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Fractional exhaled nitric oxide (FeNO) and respiratory symptoms in junior high school students in Penang, Malaysia: the role of household exposure

Dan Norbäck [a], Jamal Hisham Hashim [b], Zailina Hashim [c] and Gunilla Wieslander [a]

[a]Department of Medical Science, Occupational and Environmental Medicine, University Hospital, Uppsala, Sweden; [b]Department of Environmental Health and Occupational Safety, Universiti Selangor, Shah Alam, Malaysia; [c]Department of Environmental and Occupational Health, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Malaysia

ABSTRACT
We studied associations between fractional exhaled nitric oxide (FeNO), health and household exposure among school children (N = 348) in Penang, Malaysia. Multiple logistic regression and linear mixed models were applied. Overall, 46.0% had elevated FeNO (>20 ppb) and 10.6% diagnosed asthma. Male gender (p = 0.002), parental asthma or allergy (p = 0.047), cat allergy (p = 0.009) and seafood allergy (p < 0.001), diagnosed asthma (p = 0.001), wheeze (p = 0.001), ocular symptoms (p = 0.001), rhinitis (p = 0.002) and respiratory infections (p = 0.004) were all associated with FeNO. Students exposed to ETS had lower FeNO (p = 0.05). Dampness and mould was associated with wheeze (p = 0.038), especially in wooden homes (interaction p = 0.042) and among students with elevated FeNO (interaction p = 0.024). Cat keeping increased rhinitis (p = 0.041) and respiratory infections (p = 0.008) and modified the dampness associations. In conclusion, FeNO can be associated with ocular and respiratory symptoms. Elevated FeNO, cat keeping and a wooden house can enhance the risk of wheeze when exposed to dampness and mould.

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Introduction

Childhood asthma and allergic diseases are increasing in Asia (Asher et al. 2006) and early life exposure to home environmental factors can influence childhood respiratory illnesses (Lu et al. 2022a, 2022b). Malaysia is a middle-income tropical country with three ethnic groups with different prevalence of asthma (Norback et al. 2021). Older studies reported that 3–10% of Malaysian school children had diagnosed asthma and 5–8% had current wheeze (Omar 1990; Leung and Ho 1994). Newer studies found 8–13% diagnosed asthma (Cai et al. 2011; Ma'Pol et al. 2020; Mohd Isa et al. 2022) and 4–14% current wheeze (Cai et al. 2011; Ma'Pol et al. 2020) in Malaysian children, suggesting an increase of childhood asthma.

Fractional exhaled nitric oxide (FeNO) is a well-established marker of TH2 airway inflammation associated with allergic asthma (Alving and Malinovschi 2010) and rhinitis (e.g. Zhao et al. 2013; Prapamontol et al. 2022). FeNO is elevated if it is above 20 ppb in children (Dweik et al. 2011). FeNO can be associated with height, male gender and immediate-type allergies, while tobacco

CONTACT Dan Norbäck dan.norback@medsci.uu.se Department of Medical Science, Occupational and Environmental Medicine, Uppsala University, University Hospital, Uppsala 75185, Sweden
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smoking can reduce FeNO because nicotine interacts with cellular production of NO (Alving and Malinovschi 2010).

Household air pollution (HAP) can influence asthma and rhinitis (e.g. Raju et al. 2020) but few studies exist on how HAP influences FeNO. Dampness, water leakage and mould can cause microbial growth and chemical degradation of building materials, leading to indoor exposure to microbial volatile organic compounds (MVOC), mould allergens, mycotoxins and other microbial compounds (Norbäck and Cai 2020). However, it is unclear how dampness influences FeNO. Exposure to endotoxin (Casas et al. 2013), the gram-positive bacteria *Streptomyces* sp. (Johansson et al. 2013) and dogs (Casas et al. 2013) have been associated with lower FeNO. In a recent study from Thailand, visible indoor mould at home was associated with lower FeNO in school children (Prapamontol et al. 2022).

We have published results on the role of mould DNA in schools for FeNO (Norbäck et al. 2017a) and ocular health (Norbäck et al. 2017b) in schools in Penang, Malaysia. The first aim of this publication was to investigate associations between FeNO and asthma, reported allergies and respiratory and ocular symptoms in this Penang study. The second aim was to evaluate associations between the home environment (type of house, dampness and mould, environmental tobacco smoke (ETS), cat and dog keeping, new floor materials, and indoor paint emissions) and FeNO. The third aim was to study associations between the home environment and wheeze, rhinitis, ocular and respiratory infections and to evaluate if elevated FeNO enhances health effects of the home environment and to study if there is interaction between different indoor exposures.

