pm$ 1.4	<.001
		$(p = .29)^*$		

Notes: ^aIncluding the possible combination of other types of diseases.

* $p = .001$ and $p = .05$ refer to the comparisons between with and without asthma in groups of AD and AR, respectively; $p = .29$ refers to the comparison between groups with AD and/or AR and without AD and AR in the asthma group.

group, children with AD and/or AR (42.4 ± 1.6 ppb) had a higher FeNO level than those without AD and AR (34.9 ± 1.7 ppb), but did not reach statistical significance ($p = .29$).

Multivariate Regression on FeNO Levels

To estimate and differentiate the predictive power of AD, AR, and asthma on FeNO levels in subjects combining cases and controls, a multivariate linear regression model was applied, controlling for the unbalanced distributed factors, including parental asthma/allergic diseases, mother's exposure to new decoration during pregnancy, and children's exposure to new decoration since birth. The results showed that physician-diagnosed asthma

TABLE 3.—Multivariate linear regression for FeNO levels combining cases and controls ($n = 130$).

	β (95% CI)	P-value
AD	0.096 (−0.016–0.207)	.091
AR	0.157 (0.046–0.268)	.006
Asthma	0.330 (0.219–0.441)	<.001
Parental asthma/allergic diseases	−0.01 (−0.127–0.107)	.863
Mother's exposure to shorter than half a year new decoration	0.084 (−0.060–0.227)	.251
Children's exposure to shorter than half a year new decoration	−0.074 (−0.182–0.034)	.179

Notes: The FeNO level was log-transformed, and the model controlled for the unbalanced distribution of parental and living environmental factors between cases and controls including: the parental asthma/allergic diseases, mother's exposure to new decoration during pregnancy, and children's exposure to new decoration since birth. AD, atopic dermatitis; AR, allergic rhinitis; CI, confidence interval.

($p < .001$) and physician-diagnosed AR ($p = .006$) were independent significant predictors for FeNO levels (Table 3). Correlation analyses were performed in the cases and showed that there was no significant correlation between asthma and AR (Pearson's correlation coefficient, -0.107 , $p = .398$).

DISCUSSION

In this study, FeNO levels were significantly higher in the cases than in the healthy controls. This difference was predicted mainly by asthma and AR, independently, while AD seemed not to be related with FeNO levels. The GM of FeNO in normal healthy children in our study in Shanghai was 13.3 ± 1.7 ppb, and within the FeNO range of 10.72–13.80 ppb measured by Li et al. (18) in the healthy children of Beijing (11–18 years of age). Until now, there are no much data on FeNO levels in the normal Chinese population published in international scientific journals (19). Our study is also unique in that we have taken three normal allergic diseases into consideration simultaneously in the investigation of the interrelationship effects on FeNO levels.

Besides asthma, AR was shown as an independent factor in increasing the FeNO levels in our study. In this study, AR and asthma were not correlated with each other by statistical analysis ($p = .398$) [there were 11 (19.3%) cases with concomitant asthma and AR out of 57 cases with either asthma or AR], indicating that we could study them independently by multiple regression models. Clinically, however, AR and asthma are closely related diseases (united airway diseases) (20, 21). As a marker of airway inflammation, FeNO is predominantly indicative of eosinophilic airway inflammation. Some studies have shown direct evidence for the presence of bronchial inflammation indicated by eosinophil counts in induced sputum in non-asthmatic subjects with AR (22), in bronchoalveolar lavage fluid (23), and bronchial biopsy specimens (24). Thus, AR

per se exhibiting high FeNO levels, independent of other diseases, is supported by clinical pathophysiological tests. Our study provides further evidence in Chinese children indicating that asthma and AR are the upper and lower respiratory tract manifestations in the united airway diseases characterized by inflammation of the respiratory tract (21). This concept has not been substantially emphasized in clinical diagnoses in China. Thus, another potential reason for the high FeNO in AR cases could be underdiagnosed asthma in the AR patients.

