Journal of Asthma

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ijas20

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To cite this article: Dan Norbäck, Jamal Hisham Hashim, Zailina Hashim, Juliana Jalaludin, Rohaida Ismail, Gunilla Wieslander, Bambang Wispriyono, Lolita Sary, Satria Pratama, Meliana Sari, Tiaraima Sisinta, Hondli Putra, Agung Aji Perdana, Nova Muhani, Sri Maria Puji Lestari, Ririn Wulandari & Eliza Eka Nurmala (2024) Fractional exhaled nitric oxide (FeNO) among school children in Java and Sumatra, Indonesia: associations with respiratory symptoms, house dust mite sensitization and the home environment, Journal of Asthma, 61:12, 1772-1780, DOI: 10.1080/02770903.2024.2383627

To link to this article: https://doi.org/10.1080/02770903.2024.2383627

Published online: 27 Jul 2024.

JOURNAL OF ASTHMA
2024, VOL. 61, NO. 12, 1772–1780
https://doi.org/10.1080/02770903.2024.2383627

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Fractional exhaled nitric oxide (FeNO) among school children in Java and Sumatra, Indonesia: associations with respiratory symptoms, house dust mite sensitization and the home environment

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ABSTRACT

Objective: To study associations between fractional exhaled nitric oxide (FeNO) and asthma, airway symptoms, sensitization to common allergens, outdoor pollution and home environment among 380 students in eight junior high schools in two areas in Indonesia.
Methods: Data on health and home were collected by a face-to face interview before measuring FeNO and performing skin prick test against common allergens. Exploratory linear mixed and logistic regression models were employed.
Results: Geometric mean of FeNO was 17.8 ppb (GSD 2.09) and 139 students (36.6%) had elevated FeNO (>20 ppb). In total, 107 students (28.2%) were sensitized to house dust mite (HDM) (Der p1 or Der f1), 4 (1.1%) to cat and 3 (0.8%) to mold (*Cladosporium* or *Alternaria*). Moreover, 20 students (5.3%) had diagnosed asthma, 38 (10.0%) had current wheeze, and 107 (28.2%) had current rhinitis. HDM sensitization, diagnosed asthma, current wheeze, and current rhinitis were associated with FeNO. In total, 281 students (73.9%) had mold or dampness, 232 (61.1%) had environmental tobacco smoke (ETS) and 43 (11.3%) had other odor at home. Indoor mold or dampness and other odor at home were associated with FeNO. ETS was negatively associated with FeNO.
Conclusion: HDM sensitization and elevated FeNO can be common among children in this part of Indonesia. The high prevalence of elevated FeNO indicate that undiagnosed childhood asthma is common. Dampness, mold and odor at home can be associated with increased FeNO while ETS can be associated with decreased FeNO.

ARTICLE HISTORY
Received 26 March 2024
Revised 12 July 2024
Accepted 19 July 2024

KEYWORDS
Fractional exhaled nitric oxide; Indonesia; school children; environmental tobacco smoke; allergic sensitization; asthma; rhinitis; dampness and mold

Introduction

Asthma and allergic diseases are on the rise in Asia, especially among children (1). Indonesia is a large lower middle-income country with a population of 279 million (2). Acute respiratory infections (ARIs), pneumonia and tuberculosis are common childhood respiratory diseases in this country (3). Few studies exist on asthma or allergies in Indonesia (4). Two studies among adults found 3.8-7.0% asthma prevalence and 6.9% current wheeze prevalence. The review (4) mentioned that in the International Study on Asthma and Allergy in Childhood (ISAAC study) in Indonesia, 4.2% of 13-14 y old children had wheeze and 6.6% had ever had asthma. The most common allergic sensitization among secondary school children in Indonesia was against house dust mites (19.46%), American cockroach (11.31%), the mold *Mucor mucedo* (8.60%) and crab (6.33%) (5). The most

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common pollen sensitization was against goosefoot (5.7%), rye (4.7%), plantain (4.7%) and wall pellitory pollen (4.7%) (6).

Fractional exhaled nitric oxide (FeNO) is a commonly used biomarker of airway inflammation, related to asthma and IgE-mediated allergic diseases (7–11). Household air pollution is a well-known risk factor for childhood asthma, rhinitis and otitis media (12) but few previous studies exist on how the home environment influences FeNO. Bacterial exposure (13,14), indoor mold (9) and dog keeping (12,15) has been reported to be associated with lower FeNO. In contrast, exposure to house dust allergens (16,17) and indoor $PM_{2.5}$ (18) could increase FeNO. Moreover, one review concluded that outdoor air pollution (PM_{10}, $PM_{2.5}$, NO_2, SO_2 and black carbon) can increase FeNO (19).

