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## FeNO level and allergy status among school children in Terengganu, Malaysia

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### ABSTRACT

**Background:** Almost one third of the world population suffers from allergic conditions. Respiratory symptoms are common in Malaysian children but there are few studies on fractional exhaled nitric oxide (FeNO), inclusive of field clinical test for asthma among children in Malaysia. The aim was to provide insight on factors related to level of FeNO among students in Terengganu, Malaysia.

**Methods:** In total, 487 randomly selected students from eight secondary schools participated (13–14 years old). A Standardized questionnaire was used to obtain information on doctors' diagnosed asthma, current asthma and respiratory symptoms. FeNO measurement and skin prick test (SPT to common allergen) were conducted.

**Results:** The geometric mean FeNO was 16.7 ppb. Totally, 38.4% of students had elevated FeNO level (>20 ppb) and 40.3% had had positive SPT to house dust mites allergens (HDM), *Dermatophagoides pteronyssinus* (Der p 1), *Dermatophagoides farinae* (Der f 1) or *Felis domesticus* (cat). Male gender, height, parental history of allergy, self-reported allergy, and atopy were associated with FeNO. In particular, a combination of sensitization to HDM or cat and elevated FeNO were associated with doctor-diagnosed asthma and self-reported allergy to food, pollen and cat.

**Conclusion:** Asthma, respiratory symptoms and sensitization to HDM and cat are common among students and presence of elevated FeNO levels indicate ongoing airway inflammation.

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### KEYWORDS

Students; FeNO; asthma; allergy; Malaysia

## Introduction

Allergic respiratory conditions are a major public health issue worldwide. The World Health Organization (WHO) estimates that asthma alone is accountable for morbidity among 300 million people and for 250,000 lives lost annually (1). Almost one third of the world population suffers from allergic conditions (2). Asthma and allergies are increasing globally, especially in Asia and middle income countries (3,4). Poor asthma control is associated with impaired quality of life, absenteeism from the workplace, and substantial financial loss (5). Existing standard methods and protocols only demonstrate a fraction of the severity and complexity of the disease that affects children and young adults (6). Different methodologies and lack of precise definitions make reliable international comparisons difficult (2,7). Standardized questionnaires related to symptoms of asthma, allergic rhinoconjunctivitis, and eczema are

important to detect asthma associated hypersensitivity (8). However, allergy testing is critical in providing meaningful information for a continuous therapeutic plan of interventions for atopic individuals. Skin-prick testing (SPT) is usually the preferred choice in the diagnostic work-up for allergies (9). Fractional Exhaled Nitric Oxide (FeNO) is a convenient clinical test to identify subjects with asthma. Factors that may affect FeNO levels include age, sex, atopy, height, current smoking, and diet (10). The American Thoracic Society (ATS) recommended that low FeNO less than 20 ppb in children should be used to indicate that eosinophilic inflammation and responsiveness to corticosteroids are less likely; and FeNO greater than 35 ppb in children who are symptomatic should be used to indicate that eosinophilic inflammation and responsiveness to corticosteroids are likely. FeNO values between 20 and 35 ppb in children should be interpreted cautiously and with reference to the

clinical context (11). Controlling disease progress based on this information can help clinicians to calibrate the individual needs of steroid medications (12). FeNO and SPT can be conducted in a population based study because they are reliable, safe, convenient, inexpensive, minimally invasive, and provide real time results.

Studies done prior were on more affluent state shows high prevalence of elevated FeNO (45%) among Malaysian Children (13) but most studies are hospital based, which tend to overestimate the level of control and do not account for coverage of general population (14). Constant high temperature and high humidity throughout the year in countries like Malaysia, Singapore, and Thailand provide an ideal environment for the accumulation of indoor and outdoor allergens that are highly related to asthma prevalence. To date, most studies from Asia are from affluent countries sharing comparable socioeconomic indices as Western Europe, which may not accurately reflect the whole region (15). Based on the International Study of Asthma and Allergies in Childhood (ISAAC III), overall asthma prevalence in Asian countries can vary between 4.1% and 32.1% depending on the location and subpopulations. In less than 5 years, asthma prevalence in Southeast Asia increased from 9% to 13% among children aged 13 to 14 years old (16).

Asthma exacerbations are higher among individuals with preexisting allergic conditions. Sensitization to aeroallergens is relatively common in Malaysian children (13). Data on FeNO level can be useful in investigating asthma and allergy in a tropical country. Limited studies have been reported with regard to school condition in the East Coast of Malaysia (17). To our knowledge no previous publication from Malaysia on association between FeNO and Skin Prick Test done outside hospital setting been reported. The aim was to study associations between FeNO and atopic sensitization among Malaysia less affluent cohorts, to be more reflective of the region as a whole.