In line with the literature, we found that asthmatic children had higher FeNO levels than non-asthmatics. We used physician-diagnosed asthma in the questionnaire as the definition of “asthma” in this study. Currently, the clinical standard of asthma diagnosis in mainland China is based mainly on asthma-related symptoms, or it is combined with the bronchial hyper-responsiveness (BHR) test or the lung function test (25). Evaluation of the level of airway inflammation is almost never applied. In this study, none of the children used any asthma medication within 2 weeks leading up to the FeNO test. The presence of higher FeNO levels indicated the existence of airway inflammation, even in a relatively “healthy” status. Actually, there is a relatively lower prevalence of chronic steroid application in children with asthma in China, and a survey performed in a large children’s hospital showed that only 43.3% of parents reported adherence to prescribed anti-asthma medications for their children (26). High airway inflammation could be a risk factor for subsequent asthma relapse (27); this indicated that it is important to control airway inflammation in the asthmatic patients even without clinical symptoms.

We did not find that physician-diagnosed AD played an important role in predicting the FeNO levels when comparing cases and controls. However, the higher FeNO levels in the AD *only* group (with no asthma and no AR) were detected despite not reaching statistical significance. Whether these children develop AR or asthma later in life is of great interest, based on the concept of the atopic march (15), and another independent study on a larger subject sample is needed.

We do not believe our results were biased with respect to study design or data collection. This case-control study was designed by 1:1 matching of age and gender. The matching was successful, with a balanced distribution of age and gender between cases and controls. The distribution of parental asthma/allergic diseases, however, was not equal. Other environmental exposures, such as the exposure of the mother to new decoration during pregnancy, and children’s exposure to new decoration since birth were also higher in the cases. All these factors were controlled in the multivariate regression, since related parental diseases may reflect the subjects’ genetic predisposition, and the potential indoor exposure to decoration-related substances has been found to be related to high FeNO levels (28, 29). In healthy controls, we found that height is a significant factor predicting higher FeNO levels.

However, this does not influence our comparison of FeNO levels, since there was no difference in height between the cases and controls. The relatively lower percentage of girls whose parents agreed to the FeNO measurement was not expected. We speculated that girls were more susceptible to be protected by parents confronted with relatively new tests or measurements in schools. However, this would not influence our comparisons, since gender was matched in the cases and controls.

CONCLUSIONS

Asthma and AR were two independent factors predicting the high FeNO levels, whereas AD seemed not to be related to FeNO. This observation suggests that when taking FeNO measurements as a screening tool for asthmatic children in communities, other diseases, for example, AR, need to be considered simultaneously. This is the first contemporary study from mainland China investigating FeNO levels in relation to asthma, AR, and AD. It extends our understanding in this area and provides a valuable platform for future study.

ACKNOWLEDGMENT

We are indebted to the school principals, schoolteachers, and participating subjects in this study, as well as the physicians in the community.

DECLARATION OF INTEREST

This work was supported by the National Natural Science Foundation of China (NSFC no. 30800894), 3-Year Public Health Construction Fund for Excellent Young Scientists by Shanghai Municipal Health Bureau, Scientific Research Foundation (SRF) for the Returned Overseas Chinese Scholars (ROCS), State Education Ministry (SEM), and supported by the Leading Academic Discipline Project of Shanghai Municipal Education Commission, project number: J50502.

REFERENCES

1. Chen YZ. Comparative analysis of the state of asthma prevalence in children from two nation-wide surveys in 1990 and 2000 year (in Chinese). *Zhonghua Jie He He Hu Xi Za Zhi* 2004; 27:112–116.
2. National Asthma Education and Prevention Program. Guidelines for the diagnosis and management of asthma: Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health. 1997. Available at: <http://www.nhlbi.nih.gov>. Accessed on August 8th, 2011
3. Barnes PJ, Liew FY. Nitric oxide and asthmatic inflammation. *Immunol Today* 1995; 16:128–130.
4. Saito J, Inoue K, Sugawara A, Yoshikawa M, Watanabe K, Ishida T, Ohtsuka Y, Munakata M. Exhaled nitric oxide as a marker of airway inflammation for an epidemiologic study in schoolchildren. *J Allergy Clin Immunol* 2004; 114:512–516.
5. Frank TL, Adisesh A, Pickering AC, Morrison JF, Wright T, Francis H, Fletcher A, Frank PI, Hannaford P. Relationship between exhaled