Since few studies exist on personal and environmental determinants of FeNO among school children in the tropics, we have performed a FeNO study among school children in two cities in Indonesia. The study has mainly a descriptive and explorative approach. One main objective was to study the potential associations between FeNO and asthma, rhinitis, ocular symptoms, respiratory symptoms, and IgE mediated allergic sensitization measured by skin prick tests. Another main objective was to study the potential associations between FeNO and selected home environmental factors (type of building, keeping cats, dogs and birds, recent indoor painting, new floor materials, indoor odors, water leakage, dampness and indoor mold growth). A third and secondary objective was to investigate the potential associations between FeNO and outdoor air pollution (PM_{10}, NO_2, and ozone) measured outside the schools.

Materials and methods

Ethics statement

This study was approved by the Research and Community Engagement Ethical Committee, Faculty of Public Health, University of Indonesia (Ref: 376/H2.F10/PPM.00.02/2017). The parents of the invited students were contacted by a letter and we obtained written informed consent from participating students and their parents.

Study population

In Depok, a city with 2.0 million inhabitants which is a suburb of Jakarta on the island of Java, four junior high schools were randomly selected. Additionally, we randomly selected four schools in Bandar Lampung, a city with 1.2 million inhabitants located on the southern tip of Sumatra Island. We obtained lists of all second grade classes in each of these eight selected schools, and randomly selected four second grade classes in each school. Additionally, we collected lists of names of all students in these 32 selected classes. Data collection was carried out in spring 2017. There were no exclusion criteria in the study. We used the same study design and population size as in three similar school studies in Malaysia, where we found associations between home environment, school environment, respiratory health and FeNO among second grade junior high school students (11,20,21).

Demographics and health data

We distributed questionnaires to students of selected schools and classes before our field work. The self-administered questionnaire has been used in school environment studies in different Asian countries (9–11,22–24). The questionnaire was translated from the Malaysian to the Indonesian language by an Indonesian public health lecturer in Bandar Lampung and then cross-checked by another Indonesian lecturer. Firstly, the children answered the questions at home together with their parents. Subsequently, researchers conducted a face-to-face interview with the students in order to clarify unclear or missing answers. There were questions on smoking, parental allergy/asthma, own allergies, and respiratory health. The questions were compiled from previous large epidemiological studies such as the European Respiratory Health Survey (ECRHS) (25) and our previous school environment studies in Asia (9–11,22–24).

We asked about diagnosed asthma, current asthma medication, asthmatic attacks, current wheeze, daytime and nighttime attacks of shortness of breath (yes/no questions with 12 months recall period). Moreover, there were questions on rhinitis and ocular symptoms used in subsequent school investigations (20) (3 months recall period). There were four possible answers on the frequency of these symptoms: (never, seldom, weekly, and daily), dichotomized into daily or weekly symptoms (yes/no). Finally, we asked about respiratory infections in the past week. These questions were answered when we performed the FeNO test.

Skin prick testing (SPT)

We used six allergen extracts from ALK-Abello, Hørsholm, Denmark, including Dermatophagoides farinae (Der f 1), Dermatophagoides pteronyssinus (Der p 1), Felis domesticus (Cat), *Equus ferus caballus* (Horse), mold family *Alternaria,* and mold family *Cladosporium.* All allergens were in 10 Histamine Equivalent in Prick testing (HEP) concentrations. A 10 mg/mL histamine solution was used as the positive control and a normal saline solution as the negative control. An average wheal diameter of at least 3 mm was considered positive. Details of the methodology have been published previously (11).

Measurement of FeNO

We measured FeNO using the NIOX-MINO instrument (Aerocrine AB, Solna, Sweden) using 5 s exhalation time, as described in the guidelines by the manufacturer.

Data on household exposure

There were 14 questions on current home environment:

1. Type of building (single family or multi-family building)
2. Type of house (wooden or concrete building)
3. Any indoor painting in the past 12 months (Yes/No)
4. Any new floor materials installed in the past 12 months (Yes/No)
5. Any cats in the home (Yes/No)
6. Any dogs in the home (Yes/No)
7. Any birds kept at home (Yes/No)
8. Signs of leaking water or flooding in the past 12 months (Yes/No)
9. Signs of floor dampness in the past 12 months (Yes/No)
10. Visible mold on indoor surfaces in the past 12 months (Yes/No)
11. Mold odor in the home in the past 12 months (Yes/No)
12. Other odor in the home in the past 12 months (Yes/No)
13. Any flooding, leaking water or indoor mold in the past 5 years (Yes/No)
14. Any tobacco smoking (ETS) in the home (Yes/No)

We created a combined dampness variable, by combining data from question 8, 9, 10, 11, and 13. The variable was coded 0 if there were no yes answers on all five questions. The variable was coded 1 if there was at least one yes answer on the five questions.