## Methods and material

### Study population

We randomly selected four classes from each of eight purposely selected secondary schools in Terengganu, Malaysia. Schools selection was based on enrollment and administrative classification of the school (urban or rural). We invited 20 randomly selected students from form two classes for a total of 640 students, 13 to 14 years of age. Students with a prior history of

severe pulmonary disease other than asthma, acute asthma symptoms, very recent respiratory illness (e.g. cold, flu), or sinusitis for the last 3 days were excluded from this study. Students brought the questionnaire home to answer it together with their parents or guardians. Data collections were performed in October 2012 until February 2013.

### Assessment of health data

We utilized a self-administered questionnaire, identical to those used in previous school studies (13,18). It included questions on doctor-diagnosed asthma, reported allergies, current asthma, and respiratory symptoms obtained from the large international ISAAC study (16), the European Respiratory Health Survey (ECRHS) (19) and previous Swedish school studies (18). One set of questions asked about asthma, including doctor diagnosed asthma, current asthma medication use, and asthma attacks during the past 12 months. Another set of questions asked about airway symptoms related to asthma during the past 12 months, without using the phrase "asthma." These symptoms included: 1) wheezing or whistling in the chest the last 12 months, 2) at least one daytime attack of shortness of breath during exercise or while resting during the last 12 months (2 questions), 3) at least one nighttime awakening with attacks of breathlessness or tightness in the chest during the last 12 months (13,18). The question on wheeze during the last 12 months is identical in the ECRHS (19) and the ISAAC study (16). Moreover, the questionnaire contained questions on current smoking, parental allergy or asthma and self-reported allergy. Self-reported allergies were based on history of symptoms experience by subject. Finally, there was one question on respiratory infections during the last 3 months. Completed questionnaires were collected the same week as the physical and skin prick test were done. Trained research assistants went through the questionnaires during a face-to-face interview with the student to clarify any uncertainty in the questions.

### Skin prick test

Purified allergen extract purchased from ALK-Abello, Hørsholm, Denmark were use. Each bottle contained specific allergen material for *Dermatophagoides pteronyssinus* (Der p 1), *Dermatophagoides farinae* (Der f 1), and *Felis domesticus* (Cat) in 10 HEP (Histamine Equivalent in Prick testing) concentration dissolved in equal parts of buffered saline and sterile glycerol 2 mL

vial. A histamine solution (10 mg/mL) and a saline solution were used as controls. SPT were performed on the volar side of the forearm. Each allergen solution and the controls were applied using a droplets nozzle on clean and dry skin in comparable and appropriate distance from each other. Superficial layer of the skin was pierced with a disposable ALK skin lancet, perpendicular to the skin through the droplet and held for 1 s. A new and sterile lancet was used for each allergen and control solution. Positive control was applied last and all droplets were wiped off with a tissue in rolling motion to ensure no allergen solutions were mixed. Each area was observed by measuring the reaction of allergen extract after 15 min beginning with the positive control. A positive reaction included a pale wheal (edema) with a red flare (erythema). Longest and orthogonal diameters of the wheal were measured and those with a mean wheal of at least 3 mm were considered positive.

### **FeNO measurement**

FeNO measurement was performed by the portable NIOX MINO machine (Aerocrine AB, Solna, Sweden) according to ATS/ERS guidelines (20). All measurements were performed between 9:00 a.m. and 4:00 p.m. Before measurement, participants were advised not to consume food, 3 h prior and not to perform strenuous exercise, one hour prior. Before FeNO session began, each steps required were explained to the student using verbal instruction and visual aid. Subject rested in the sitting position for at least 10 min before the measurement started. A new disposable mouthpiece was used by each subject. Briefly, students were required to empty their lungs by complete expiration. Subjects were instructed to inhale through the machine to ensure gas scrubber filtered away all ambient NO. Exhalation in a continuous manner at the pressure of 10 to 20 cm H<sub>2</sub>O was used to prevent contamination of exhaled NO with NO of nasal origin (21). FeNO was calculated during the last 2 s of the exhalation. Measurements were repeated, recorded, and taken as a calculated mean of two correct exhalations. Readings that did not deviate more than 2.5 ppb or 10% within a 15 min period and 30 s apart were taken into consideration. Each subject performed no more than a total of four attempted exhalations. No nose clip was used. The sensor in the device was replaced periodically according to the manufacturer's guide. Most of FeNO studies, including our current study, use a same flow rate measurement (50 mL/s) as recommended by ATS/ERS (20).