Materials and methods

Ethics statement

The Ethics Committee of the National University of Malaysia approved the study proposal, and we received written informed consent from the students and their parents. Moreover, the investigation had received permission from the Penang State Education Department and the schools.

Study population

In the state of Penang, we randomly selected eight junior high schools and in each school, we selected randomly four classes of grade two students. Finally, in each invited class, 20 students were randomly selected from lists of students in the class and then invited to participate in the FeNO study. The random selection procedure included numbering of schools, classes and student and selection by generating random numbers. Data collection was done in September and October 2012 (dry season). In total, 348 students participated. Associations between home environment factors and medical symptoms were analysed in an extended study population (N = 620), adding all grade two students in two additional randomly selected schools in Penang (totally 10 schools). The students in the two additional schools answered the questionnaire but had no FeNO test.

Demographics and medical data

A standardized questionnaire used in previous school studies (Cai et al. 2011; Zhao et al. 2013; Ma'Pol et al. 2020; Norback et al. 2021; Prapamontol et al. 2022) was given to the invited students by their class teacher, and brought home. Initially, the students answered the questionnaire at home with help of their parents or guardians and bought it back to school. After that, staff from our research team went through the answers in the questionnaire in a face-to-face interview to clarify unclear or missing answers.

The questionnaire included yes/no questions on smoking habits, allergies and parental allergy/asthma. Questions on asthma and respiratory health were obtained from the ISAAC study (Asher et al. 2006), the European Respiratory Health Survey (ECRHS) (Janson et al. 2001) and previous school investigations (Cai et al. 2011; Zhao et al. 2013; Ma'Pol et al. 2020; Prapanmontol et al. 2022; Norback et al. 2021).

Questions on respiratory health included yes/no questions on doctors' diagnosed asthma, asthma attacks, asthma medication, wheeze, daytime attacks of shortness of breath during exercise or while resting (two questions) and night-time awakening because of attacks of breathlessness. The recall period was 12 months. Moreover, we asked about rhinitis and ocular symptoms, using questions from previous school studies (e.g. Norbäck et al. 2016). The recall period was 3 months. We dichotomized these symptom variables into weekly or daily symptoms (yes/no). Finally, there was one yes/no question asking if the student have had any respiratory infection within 7 days before the FeNO test was performed.

Measurement of FeNO

We used a small hand-held instrument (NIOX-MINO; Aerocrine AB, Solna, Sweden) to measure FeNO, with 5 seconds exhalation time, following manufacturer's guidelines.

Data on the home environment

We asked yes/no question on type of home (apartment or single-family house), construction material (wood or concrete), cat keeping, dog keeping, tobacco smoke (ETS), new floor materials and indoor painting (recall period 12 months). Moreover, there were four yes/no questions on mould and dampness; water leakage, dampness in the floor materials, visible mould and mould odour (recall period 12 months for all four questions) and one yes/no question on water leakage, flooding or mould growth at home in the last 5 years. One combined yes/no variable was created; any dampness, water leakage or mould in the home, based on the five questions.

Data on climate and air pollution outside the schools

Outside each school, we measured temperature and relative air humidity (RH) by a direct reading instrument and nitrogen dioxide (NO_2) by diffusion sampling, as in previous school studies (e.g. Norback et al. 2021).