Data on outdoor environment

We measured outdoor relative air humidity (RH), temperature and PM_{10} at each school on days when we performed the medical investigations. The air monitoring instrument Q-trak, (TSI Inc., St. Paul, MN, USA) was utilized to measure RH and temperature. The Dust Track II Aerosol monitor (from TSI Inc.), was used to measure PM_{10}. We also measured nitrogen dioxide (NO_2) and ozone (O_3) by two diffusion samplers placed continuously over a seven-day period (24 h/day). The samplers were manufactured by the Swedish Environmental Research Institute Limited (IVL), Gothenburg, Sweden. They were protected from rain and were put 2.5–3.5 m above the ground, and were analyzed by IVL. Concentrations were reported as 7-days average values.

Statistical analysis

We 10log-transformed FeNO data to make the variable more normally distributed and tested the differences in log FeNO between groups by Student t-test. Geometric mean (GM) and geometric standard deviation (GSD) were reported for FeNO. We used Mann-Whitney U-test to compare differences in outdoor pollution data between the two cities, due to low number of observations (one sample per school). Correlations between independent variables included in mutually adjusted models were calculated by Spearman rank correlation test. Moreover, for descriptive purpose, we divided FeNO levels into three groups; high (>35 ppb), intermediate (20-35 ppb) and low FeNO (<20 ppb), as suggested by the ATS standard (Dweik et al., 2011).

Since data had a hierarchic structure, we initially created linear mixed models (3-levels; school, classroom, child) using 10log-transformed FeNO as dependent variable and keeping four potential confounders (gender, current smoking, height and city) in all models. These demographic potential confounders were selected *a priori*, before conducting statistical analysis, based on the literature. Age is another potential confounder, but since all students were from the same grade, age had little variation and was not included in the models. We investigated interclass correlations in the models, calculated by the Stata command "estat icc", in all models. We found that level-3 intraclass correlations (ICC), the correlations between the dependent variable in the same school, were very low (<0.1). Moreover, the level-2 intraclass correlations, the correlations between the dependent variable in the same school and classroom, were very low (<0.1). Due to this low ICC we performed the final calculations by normal one level linear mixed models. In all the linear mixed models, we expressed associations between independent variables and FeNO as antilog beta values with 95% intervals.

As a first step we analyzed associations between health variables and log FeNO as dependent variable by linear mixed models keeping the four potential confounders and one health variable in each model. Models were created for health variables with $p < 0.2$ in the bivariate analysis of log FeNO by Student-t-test. As a next step, we analyzed associations between home environment variables and log FeNO by linear mixed models keeping the four potential confounders and one home environment variable in each model. Models were created for home environment variables with $p < 0.2$ in the bivariate analysis of log FeNO by Student-t-test. Moreover, we performed stratified analyses of associations between log FeNO and health variables and home environment variables (by the same linear mixed models) stratifying the material into two groups, children with and without house dust mite sensitization.

Based on results from these linear mixed model analysis, we created a mutually adjusted model to further explore the role of HDM sensitization and selected home environment variables for FeNO. This linear mixed model included the four potential confounders, house dust mite sensitization and the home environment variables included in the previous models. Moreover, we performed stratified analyses of associations between log FeNO and the independent variables (by the same linear mixed models) stratifying the material into two groups, children with and without current rhinitis.

Finally, we analyzed relationships between six respiratory health variables (as dependent variables) and FeNO (as a categorized independent variable). Initially, we used multi-level logistic regression models (3-level models; school, classroom, child) including the four co-variates and the categorized FeNO variable in each logistic regression model. When investigation interclass correlation in the models, calculated by the Stata command "estat icc", the level-3 intraclass correlations (ICC) the correlations between the dependent variable in the same school were always very low (<0.1). Moreover, the level-2 intraclass correlations between the dependent variable in the same school and classroom were very low (<0.1 except in one model with ICC = 0.37). Due to this low ICC we performed the final calculations by logistic regression (one level models).

We used STATA 12.0 in all statistical analysis. Associations were expressed as antilog-beta with 95% CI (confidence intervals) in the linear mixed models and as odds ratio (OR) with a 95% CI in the logistic regression models. We used two-tailed statistical test and 5% significance level.

Results

Demographics and descriptive health data

In total, 380 out of 640 invited students joined the study (59% participation rate). The age was between 14 and 16 years (mean 14 y) and 64.5% were girls. Smoking was uncommon (6.9%). In total, 28.2% were sensitized to HDM (house dust mite) allergens (Der p1 or Der f1), 1.1% were sensitized to cat allergen and 0.8% were sensitized to mold *Cladosporium* or *Alternaria)*. No student was sensitized to horse allergen (Table 1). In total, 5.3% had doctor diagnosed asthma, 1.6% current asthma medication, 5.5% current asthma and 10.0% had current wheeze. Moreover, 59.4% had weekly ocular symptoms, 28.2% weekly rhinitis symptoms (runny nose or nasal congestion) and 58.7% reported a respiratory infection in the 7 days period prior to the FeNO testing. One fourth (25.3%) had at least one parent (father or mother or both) with allergic rhinitis or asthma (Table 2).