### **Statistical analysis**

Since normality assumptions were met for the logarithm of FeNO, the logarithm-transformed value was used to calculate the mean  $\pm$  two standard deviations (SD) and then back-transformed values were estimated (22). Comparison between groups of population characteristics and symptoms were tested with the  $\chi^2$  test or exact Fisher test for categorical variables. The sensitivity and specificity of self-reported cat allergy were calculated using the cat SPT result as the gold standard. A paired *t*-test was used for comparison of continuous variables within each group. Factors influencing the FeNO values were examined with a generalized linear model. Gender, doctor-diagnosed asthma, allergy status, height, reported family medical conditions, and self-reported allergy were included as independent factors in the model. The same factors were adjusted in multiple logistic regressions to evaluate associations between respiratory conditions with a combination of SPT result and FeNO level. An odds ratio (OR) with a 95% confidence interval (95% CI) were calculated for the logistic regression analyses. Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS version 20.0; SPSS Inc., Chicago, IL).

### **Ethics statement**

The study was approved by an independent review board, Medical Research and Ethics Committee in the National University of Malaysia. Data were collected after all permissions were obtained from Malaysia Ministry of Education, Terengganu State Education Department, principals of each school, and teachers of each class. Information regarding the purpose of the study and the importance of valid answer were given prior obtaining informed written consent from all parent or legal guardian of selected students.

### **Results**

Demographic data, characteristics, and FeNO level among students are shown in Table 1. A total of 487 students (76.1%) completed the questionnaire, 370 (57.8%) managed to obtained written consent to performed skin prick testing and 365 (57.0%) of them managed to produce an acceptable FeNO reading. Students with elevated FeNO level were 140 (38.4%), while 82 (23.0%) had clinical allergy to both HDM and cat with increased FeNO (>20 ppb) level. Majority (99.0%) were Malays; 182 (37.4%) were male and half of them went to school in urban areas. There

were only 18 current smokers (3.7%) but 260 (53.4%) reported exposure to cigarette smoke at home (ETS). Prevalence of overweight or obesity was 17.1%. The

**Table 1.** Demographic data, respondent characteristics, and FeNO levels among school children.

| Variables                                           | Total participant n: 487 (%)/<br>mean (SD)/GM (GSD) |
|-----------------------------------------------------|-----------------------------------------------------|
| Male                                                | 182 (37.4)                                          |
| Urban school                                        | 245 (50.3)                                          |
| Current smoker                                      | 18 (3.7)                                            |
| Ever asthma                                         | 54 (11.1)                                           |
| Doctor diagnosed asthma                             | 41 (8.4)                                            |
| Present cigarette smoke in house (ETS) <sup>a</sup> |                                                     |
| No, never                                           | 227 (46.6)                                          |
| Yes, at least once a week                           | 91 (18.7)                                           |
| Yes, every day                                      | 169 (34.7)                                          |
| Having cat at home                                  | 174 (35.7)                                          |
| Elevated FeNO (>20 ppb) (n = 365)                   | 140 (38.4)                                          |
| High FeNO level (>35 ppb) (n = 365)                 | 60 (16.4)                                           |
| Atopy and elevated FeNO (n = 358)                   | 82 (22.9)                                           |
| Overweight or obese <sup>b</sup> (n = 375)          | 64 (17.1)                                           |
| Height                                              | 155 (±0.4) cm                                       |
| Weight                                              | 50.3 (±0.7) kg                                      |
| FeNO (GM ± GSD) (n = 365)                           | 16.7 ppb (±1.9)                                     |

All participants were at age of 13 and 14 years old.

<sup>a</sup>ETS exposed were student exposed to cigarette smoke at home.

<sup>b</sup>BMI based on age.

geometric mean FeNO for all subjects was 16.7 ppb with ±2.0 ppb GSD. Prevalence of asthma and having asthma diagnosed by a certified medical doctor was 11.1% and 8.4%, respectively. Majority had allergy to house dust mites allergens (HDM), namely *Dermatophagoides pteronyssinus* (Der p 1) 34.3% and *Dermatophagoides farinae* (Der f 1) 32.7% (Table 2). Prevalence of allergy to HDM or cat was 40.3% (145). Calculated sensitivity and specificity for reported cat allergy were 12.5% and 95.5%, respectively.