- nitric oxide and childhood asthma. *Am J Respir Crit Care Med* 1998; 158:1032–1036.
6. Franklin PJ, Turner SW, Le Souef PN, Stick SM. Exhaled nitric oxide and asthma: complex interactions between atopy, airway responsiveness, and symptoms in a community population of children. *Thorax* 2003; 58:1048–1052.
 7. Jouaville LF, Annesi-Maesano I, Nguyen LT, Bocage AS, Bedu M, Caillaud D. Interrelationships among asthma, atopy, rhinitis and exhaled nitric oxide in a population-based sample of children. *Clin Exp Allergy* 2003; 33:1506–1511.
 8. Malinovschi A, Janson C, Hogman M, Rolla G, Toren K, Norback D, Olin AC. Both allergic and nonallergic asthma are associated with increased FE(NO) levels, but only in never-smokers. *Allergy* 2009; 64:55–61.
 9. Olin AC, Rosengren A, Thelle DS, Lissner L, Bake B, Toren K. Height, age, and atopy are associated with fraction of exhaled nitric oxide in a large adult general population sample. *Chest* 2006; 130:1319–1325.
 10. Travers J, Marsh S, Aldington S, Williams M, Shirtcliffe P, Pritchard A, Weatherall M, Beasley R. Reference ranges for exhaled nitric oxide derived from a random community survey of adults. *Am J Respir Crit Care Med* 2007; 176:238–242.
 11. Wong GW, Liu EK, Leung TF, Yung E, Ko FW, Hui DS, Fok TF, Lai CK. High levels and gender difference of exhaled nitric oxide in Chinese schoolchildren. *Clin Exp Allergy* 2005; 35:889–893.
 12. Pijnenburg MW, De Jongste JC. Exhaled nitric oxide in childhood asthma: a review. *Clin Exp Allergy* 2008; 38:246–259.
 13. Welsh L, Lercher P, Horak E. Exhaled nitric oxide: interactions between asthma, hay fever, and atopic dermatitis in school children. *Pediatr Pulmonol* 2007; 42:693–698.
 14. Cardinale F, de Benedictis FM, Muggeo V, Giordano P, Loffredo MS, Iacoviello G, Armenio L. Exhaled nitric oxide, total serum IgE and allergic sensitization in childhood asthma and allergic rhinitis. *Pediatr Allergy Immunol* 2005; 16:236–242.
 15. Zheng T, Yu J, Oh MH, Zhu Z. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *Allergy Asthma Immunol Res* 2011; 3:67–73.
 16. Leung TF, Wong GW, Ko FW, Lam CW, Fok TF. Clinical and atopic parameters and airway inflammatory markers in childhood asthma: a factor analysis. *Thorax* 2005; 60:822–826.
 17. Gu H, Chen XS, Chen K, Yan Y, Jing H, Chen XQ, Shao CG, Ye GY. Evaluation of diagnostic criteria for atopic dermatitis: validity of the criteria of Williams et al. in a hospital-based setting. *Br J Dermatol* 2001; 145:428–433.
 18. Li S, Lou XS, Ma Y, Han SL, Liu CH, Chen YZ. Exhaled nitric oxide levels in school children of Beijing. *Zhonghua Er Ke Za Zhi* 2010; 48:148–152.
 19. Hon KL, Leung TF, Kam WY, Lam MC, Wong KY, Yung E, Fok TF. Exhaled nitric oxide levels are not correlated with eczema severity in Chinese children with atopic dermatitis. *J Asthma* 2006; 43:417–419.