Table 1. Demographics and allergy testing results among school children in two cities in Indonesia ($N = 380$).

	Depok ($N = 156$)	Bandar Lampung ($N = 224$)	p-value	Total ($N = 380$)
Demographic variables	Mean (SD)	Mean (SD)		Mean (SD)
Height (cm)	156 (11)	154 (10)	0.056	155 (10)
Weight (kg)	51.7 (11.6)	46.1 (11.5)	**<0.001**	48.4 (11.7)
Body mass index (BMI)	22.1 (14.2)	20.0 (13.4)	0.152	20.9 (13.7)
Number of siblings living at home	1.6 (1.0)	1.8 (1.2)	0.064	1.7 (1.1)
	N (%)	N (%)		N (%)
Girl (%)	101 (64.7)	144 (64.3)	0.927	245 (64.5)
Current smoker (%)	0 (0)	26 (11.6)	**<0.001**[a]	26 (6.9)
Positive skin prick test	N (%)	N (%)		N (%)
House dust mite Der p 1	35 (22.4)	47 (21.0)	0.735	82 (21.6)
House dust mite Der f 1	38 (24.4)	52 (23.2)	0.796	90 (23.7)
Cladosporium sp.	0 (0)	1 (0.4)	0.589[a]	1 (0.3)
Alternaria sp	1 (0.6)	1 (0.4)	0.653[a]	2 (0.5)
Cat	2 (1.3)	2 (0.9)	0.543a	4 (1.1)
Horse	0 (0)	0 (0)	NA	0 (0)
Any house dust mite allergy	48 (30.8)	59 (26.3)	0.345	107 (28.2)
Any mold allergy	1 (0.6)	2 (0.9)	0.633[a]	3 (0.8)
Any SPT positivity	48 (30.8)	59 (26.3)	0.345	107 (28.2)

[a]By Fishers exact test (otherwise Student t-test or Chi 2 test for 2*2 tables). Significant p-values ($p<0.05$) are indicated by bold p-values.

Descriptive data on the home environment

Almost all students lived in single-family houses made of bricks or concrete (few wooden buildings). The majority of the homes had ETS at home and more than half of the homes had the interior painted in the last 12 months. The prevalence of cat keeping was 21.3% and 17.1% had birds at home. No student had a dog at home. In total 11.3% reported other odor than mold odor at home. The other odors were described as "odor from dead rats, cockroaches or other animals, waste burning, dusty smell, gas smell or sewage smell". There was no correlation between ETS and other odors except for mold odor (Kendal Tau beta 0.03; $p = 0.58$). The majority of the homes (73.9%) had any dampness or mold at home. Water leakage was the most common sign of dampness (65.0%) (Table 2).

Bivariate associations between respiratory health, home environment and FeNO

For FeNO, GM was 17.8 ppb FeNO (GSD 2.09). In the bivariate analysis, FeNO was associated with ever asthma, diagnosed asthma, current wheeze, asthmatic attacks, rhinitis, respiratory infections in the last 7 days, and HDM sensitization ($p < 0.001$). Daytime attacks of breathlessness were more prevalent at lower FeNO. Among the home environment variables, ETS was negatively associated FeNO and other odor than mold odor was directly associated with FeNO (Table 3).

Linear mixed models for FeNO associations

Associations between FeNO, respiratory health and home environment were analyzed by linear mixed models (3-levels) including the four co-variates mentioned above (one study variable per model). FeNO was associated with ever asthma, diagnosed asthma, current wheeze, rhinitis, current asthma, and airway infections in the past week ($p < 0.001$). Among the home environment variables, ETS was related to lower FeNO and odor was associated with increased FeNO. Moreover, dampness or mold (the combined variable) was associated with higher FeNO (Table 4). In stratified analysis, children with HDM sensitization had higher FeNO if having asthma, current asthma, rhinitis, respiratory infections and dampness or mold at home (combined variable). Children without HDM sensitization had higher FeNO if having ever asthma, doctor diagnosed

Table 2. Respiratory health and home environment among children in two cities in Indonesia ($N = 380$).