Geometric mean FeNO after excluding students with positive SPT to HDM or cat or with doctor-diagnosed asthma was 15.4 ppb (GSD 1.7) for males and 12.6 ppb (GSD 1.7) for females. Gender, school location, family history of allergy, and asthma status were associated with FeNO. Higher FeNO level were associated with night time breathlessness, self-reported allergy to food, pollen, and cat, and positive skin reaction against *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Felis domesticus*. Proportion of subjects with elevated levels of FeNO and allergic conditions by risk factor are shown in

**Table 2.** FeNO levels of school children by selected risk factors.

| Variables                                                 | Prevalence (%) | Yes |               | No  |               | p-value |
|-----------------------------------------------------------|----------------|-----|---------------|-----|---------------|---------|
|                                                           |                | N   | GM FeNO (GSD) | N   | GM FeNO (GSD) |         |
| Gender (male)                                             | 38.1           | 139 | 19.2 (2.0)    | 226 | 15.4 (2.0)    | <0.01*  |
| Urban school                                              | 47.9           | 175 | 18.2 (2.0)    | 190 | 15.4 (1.9)    | 0.02    |
| Smoking                                                   | 3.0            | 11  | 18.3 (1.9)    | 354 | 16.7 (2.0)    | 0.66    |
| ETS exposed <sup>a</sup>                                  | 63.0           | 230 | 16.8 (2.0)    | 135 | 16.6 (1.9)    | 0.84    |
| Overweight and obese                                      | 16.7           | 61  | 16.8 (1.9)    | 303 | 16.7 (2.0)    | 0.98    |
| Reported family history                                   |                |     |               |     |               |         |
| Mother has allergy                                        | 14.5           | 53  | 21.2 (2.1)    | 312 | 16.1 (2.0)    | 0.01    |
| Mother has asthma                                         | 8.2            | 30  | 19.0 (2.3)    | 335 | 16.5 (2.0)    | 0.37    |
| Father has allergy                                        | 11.0           | 40  | 22.3 (2.1)    | 325 | 16.2 (2.0)    | 0.01    |
| Father has asthma                                         | 5.8            | 21  | 21.0 (1.8)    | 344 | 16.5 (2.0)    | 0.07    |
| Asthma status                                             |                |     |               |     |               |         |
| Ever Asthma <sup>b</sup>                                  | 10.7           | 39  | 23.2 (2.0)    | 326 | 16.1 (2.0)    | <0.01*  |
| Doctor diagnosed asthma                                   | 7.7            | 28  | 25.1 (2.0)    | 337 | 16.2 (2.0)    | <0.01*  |
| Current asthma <sup>c</sup>                               | 4.7            | 17  | 27.5 (1.7)    | 348 | 16.3 (2.0)    | <0.01*  |
| Respiratory symptoms                                      |                |     |               |     |               |         |
| Any respiratory symptoms <sup>d</sup>                     | 30.8           | 101 | 17.0 (2.0)    | 264 | 16.6 (2.0)    | 0.77    |
| Wheeze                                                    | 13.7           | 39  | 19.3 (2.2)    | 326 | 16.5 (2.0)    | 0.18    |
| Day breathlessness                                        | 23.2           | 32  | 16.2 (1.9)    | 333 | 16.8 (2.0)    | 0.75    |
| Night breathlessness                                      | 6.0            | 24  | 21.8 (1.9)    | 341 | 16.4 (2.0)    | 0.04    |
| Self-reported allergy                                     |                |     |               |     |               |         |
| Food allergy                                              | 27.1           | 102 | 20.3 (2.2)    | 263 | 15.5 (1.9)    | <0.01*  |
| Pollen allergy                                            | 12.1           | 39  | 21.7 (2.0)    | 326 | 16.2 (2.0)    | 0.02    |
| Mold allergy                                              | 10.5           | 40  | 17.2 (2.2)    | 325 | 16.7 (2.0)    | 0.82    |
| Cat allergy                                               | 5.3            | 20  | 31.5 (2.2)    | 345 | 16.1 (2.0)    | <0.01*  |
| Skin prick response (n = 358)                             |                |     |               |     |               |         |
| HDM or Cat                                                | 40.3           | 145 | 22.4 (2.2)    | 212 | 13.8 (1.7)    | <0.01** |
| House dust mite <sup>e</sup>                              | 39.2           | 141 | 22.7 (2.2)    | 217 | 13.8 (1.7)    | <0.01** |
| <i>Derm. pteronyssinus</i>                                | 34.3           | 123 | 22.9 (2.2)    | 235 | 14.3 (1.8)    | <0.01** |
| <i>Derm. farinae</i>                                      | 32.7           | 116 | 23.8 (2.2)    | 242 | 14.2 (1.8)    | <0.01** |
| <i>Felis domesticus</i>                                   | 10.8           | 40  | 22.1 (2.0)    | 317 | 16.2 (2.0)    | <0.01*  |
| Student with HDM and cat and with doctor-diagnosed asthma | 4.9            | 18  | 30.9 (1.9)    | 347 | 16.2 (2.0)    | <0.01*  |

Significant values are in bold.