 20. Bousquet J, Khaltav N, Cruz AA, Denburg J, Fokkens WJ, Togias A, Zuberbier T, Baena-Cagnani CE, Canonica GW, van Weel C, Agache I, Ait-Khaled N, Bachert C, Blaiss MS, Bonini S, Boulet LP, Bousquet PJ, Camargos P, Carlsen KH, Chen Y, Custovic A, Dahl R, Demoly P, Douagui H, Durham SR, van Wijk RG, Kalayci O, Kaliner MA, Kim YY, Kowalski ML, Kuna P, Le LT, Lemiere C, Li J, Lockey RF, Mavale-Manuel S, Meltzer EO, Mohammad Y, Mullol J, Naclerio R, O'Hehir RE, Ohta K, Ouedraogo S, Palkonen S, Papadopoulos N, Passalacqua G, Pawankar R, Popov TA, Rabe KF, Rosado-Pinto J, Scadding GK, Simons FE, Toskala E, Valovirta E, van Cauwenberge P, Wang DY, Wickman M, Yawn BP, Yorgancioglu A, Yusuf OM, Zar H, Annesi-Maesano I, Bateman ED, Ben Kheder A, Boakye DA, Bouchard J, Burney P, Busse WW, Chan-Yeung M, Chavannes NH, Chuchalin A, Dolen WK, Emuzyte R, Grouse L, Humbert M, Jackson C, Johnston SL, Keith PK, Kemp JP, Klossek JM, Larenas-Linnemann D, Lipworth B, Malo JL, Marshall GD, Naspitz C, Nekam K, Niggemann B, Nizankowska-Mogilnicka E, Okamoto Y, Orru MP, Potter P, Price D, Stoloff SW, Vandenplas O, Viegi G, Williams D. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008; 63:8–160.
 21. Rimmer J, Ruhno JW. 6: Rhinitis and asthma: united airway disease. *Med J Aust* 2006; 185:565–571.
 22. Gutierrez V, Prieto L, Torres V, Morales C, Gonzalez E. Peak flow variability and sputum eosinophilia in allergic rhinitis. *Ann Allergy Asthma Immunol* 1998; 81:143–150.
 23. Sedgwick JB, Calhoun WJ, Gleich GJ, Kita H, Abrams JS, Schwartz LB, Volovitz B, Ben-Yaakov M, Busse WW. Immediate and late airway response of allergic rhinitis patients to segmental antigen challenge. Characterization of eosinophil and mast cell mediators. *Am Rev Respir Dis* 1991; 144:1274–1281.
 24. Djukanovic R, Lai CK, Wilson JW, Britten KM, Wilson SJ, Roche WR, Howarth PH, Holgate ST. Bronchial mucosal manifestations of atopy: a comparison of markers of inflammation between atopic asthmatics, atopic nonasthmatics and healthy controls. *Eur Respir J*. 1992; 5: 538–544.
 25. The Subspecialty Group of Respiratory Diseases TSoPCMA, The Editorial Board CJoP. Diagnosis and prevention guideline for bronchial asthma in childhood. *Zhonghua Er Ke Za Zhi* 2008; 46:745–753.
 26. Zhao X, Furber S, Bauman A. Asthma knowledge and medication compliance among parents of asthmatic children in Nanjing, China. *J Asthma* 2002; 39:743–747.
 27. van Den Toorn LM, Prins JB, Overbeek SE, Hoogsteden HC, de Jongste JC. Adolescents in clinical remission of atopic asthma have elevated exhaled nitric oxide levels and bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 2000; 162:953–959.
 28. Franklin P, Dingle P, Stick S. Raised exhaled nitric oxide in healthy children is associated with domestic formaldehyde levels. *Am J Respir Crit Care Med* 2000; 161:1757–1759.
 29. Flamant-Hulin M, Caillaud D, Sacco P, Penard-Morand C, Annesi-Maesano I. Air pollution and increased levels of fractional exhaled nitric oxide in children with no history of airway damage. *J Toxicol Environ Health A* 2010; 73:272–283.

Copyright of Journal of Asthma is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.