	Depok ($N = 156$)	Bandar Lampung ($N = 224$)		Total ($N = 380$)
Health variables	N (%)	N (%)	*p*-value[a]	N (%)
Ever had asthma	12 (7.7)	16 (7.1)	0.840	28 (7.4)
Doctor's diagnosed asthma	8 (5.1)	12 (5.4)	0.922	20 (5.3)
Current wheeze	13 (8.3)	25 (11.2)	0.366	38 (10.0)
Current attacks of daytime breathlessness (rest or exercise)	62 (39.7)	84 (37.5)	0.658	146 (38.4)
Current nocturnal attacks of breathlessness	10 (6.4)	23 (10.3)	0.189	33 (8.7)
Current asthma	6 (3.8)	15 (6.7)	0.232	21 (5.5)
Weekly nose symptoms (rhinitis)	43 (27.7)	64 (28.6)	0.860	107 (28.2)
Weekly ocular symptoms last 3 months	97 (62.6)	128 (57.1)	0.289	225 (59.4)
Respiratory infection last 7 days	105 (67.3)	118 (52.7)	**0.004**	223 (58.7)
Parental asthma/ allergy	37 (25.0)	57 (25.4)	0.923	94 (25.3)
Home environment variable	N (%)	N (%)		N (%)
Apartment	3 (1.9)	3 (1.3)	0.693	6 (1.6)
Wooden house	1 (0.6)	16 (7.1)	**0.002**	17 (4.5)
Cat keeping	28 (17.9)	53 (23.7)	0.181	81 (21.3)
Bird keeping	17 (10.9)	48 (21.4)	**0.007**	65 (17.1)
ETS at home	76 (48.7)	156 (69.6)	**<0.001**	232 (61.1)
Indoor painting last 12 months	84 (54.9)	135 (60.5)	0.276	219 (58.2)
New floor materials12 months	26 (18.6)	47 (21.1)	0.562	73 (20.1)
Other odor than mold odor	17 (10.9)	26 (11.6)	0.830	43 (11.3)
Water leakage last 12 months	111 (71.2)	136 (60.7)	**0.036**	247 (65.0)
Floor dampness last 12 months	6 (3.8)	11 (4.9)	0.621	17 (4.5)
Visible mold last 12 months	38 (24.4)	28 (12.5)	**0.003**	66 (17.4)
Mold odor last 12 months	2 (1.3)	4 (1.8)	0.522[b]	6 (1.6)
Any dampness or mold last 5 years	41 (26.3)	76 (33.9)	0.112	117 (30.8)
Any dampness or mold	125 (80.1)	156 (69.6)	**0.022**	281 (73.9)

[a]P-value calculated by Chi 2 test for 2*2 tables).
[b]P-value by Fishers exact test.
Significant *p*-values ($p<0.05$) are indicated by bold *p*-values.

asthma, wheeze and current asthma. Children without HDM sensitization had reduced FeNO if exposed to ETS at home (Table 4).

Mutually adjusted FeNO models

Then we created mutually adjusted linear mixed model including gender, current smoking, height, HDM sensitization, city and household environment factors with $p < 0.2$ in the one exposure models in Table 3. (Table 5). We investigated correlations between all eight independent variables included in the model. All correlations were low (Spearman's rho <0.4) suggesting that these variables could be in the same model. Students with HDM sensitization, odor at home and dampness or mold at home (the combined variable) had higher FeNO. Children with ETS at home had lower FeNO. In the group with rhinitis, HDM sensitization and odor at home was directly associated with FeNO and ETS was negatively associated with FeNO. In the non-rhinitis group, only HDM was directly associated with FeNO (Table 5).

Categorized FeNO models

In total, 19.0% had high FeNO (>35 ppb), 17.6% had FeNO at intermediate level (20-35 ppb) and 63.4% had low FeNO (<20 ppb). Boys tended to have higher FeNO ($p = 0.087$) and those sensitized to HDM had more often high FeNO ($p < 0.001$). FeNO was high (>35 ppb) among 16.7% in Depok and 20.5% in Bandar Lampung, a non-significant difference (data reported in text only). Finally, we investigated the relationships between the health variables and the categorized FeNO, using logistic regression models (normal FeNO was the reference category and the health variables were dependent variables). Gender, current smoking, and city were include as co-variates. Only rhinitis was associated with intermediate FeNO. All six health variables were associated with high FeNO (Table 6).

Outdoor air pollution and FeNO

Mean air pollution concentrations outside the schools were 135 µg/m³ for PM_{10} (range 54-256), 16 µg/m³ for NO_2 (range 7-30) and 27 µg/m³ for ozone (range 17-40). The mean concentration of NO_2 was higher in Depok (22.3 µg/m³) than in Bandar Lampung (9.2 µg/m³) ($p = 0.03$), but PM_{10} or ozone did not differ significantly between the cities. There were no significant associations between FeNO and PM_{10}, NO_2 or ozone by linear mixed models including the four co-variates (gender, current smoking, height and city) and one outdoor exposure variable. For PM_{10}, antilog-beta for FeNO was 0.95 (95% CI 0.81-1.18) and $p = 0.49$ (calculated for a change of PM_{10} by 100 µg/m³). For NO_2, antilog-beta for FeNO was 1.03 (95% CI 0.83-1.30) and $p = 0.78$ (calculated for a change of NO_2 by 10 µg/m³). For ozone, antilog-beta for FeNO was 0.95 (95% CI 0.84-1.08) and $p = 0.45$ (calculated for a change of ozone by 10 µg/m³) (data shown in text only).