<sup>a</sup>ETS exposed were student exposed to cigarette smoke at home.

<sup>b</sup>Ever had asthma were ever asthma without doctor diagnosed, doctor diagnosed asthma or asthma on medication.

<sup>c</sup>Current asthma were either on asthma medication or had any asthma attack for last 12 months.

<sup>d</sup>Any respiratory symptom was student having any type of wheezing, any type of day breathlessness or any type of night breathlessness.

<sup>e</sup>House dust mite were student had skin swelling more than 3 mm on *Derm. Pteronyssinus* or *Derm. Farinae*.

\* $p < 0.005$ .

\*\* $p < 0.001$ .

**Table 2.** Increasing height, male students, parental history of allergy (mother or father has allergy), self-reported allergy and sensitization to HDM or cat (*Felis domesticus*) were associated with increased FeNO level among students (Table 3). Finally, we analyzed associations between a combined variable including FeNO and sensitization to HDM or cat, with respiratory symptoms, asthma status and self-reported allergy (Table 4). Students with a positive SPT (HDM or cat allergy) combined with high FeNO

level (>35 ppb) were more likely to have night breathlessness, wheeze, ever had asthma, doctor-diagnosed asthma, current asthma, and a self-reported allergy to food, pollen, and cat.

## Discussion

In this study, we enrolled a random sample of children from all classes. Even though data on asthma related symptoms were collected based on answers from the questionnaire, both student and teachers were given explanation on how to complete the questionnaire. One of research team member checked the questionnaire to ensure the information were correct and complete. This enabled us to get higher accuracy in this study. Secondary school students were chosen for the study as student of this age group were expected not be influenced by major academic tests planned by the Malaysian Ministry of Education. Information bias was handled by completing questionnaires first, before students participated in the clinical examination, which means that data from the questionnaire was not influenced by knowing the FeNO values measured. There was no trend in FeNO based on individual schools. Mutual adjustment to control for confounders during bivariate and multivariate analyses further helped to reduce selection bias in our study. Results from different statistical analyses were mostly the same. Thus, it can be concluded that the study was not seriously influenced by selection bias or information bias. Nevertheless, the possibility to draw conclusions on causality is limited by the cross-sectional study design.

**Table 3.** Level of log FeNO by selected factors using generalized linear models analysis (N = 365).

| Variable                                 | Slope | 95% CI    |       | p-value |
|------------------------------------------|-------|-----------|-------|---------|
|                                          |       | Lower     | Upper |         |
| Intercept                                | 0.15  | -0.44     | 0.75  | 0.62    |
| Height                                   | 0.01  | 0.01      | 0.10  | <0.01*  |
| Male                                     | 0.07  | 0.01      | 0.14  | 0.02    |
| Urban school                             | 0.02  | -0.04     | 0.08  | 0.52    |
| Night breathlessness                     | 0.06  | -0.06     | 0.18  | 0.34    |
| ETS at home <sup>a</sup>                 |       |           |       |         |
| Every day                                | 0.02  | -0.05     | 0.08  | 0.59    |
| Once a week                              | -0.03 | -0.10     | 0.05  | 0.52    |
| Never                                    |       | Reference |       |         |
| Asthma presentations                     |       |           |       |         |
| Current asthma <sup>b</sup>              | -0.07 | -0.23     | 0.09  | 0.38    |
| Ever asthma                              | -0.02 | -0.21     | 0.16  | 0.82    |
| Non asthma                               |       | Reference |       |         |
| Parental history of allergy <sup>c</sup> | 0.10  | 0.03      | 0.17  | <0.01*  |
| Self-reported allergy <sup>d</sup>       | 0.06  | 0.01      | 0.12  | 0.04    |
| HDM or cat                               | 0.19  | 0.13      | 0.24  | <0.01** |

Significant values are in bold.

<sup>a</sup>ETS exposed were student exposed to cigarette smoke at home.

<sup>b</sup>Current asthma were either on asthma medication or had any asthma attack for last 12 months.

<sup>c</sup>Parental allergy were reported mother or father had history of allergy.

<sup>d</sup>Reported allergy were ever reported history of food or pollen or cat allergy.

\* $p < 0.005$ .

\*\* $p < 0.001$ .