Statistical analysis

FeNO was 10 log-transformed as in previous studies (e.g. Zhao et al. 2013; Ma'Pol et al. 2020; Prapanmontol et al. 2022). Initially, we used independent *t*-test to test differences in log FeNO between groups (home exposure and health variables). Then, we constructed a two-level linear mixed models (classroom, student) including four co-variates (gender, ethnicity, current smoking, ETS at home). As in a previous epidemiological study (Wang et al. 2022), study variables with $p < 0.2$ in the bivariate analysis were then included in the models, adjusting for the co-variates. Moreover, we stratified the analysis of significant health variables with respect to any reported allergy (yes/no) and any respiratory infection in the last 7 days. Then, we divided FeNO level into three groups: low FeNO (<20 ppb), intermediate FeNO (20–35 ppb) and high FeNO (>35 ppb), as previously suggested (Dweik et al. 2011). Then, we analysed associations between selected respiratory health variables (as dependent variables) and the categorised FeNO variables (normal, intermediate, high FeNO), in two level (class, student) multi-level logistic regression models including the four co-variates. Moreover, we analysed associations between prevalent home exposure variables (>20% prevalence) and four key health variables, adjusting for ethnicity, smoking, parental asthma/allergy and reported allergy (pollen, cat or dog allergy). Finally, we stratified the analysis with respect to normal or elevated FeNO (less than 20 ppb v.s. 20 ppb or above) as well as for selected home environment variables and calculated p-values for interaction (interaction $p < 0.1$ was considered a significant interaction). We used STATA 12.0 in all calculations. Associations of the linear mixed models were reported as antilog-beta with 95% confidence intervals (CI). Associations in the logistic regression models were reported as odds ratio (OR) with a 95% confidence interval (CI).

Results

Totally, 348 students participated (58%), 52.9% were girls. The age ranged from 14 to 16 years (mean 14 y) and 70.4% were Malay, 13.8% Chinese and 15.8% Indian. Tobacco smoking was uncommon. The majority lived in single family houses, one-fifth had a cat but dog keeping was uncommon. Indoor painting, ETS and dampness, water leakage and mould were common (Table 1). The geometric mean (GM) for FeNO was 19.9 ppb, and geometric standard deviation (GSD) was 2.37. In the bivariate analysis, boys had higher FeNO ($p = 0.002$) (data shown in text only) and there was a tendency of lower FeNO in students with ETS exposure ($p = 0.065$) (Table S1). No associations were found between any other home variable and FeNO (Table S1). Outside the schools, the mean daytime temperature was 28.9 °C (range 26.1–31.8) and mean RH was 75% (range 61–86). The mean concentration of NO_2 outside the schools (7-day mean value) was 19.9 µg/m^3 (range 15.9–22.9)

In the bivariate analysis, students with asthma ($p < 0.001$), diagnosed asthma ($p < 0.001$), wheeze ($p = 0.001$), current asthma ($p = 0.007$), weekly eye symptoms (<0.001), weekly rhinitis symptoms ($p = 0.001$) and current respiratory infections ($p = 0.003$) had higher FeNO. Moreover, those with cat allergy ($p = 0.004$) and seafood allergy ($p = 0.003$) had higher FeNO, and there was a tendency of higher FeNO if at least one of the parents had asthma or rhinitis ($p = 0.069$) (Table 2).

In the multivariate analysis, students with diagnosed asthma ($p = 0.001$), wheeze ($p = 0.001$), current asthma ($p = 0.002$), weekly eye symptoms ($p = 0.002$) and weekly rhinitis ($p = 0.002$) and current respiratory infections ($p = 0.008$) had higher FeNO. Moreover, those with cat allergy ($p = 0.009$), seafood allergy ($p < 0.001$) and with parental allergy or asthma ($p = 0.047$) had higher FeNO (Table 3). In a model including only the four co-variates, males had higher FeNO ($p = 0.002$) and those exposed to ETS had lower FeNO ($p = 0.051$) (shown in text only).

Then, we performed a sensitivity analysis, stratifying with respect to reported allergy (pollen, cat or seafood allergy). In the group reporting allergy, only current asthma was associated with higher

Table 1. Demographics and home environment of the students in Penang (N = 348).

	N	Prevalence (%)
Demographic variables		
Girl (%)	184	52.9
Current smoker (%)	10	2.9
Malay	245	70.4
Chinese	48	13.8
Indian	55	15.8
Home environment variables		
Apartment	153	44.0
Wooden house	71	21.1
Cat keeping	70	20.1
Dog keeping	24	6.9
Keeping birds	11	3.2
ETS at home	167	48.3
Any dampness or mould last 12 months[a]	122	35.1
Any dampness, water leakage or mould last 5 years	72	21.1
Any dampness, water damage or mould last 12 months or last 5 years	157	45.1
Indoor painting last 12 months	146	43.2
New floor materials last 12 months	42	12.4

[a]Flooding or water leakage, floor dampness, indoor mould or mould odour.

Table 2. Bivariate associations between FeNO and health variables (N = 348)[a].