Discussion

More than one third (36.6%) of the children had intermediate or high FeNO (elevated FeNO) according to the ATS standard (26). The overall GM value was 17.8 ppb. To our knowledge, our investigation is the first on FeNO in school children in Indonesia. However, mean FeNO levels in our study were similar as in three studies among children of similar age in Malaysia, a neighbor country. They found a GM value of 15.7 ppb in Terengganu schools (11), 19.9 ppb in Penang schools (21) and 19.5 ppb Melaka and Putrajaya school children (22). Few population studies exist on childhood asthma in tropical countries, using clinical tests to verify asthma diagnosis. Our study from Indonesia, and

Table 3. Associations between FeNO (ppb), health and home environment variables among school children in two cities in Indonesia ($N = 380$).

	Yes (N)	FeNO GM (GSD)	No (N)	FeNO GM (GSD)	*p*-value[a]
Health and allergy variables					
Ever had asthma	28	30.74 (2.24)	352	17.01 (2.03)	**0.002**
Doctor's diagnosed asthma	20	32.80 (2.75)	360	17.18 (2.03)	**0.011**
Current wheeze	38	24.29 (2.34)	342	17.16 (2.05)	**0.006**
Current daytime attacks of breathlessness (rest or exercise)	146	15.80 (2.08)	234	19.12 (2.08)	**0.014**
Current nocturnal attacks of breathlessness	33	22.49 (2.51)	347	17.38 (2.05)	0.055
Current asthma	21	30.95 (2.32)	359	17.20 (2.06)	**<0.001**
Weekly nose symptoms last 3 months (rhinitis)	107	21.29 (2.29)	273	16.48 (1.90)	**0.005**
Weekly ocular symptoms last 3 months	225	18.34 (2.21)	154	16.84 (1.91)	0.254
Respiratory infection last 7 days	223	19.87 (2.18)	157	15.16 (1.91)	**<0.001**
House dust mite allergy	107	25.96 (2.29)	273	15.32 (1.90)	**<0.001**
Parental asthma/allergy	94	19.03 (2.24)	278	17.29 (2.06)	0.280
City and home environment factors					
Megacity (Bandar Lampung = No Depok = Yes)	156	16.46 (2.09)	224	18.75 (2.09)	0.091
Keeping cats	81	18.60 (2.04)	299	17.55 (2.11)	0.532
Keeping birds	65	17.75 (2.11)	315	17.77 (2.09)	0.990
ETS at home	232	16.69 (2.01)	148	19.61 (2.20)	**0.038**
Indoor painting last 12 months	219	17.80 (2.08)	157	17.9 (2.10)	0.967
New floor materials last 12 months	73	17.4 (2.05)	290	17.86 (2.10)	0.781
Odor other than mold odor	43	23.10 (2.31)	337	17.19 (2.05)	**0.013**
Water leakage last 12 months	247	18.39 (2.07)	133	16.68 (2.12)	0.222
Visible mold last 12 months	66	16.38 (2.07)	314	18.08 (2.10)	0.324
Dampness or mold last 5 years	117	19.78 (2.16)	263	16.94 (2.09)	0.059
Any dampness or mold	281	18.42 (2.11)	99	16.04 (2.02)	0.108

GM = Geometric mean GSD = Geometric standard deviation.
[a]All *p*-values were calculated by Student t-test for log FeNO data.
Significant *p*-values ($p<0.05$) are indicated by bold *p*-values.

Table 4. Linear mixed models[a] on relationships between FeNO (ppb) and health and home environment ($N = 380$), stratified by house dust mite (HDM) sensitization.

	HDM allergy ($N = 107$)		No HDM allergy ($N = 273$)		Total ($N = 380$)	
Health variables	FeNO antilog-beta (95%CI)	*p*-value	FeNO antilog-beta (95%CI)	*p*-value	FeNO antilog-beta (95%CI)	*p*-value
Ever had asthma	1.55 (1.02-2.38)	**0.041**	1.49 (1.05-2.12)	**0.025**	1.76 (1.33-2.32)	**<0.001**
Diagnosed asthma	1.42 (0.89-2.29)	0.145	1.67 (1.07-2.59)	**0.023**	1.85 (1.34-2.56)	**<0.001**
Current wheeze	1.34 (0.85-2.14)	0.211	1.33 (1.02-1.73)	**0.035**	1.41 (1.10-1.81)	**0.006**
Current daytime attacks of breathlessness (rest or exercise)	0.70 (0.50-0.96)	**0.029**	0.94 (0.80-1.09)	0.405	0.85 (0.72-0.99)	**0.039**
Current nocturnal attacks of breathlessness	1.42 (0.89-2.26)	0.139	1.11 (0.83-1.47)	0.710	1.25 (0.96-1.62)	0.092
Current asthma	2.16 (1.26-3.73)	**0.006**	1.44 (1.01-2.05)	**0.043**	1.76 (1.28-2.41)	**0.001**
Nose symptoms (rhinitis)	1.36 (1.00-1.85)	**0.047**	1.16 (0.98-1.38)	0.088	1.29 (1.02-1.51)	**0.002**
Respiratory infection last 7 days	1.79 (1.30-2.47)	**<0.001**	1.12 (0.96-1.30)	0.145	1.36 (1.18-1.58)	**<0.001**
Home environment factors						
ETS	0.78 (0.57-1.06)	0.111	0.85 (0.72-0.99)	**0.038**	0.81 (0.70-0.95)	**0.009**
Other odor than mold odor	1.44 (0.90-2.30)	0.125	1.26 (0.99-1.60)	0.057	1.34 (1.06-1.68)	**0.014**
Any dampness or mold	1.48 (1.07-2.03)	**0.017**	1.10 (0.92-1.32)	0.286	1.19 (1.00-1.41)	**0.047**