**Table 4.** Respiratory symptom, asthma, and reported allergy by combination of FeNO and SPT (HDM or cat) (N = 365) using multiple logistic regressions analysis.

| Independent variable                  | Reference group | SPT negative and FeNO Low |        |       |         | SPT positive and FeNO low |        |       |         | SPT positive and FeNO high |        |       |         |
|---------------------------------------|-----------------|---------------------------|--------|-------|---------|---------------------------|--------|-------|---------|----------------------------|--------|-------|---------|
|                                       |                 | OR                        | 95% CI |       | p-value | OR                        | 95% CI |       | p-value | OR                         | 95% CI |       | p-value |
|                                       |                 |                           | Lower  | Upper |         |                           | Lower  | Upper |         |                            | Lower  | Upper |         |
| Any respiratory symptoms <sup>a</sup> | 1               | 1.40                      | 0.73   | 2.67  | 0.31    | 1.99                      | 0.99   | 3.98  | 0.05    |                            |        |       |         |
| Day breathlessness                    | 1               | 1.14                      | 0.57   | 2.29  | 0.71    | 1.41                      | 0.67   | 2.96  | 0.37    |                            |        |       |         |
| Night breathlessness                  | 1               | 1.33                      | 0.38   | 4.70  | 0.66    | 3.87                      | 1.32   | 11.30 | 0.01    |                            |        |       |         |
| Wheeze                                | 1               | 0.98                      | 0.36   | 2.72  | 0.97    | 3.53                      | 1.46   | 8.51  | <0.01*  |                            |        |       |         |
| Ever asthma                           | 1               | 1.42                      | 0.49   | 4.10  | 0.52    | 5.74                      | 2.47   | 13.35 | <0.01** |                            |        |       |         |
| Doctor diagnosed asthma               | 1               | 2.41                      | 0.67   | 8.63  | 0.18    | 5.85                      | 2.19   | 15.63 | <0.01** |                            |        |       |         |
| Current asthma <sup>b</sup>           | 1               | 4.87                      | 0.96   | 24.82 | 0.06    | 8.86                      | 2.06   | 38.11 | <0.01*  |                            |        |       |         |
| Food allergy                          | 1               | 1.36                      | 0.69   | 2.67  | 0.37    | 5.18                      | 2.59   | 10.38 | <0.01** |                            |        |       |         |
| Pollen allergy                        | 1               | 0.47                      | 0.13   | 1.75  | 0.26    | 2.75                      | 1.09   | 6.94  | 0.03    |                            |        |       |         |
| Cat allergy                           | 1               | 1.09                      | 0.19   | 6.19  | 0.92    | 10.22                     | 2.79   | 37.50 | <0.01*  |                            |        |       |         |

Significant values are in bold.

Each model was analyzed by logistic regression and adjusting for gender, school location, cigarette smoke exposure and height in the models. SPT negative were student had skin swelling more than 3 mm on *Derm. Pteronyssinus* or *Derm. Farinae* or *Felis Domesticus*. FeNO were divided to low FeNO (<20 ppb) and high (>35 ppb).

<sup>a</sup>Any respiratory symptom was student having any type of wheezing, any type of day breathlessness or any type of night breathlessness.

<sup>b</sup>Current asthma were either on asthma medication or had any asthma attack for last 12 month.

\* $p < 0.005$ .

\*\* $p < 0.001$ .

Prevalence of doctor-diagnosed asthma was 8.4%, but a large proportion of students reported food allergy (27.1%) and sensitized to cat or HDM (40.3%). Moreover, keeping a cat at home was very common (35.7%). We found that self-reported cat allergy had high specificity but low sensitivity, suggesting that cat allergy can be a major allergy, requiring allergy testing to determine the true prevalence. In this study, the geometric mean FeNO level among 13 and 14 years old students in Terengganu, Malaysia were 16.73 ppb (GSD 1.99). A large proportion (34.4%) of students had elevated FeNO levels. FeNO levels were related to height, gender, history of allergy (parental history, self-reported food, pollen and cat allergy), and HDM and cat allergy. Moreover, our study suggests that FeNO levels were associated with respiratory symptoms. The subgroup with parental allergy, reported asthma conditions, and reported night breathlessness had higher FeNO levels. Increased FeNO among children with self-reported allergy have been reported by previous studies (21), but higher FeNO among sensitized, asymptomatic children may occur because allergen exposure among children are common (22). Adjustments for school was still considered because subjects were sampled in their class groups in the assigned schools and not randomly in the communities. Environmental pollution exposure associated with different FeNO levels among asthmatic compared to non-asthmatic children could have attenuated the role of individual susceptibility (23). Prevalence of current smokers was low (3.7%), however, a large proportion of students were exposed to cigarette smoke at home (53.4%). Other known factors that were considered and controlled in this study were age-related (24), gender, and height (25).

We did find FeNO level differences between children with and without allergic sensitization, independent of allergic symptoms, among Malays students. FeNO is elevated by not only asthma, but also other respiratory disorders such as viral infections and allergic rhinitis (26). Geometric mean levels of FeNO were relatively low (15.4 ppb in males and 12.6 ppb in females) if subjects with doctor-diagnosed asthma and a positive SPT to cat or HDM were excluded. Among normal healthy children age 6–14 years, one study in China reported that median level was 13 ppb (range, 9–18 ppb) and lower for females, at 10 ppb (range, 8–14 ppb) (27). The mean FeNO among Japanese students between 10 and 12 years of age, was 15.1 ppb (28). More recent study among non-allergic sensitized children in Taiwan aged 5 to 18 years, the geometric mean FeNO level and the upper 95% CI were

11.2 ppb and 30.2 ppb (29). In Korea, the geometric mean and 95% CI of FeNO in healthy, non-atopic subjects were 13.76 ppb (11.68–15.84) among 12 years old children (30). We found a relationship between FeNO levels and positive skin tests in sensitized children who presented with asthma symptoms. These findings were similar with most studies, which suggest that atopy and asthma may be a consistent predictor of high FeNO levels (31). Generally, eosinophilic inflammation has an important pathophysiological role for the development of asthma symptoms (32). Higher FeNO were more common among students with asthma, especially students with symptoms related to uncontrolled asthma (33) such as night time symptoms independent of allergic conditions.

In conclusion, FeNO levels were high for children with HDM or cat sensitization independent of allergic symptoms. Our data suggest that FeNO levels were associated with height, gender, school location, parental allergy, asthma status, night breathlessness, self-reported allergy (food, pollen, and cat), and sensitization to HDM or cat. Students with higher FeNO, may indicate an ongoing allergic reaction that may requires further interventions.

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## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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## References