[a]Models including gender, current smoking, height and city as co-variates (one health or home environment variable in each model). Models were constructed for health variables with associations with FeNO with $p < 0.2$ in the crude analysis in Table 3.
Significant *p*-values ($p<0.05$) are indicated by bold *p*-values.

previous school studies from Malaysia mentioned above, all indicated a high prevalence of allergic airway inflammation. This could be due to a high prevalence of undiagnosed allergic asthma linked to allergic sensitization to house dust mite allergens. Further population studies where asthma is diagnosed clinically are needed from tropical countries.

HDM sensitization was common in our study (28.2%) while sensitization to cat or mold (*Cladosporium* or *Alternaria)* was uncommon. HDM sensitization was associated with increased FeNO. This was expected, since FeNO can be an indicator of allergic (TH2 driven) airway inflammation (7)). The prevalence of HDM sensitization was somewhat higher than that from a recent allergy study from Indonesia, which reported that 19.46% of secondary high school children had HDM sensitization (5).

Diagnosed asthma, current asthma, wheeze and rhinitis were associated with higher FeNO, as reported in previous studies among children of similar age in China (10), Malaysia (21) and Thailand (9). FeNO is elevated in persons having TH2 driven (allergic) asthma (7). However, we found that the association between FeNO and diagnosed asthma and respiratory symptoms was strong even in students without HDM sensitization. Thus it is likely that some students were sensitized to some other allergens not included in our testing. Besides HDM sensitization, sensitization to American cockroach (11.31%), the mold *Mucor mucedo* and

Table 5. Linear mixed models[a] on associations between FeNO (ppb) and co-variates and home environment variables (mutual adjustment models), stratified for current rhinitis ($N=380$).

Co-variates	Rhinitis last 3 months ($N=107$) FeNO antilog-beta (95%CI)	*p*-value	No rhinitis last 3 months ($N=273$) FeNO antilog-beta (95%CI)	*p*-value	Total material ($N=380$) FeNO antilog-beta (95%CI)	*p*-value
Male	0.79 (0.57-1.09)	0.147	0.92 (0.77-1.10)	0.358	0.87 (0.74-1.02)	0.078
Current smoker	1.08 (0.59-1.96)	0.809	0.99 (0.71-1.37)	0.936	1.04 (0.77-1.39)	0.813
Height (per dm)	1.04 (0.93-1.17)	0.487	1.07 (0.99-1.16)	0.100	1.05 (0.98-1.13)	0.144
HDM allergy	1.88 (1.43-2.46)	**<0.001**	1.55 (1.29-1.99)	**<0.001**	1.68 (1.44-1.96)	**<0.001**
City (Lampung = 0 Depok = 1)	0.85 (0.63-1.14)	0.279	0.78 (0.66-0.92)	**0.004**	0.81 (0.70-0.94)	**0.005**
Home environment variables						
ETS	0.66 (0.51-0.87)	**0.003**	0.88 (0.64-1.03)	0.116	0.80 (0.69-0.92)	**0.003**
Other odor than mold odor	1.97 (1.33-2.94)	**0.001**	1.09 (0.85-1.40)	0.498	1.30 (1.04-1.62)	**0.019**
Any dampness or mold	1.38 (0.99-1.92)	0.06	1.11 (0.93-1.32)	0.265	1.21 (1.03-1.42)	**0.019**

[a]Models including gender, current smoking, height, HDM allergy, city, ETS, one odor variable (other odor than mold odor) and a combined dampness variable.
Significant *p*-values ($p<0.05$) are indicated by bold *p*-values.

Table 6. Logistic regression models on relationships between categorized FeNO levels and respiratory health ($N=380$).