1. World Health Organisation. Asthma. Fact sheet no. 307; 2011. Available at: <http://www.who.int/media-centre/factsheets/fs307/en/index.html>.
2. Zhang Y, Zhang L. Prevalence of allergic rhinitis in china. *Allergy Asthma Immunol Res* 2014;6:105–113. doi:10.4168/aair.2014.6.2.105.
3. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, Zuberbier T. 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(Suppl 86): 8–160. doi:10.1111/j.1398-9995.2007.01620.x.
4. Anandan C, Nurmatov U, van Schayck OC, Sheikh A. Is the prevalence of asthma declining? Systematic review of epidemiological studies. *Allergy* 2010;65: 152–167. doi:10.1111/j.1398-9995.2009.02244.x.
5. Schoenwetter WF, Dupclay L, Jr., Appajosyula S, Botteman MF, Pashos CL. Economic impact and quality-of-life burden of allergic rhinitis. *Curr Med Res Opin* 2004;20:305–317.
6. Rutkowski K, Sowa P, Rutkowska-Talipska J, Sulkowski S, Rutkowski R. Allergic diseases: The price of civilisational progress. *Postepy Dermatol Alergol* 2014;31:77–83. doi:10.5114/pdia.2014.40936.
7. Leung R, Ho P, Lam CW, Lai CK. Sensitization to inhaled allergens as a risk factor for asthma and allergic diseases in Chinese population. *J Allergy Clin Immunol* 1997;99:594–599.
8. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, Boulet LP. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health* 2012;12:204. <http://www.biomedcentral.com/1471-2458/12/204>
9. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, Sigurdardottir ST, et al. The prevalence of food allergy: A meta-analysis. *J Allergy Clin Immunol* 2007;120:638–646. doi:10.1016/j.jaci.2007.05.026.
10. Cibella F, Cuttitta G, La Grutta S, Passalacqua G, Viegi G. Factors that influence exhaled nitric oxide in Italian school children. *Allergy Asthma Immunol* 2008;101: 407–412. doi:10.1016/S1081-1206(10)60318-3.
11. American Thoracic Society (ATS). An official ATS clinical practice guideline: Interpretation of exhaled nitric oxide levels (FeNO) for clinical applications. *Am J Respir Crit Care Med* 2011;184:602–615.
12. Scott M, Raza A, Karmaus W, Mitchell F, Grundy J, Kurukulaaratchy RJ, Arshad SH, Roberts G. Influence of atopy and asthma on exhaled nitric oxide in an unselected birth cohort study. *Thorax* 2010;65: 258–262. doi:10.1136/thx.2009.125443.
13. Norbäck D, Hashim JH, Hashim Z, Cai G-H, Sooria V, Ismail SA, Wieslander G. Respiratory symptoms and fractional exhaled nitric oxide (FeNO) among students in Penang, Malaysia in relation to signs of dampness at school and fungal DNA in school dust. *Sci Total Environ* 2017;577:148–154. doi:10.1016/j.scitotenv.2016.10.148.
14. Keat ST, Heong WC, Joon WM. Association between house dust mite (HDM) sensitisation and asthma control using skin prick test and HDM antigen specific IgE levels in saliva of Malaysian children. *IeJSME* 2015;9:3–12.
15. Wong GW, Leung TF, Ko FW. Changing prevalence of allergic diseases in the Asia-Pacific region. *Allergy Asthma Immunol Res* 2013;5:251–257. doi:10.4168/aair.2013.5.5.251.
16. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, Williams H, ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733–743.
17. Ismail SH, Baba MD, Abd.Mutalib L. Indoor air quality issues for non-industrial work place. *Int J Res Rev Appl Sci* 2010;5:235–244.
18. Smedje G, Norback D, Edling C. Asthma among secondary school children in relation to the school environment. *Clin Exp Allergy* 1997;27:1270–1278. doi:10.1111/j.1365-2222.1997.tb01171.x.
19. Janson C, Anto J, Burney P, Chinn S, de Marco R, Heinrich J, Jarvis D, et al. The European Community Respiratory health Survey: What are the main results so far? *Eur Respir J* 2001;18:598–611. doi:10.1183/09031936.01.00205801.
20. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. *Am J Respir Crit Care Med* 2005;171:912–930.
21. Kharitonov SA, Gonio F, Kelly C, Meah S, Barnes PJ. Reproducibility of exhaled nitric oxide measurements in healthy and asthmatic adults and children. *Eur Respir J* 2003;21:433–438.
22. Solberg HE. The International Federation of Clinical Chemistry recommendation on estimation of reference intervals. *Clin Chem Lab Med* 2004;42:710–714.
23. Stefania LG, Giuliana F, Velia M, Fabio C, Giovanni V. Environmental effects on fractional exhaled nitric oxide in allergic children. *J Allergy* 2012;2012:1–6.
24. Malmberg LP, Pelkonen AS, Haahtela T, Turpeinen M. Exhaled nitric oxide rather than lung function distinguishes preschool children with probable asthma. *Thorax* 2003;58:494–499.
25. 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. doi:10.1378/chest.130.5.1319.
26. Peña Zarza JA, Osona B, Gil-Sanchez JA, Figuerola J. Exhaled nitric oxide in acute phase of bronchiolitis and its relation with episodes of subsequent wheezing in children of preschool age. *Pediatr Allergy Immunol Pulmonol* 2012;25:92–96.
27. Zhang H, Shu L, Cai X, Wang Z, Jiao X, Liu F, Hou P, Wang L, Shan L, Chen N, et al. Gender and age affect the levels of exhaled nitric oxide in healthy children. *Exp Ther Med* 2013;5:1174–1178. doi:10.3892/etm.2013.922.
28. 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. doi:10.1016/j.jaci.2004.05.033.
29. Yao TC, Lee WI, Ou LS, Chen LC, Yeh KW, Huang JL. PATCH Study Group: Reference values of exhaled nitric oxide in healthy Asian children aged 5 to 18 years. *Eur Respir J* 2012;39:378–384.
30. Cho HJ, Jung YH, Yang SI, Lee E, Kim HY, Seo JH, Kwon JW, et al. Reference values and determinants of fractional concentration of exhaled nitric oxide (FeNO) in healthy children. *Allergy Asthma Immunol Res* 2014;6:169–174.

31. Cibella F, Cuttitta G, La Grutta S, Passalacqua G, Viegi G. Factors that influence exhaled nitric oxide in italian schoolchildren. *Ann Allergy Asthma Immunol* 2008; 101:407–412. doi:[10.1016/S1081-1206\(10\)60318-3](https://doi.org/10.1016/S1081-1206(10)60318-3).
32. Szeffler SJ, Mitchell H, Sorkness CA, Gergen PJ, O'Connor GT, Morgan WJ, Kattan M, Pongracic JA, Teach SJ, Bloomberg GR, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: A randomised controlled trial. *Lancet* 2008;372: 1065–1072. doi:[10.1016/S0140-6736\(08\)61448-8](https://doi.org/10.1016/S0140-6736(08)61448-8).
33. Pijnenburg MWH, De Jongste JC. Exhaled nitric oxide in childhood asthma: a review. *Clin Exp Allergy* 2008;38:246–259.