Dependent variable	Ever had asthma	Doctor diagnosed asthma	Wheeze in the last 12 months	Current asthma	Nasal symptoms (rhinitis)	Respiratory infection last 7 days
Cathegorized FeNO variable	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95%CI)	OR (95% CI)
Normal value (<20 ppb)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Intermediate value (20-35 ppb)	1.72 (0.61-4.84) $p=0.301$	1.26 (0.32-4.92) $p=0.744$	1.74 (0.73-4.29) $p=0.226$	1.59 (0.47-5.46) $p=0.459$	1.91 (1.06-3.44) **$p=0.031$**	1.58 (0.89-2.80) $p=0.115$
High value (>35 ppb)	2.74 (1.11-6.77) **$p=0.029$**	3.72 (1.35-10.24) **$p=0.011$**	2.47 (1.10-5.53) **$p=0.028$**	2.94 (1.07-8.14) **$p=0.037$**	2.20 (1.25-3.89) **$p=0.006$**	2.79 (1.53-5.07) **$p=0.001$**

Keeping gender, current smoking, height, city, and the categorized FeNO variable as independent variables in the models.
Significant *p*-values ($p<0.05$) are indicated by bold *p*-values.

crab was shown to be common in junior high school children in Indonesia (5).

Recent respiratory infections were common (58.7%) and we found an association between recent respiratory infection and FeNO, especially among students with HDM sensitization. Rhinovirus respiratory infections can increase FeNO but other types of respiratory infections (e.g. by influenza virus, respiratory syncytial virus (RSV), or bacteria) does not increase FeNO (27). Thus, one possibility is that rhinovirus infections were common among the students when we performed the study (spring time). Another possibility could be that some children had asthma-related respiratory symptoms that they interpreted as respiratory infections. Asthmatics are more prone to get respiratory infections and has a higher prescription of antibiotics, as compared to non-asthmatics (28). However, we found no associations between reported respiratory infections in students and wheeze, current asthma or doctor diagnosed asthma. Thus, more detailed investigations are needed in Indonesia on the role of different types of respiratory infection on FeNO.

In our study, ETS exposure reduced FeNO, which is expected since tobacco contains nicotine which can reduce production of nitric oxide (NO) at the cellular level (7). Moreover, we found that dampness and indoor mold was related to increased FeNO, especially among children sensitized to HDM and in homes without ETS. Most previous studies did not find any relationship between indoor mold and FeNO (8,10,15,21,29,30). One study from Thailand found a protective (negative) relationship between indoor mold and dampness and FeNO (9). However, specific microbial agents such as endotoxin (13) and the soil bacteria *Streptomyces sp* (14). can reduce FeNO and Aspergillus molds, such as *Aspergillus fumigatus* (31) and *Aspergillus versicolor* (23) can increase FeNO. Thus, the association between FeNO and dampness and indoor microbial exposure can be different for different microbial species. Moreover, we found that HDM sensitization could modify the association between dampness and mold with FeNO. More detailed microbiome studies on associations between indoor microorganisms and FeNO in Indonesia are needed.

We found that perception of odor was related to higher FeNO but there was no association between this odor (other odor than mold odor) and ETS in the homes. The description of the sources of this odor (cockroaches, dead rats, waste burning, gas, sewage) suggest a mixed exposure including allergens, microbial exposure and outdoor smoke particles). To our knowledge, our results is a new finding. Future studies are needed from Indonesia relating measured exposure at home to FeNO.

Our study has specific strengths. We found no previous epidemiological study on FeNO in school children in Indonesia. FeNO is an objective biomarker of inflammation in the airways and is not influenced by recall bias. In epidemiology, selection bias can be a problem but we recruited students from randomly selected classes. The response rate was relatively high (59%). Moreover, the prevalence of diagnosed asthma was 5.3% in our study, similar as the 4-7% asthma prevalence reported previously from Indonesia (4). Among the participants, 64.5% were girls (expected is about 50%). Since the literature have demonstrated that girls have lower FeNO than boys (7), the overall high FeNO values in this study is less likely to be due to gender-related selection bias This suggests that there was no major respiratory health or gender based selection bias. Another strength is that we performed allergy testing and included personal risk factors such as gender, height, and smoking in the statistical models, and included models with mutual adjustment.

However, our study has some limitations. One limitation is that we selected only eight schools in two cities in Indonesia. Another limitation is that we have no data on the socio-economic status of the families and outdoor air pollution was measured for only a short period. Moreover, the number of covariates were relatively high some statistical models. The study had mainly a descriptive and explorative approach and some of the outcomes of interest had low event rate. Finally, there were no inspections or measurement in the homes and since our study was cross-sectional it can only conclude one associations, not causality.

In conclusion, the high prevalence of students with elevated FeNO could indicate a high prevalence of undiagnosed childhood asthma in this part of Indonesia. HDM sensitization can be a major determinant for FeNO among school children in Indonesia. Dampness and indoor mold can be common in homes in this tropical country, and can increase FeNO. ETS exposure in homes in this population of Indonesian children was high enough to decrease FeNO.

Disclosure statement

The authors declare no conflict of interest.

Funding

This investigation received financial support from the Swedish Research Council (2017-05845), United Nations University-International Institute for Global Health, University Putra Malaysia, University of Indonesia and Universitas Malahayati.

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