Type of health variable	Prevalence (%)	Yes (N)	FeNO GM (GSD)	No (N)	FeNO GM (GSD)	p-value[a]
Ever had asthma	13.2	46	33.4 (2.51)	302	18.4 (2.29)	**<0.001**
Doctor's diagnosed asthma	10.6	37	32.4 (2.50)	311	18.8 (2.31)	**<0.001**
Wheeze in the last 12 months	14.1	49	28.9 (2.44)	298	18.8 (2.32)	**0.001**
Any daytime breathlessness (rest or exercise) last 12 months	38.0	130	20.8 (2.44)	218	19.4 (2.32)	0.448
Nocturnal attacks of shortness of breath last 12 months	10.8	37	18.7 (2.29)	305	20.1 (2.38)	0.631
Current asthma	7.8	27	30.5 (2.92)	320	19.1 (2.29)	**0.007**
Weekly eye symptoms last 3 months	18.0	62	28.4 (2.55)	282	18.3 (2.28)	**<0.001**
Weekly nose symptoms last 3 months (rhinitis)	31.4	108	24.9 (2.45)	236	18.1 (2.29)	**0.001**
Pollen allergy	8.6	30	24.9 (2.45)	318	19.5 (2.36)	0.135
Cat allergy	8.3	29	31.0 (2.43)	319	19.1 (2.34)	**0.004**
Dog allergy	3.2	11	23.1 (2.57)	337	19.9 (2.37)	0.561
Mould allergy	5.2	18	21.8 (2.78)	330	19.9 (2.35)	0.650
Seafood allergy	14.1	49	27.9 (2.54)	299	18.9 (2.31)	**0.003**
Parental asthma/allergy (heredity)	24.1	84	23.1 (2.45)	264	19.0 (2.50)	0.069
Respiratory infection last 7 days	27.3	95	24.9 (2.25)	253	18.3 (2.38)	**0.003**

[a]Tested by Students *t*-test for log-transformed FeNO values.
Significance for bold values is $p < 0.05$.

Table 3. Two-level linear mixed models (classroom, student) on associations between selected health variables and FeNO[a] (N = 348).

Health variables	FeNO antilog-beta (95%CI)	p-value
Doctor's diagnosed asthma	1.65 (1.23–2.19)	**0.001**
Current wheeze	1.53 (1.18–1.97)	**0.001**
Current asthma	1.71 (1.22–2.40)	**0.002**
Weekly eye symptoms	1.46 (1.15–1.83)	**0.002**
Weekly nose symptoms (rhinitis)	1.36 (1.12–1.65)	**0.002**
Pollen allergy	1.26 (0.92–1.73)	0.157
Cat allergy	1.51 (1.09–2.09)	**0.009**
Seafood allergy	1.58 (1.23–2.04)	**<0.001**
Parental asthma/allergy	1.24 (1.00–1.53)	**0.047**
Respiratory infections last 7 days	1.31 (1.07–1.60)	**0.008**

[a]Adjustment for, ethnicity, gender, smoking and ETS at home (one health variable per model). Models were created for health variables with p < 0.2 in the crude analysis.
Significance for bold values is $p < 0.05$.

FeNO (p = 0.035). In the group without reported allergy, diagnosed asthma (p = 0.014), wheeze (p = 0.003), current asthma (p = 0.035), weekly eye symptoms (p = 0.022) and weekly rhinitis (p = 0.035) were all associated with FeNO. In the group with current respiratory infections, diagnosed asthma (p = 0.013), current asthma (p = 0.008) and weekly eye symptoms (p = 0.014) were associated with FeNO. In the group without current respiratory infections, diagnosed asthma (p =

Table 4. Two-level (classroom, student) multiple logistic regression analysis of associations between selected health variables (dependent variables) and categorized FeNO levels (N = 348).

Dependent variable	Doctor diagnosed asthma	Wheeze	Current asthma	Weekly ocular symptoms	Weekly nasal symptoms (rhinitis)	Respiratory infection last 7 days
Categorized FeNO variable	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95%CI)	OR (95% CI)	OR (95% CI)
Normal (<20 ppb)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Intermediate (20–35 ppb)	1.72 (0.64–4.56) (p = 0.287)	3.00 (1.33–6.75) **(p = 0.008)**	1.02 (0.30–3.45) (p = 0.983)	0.81 (0.35–1.87) (p = 0.617)	1.12 (0.61–2.05) (p = 0.389)	2.18 (1.15–4.12) **(p = 0.023)**
High (>35 ppb)	2.68 (1.15–6.22) **(p = 0.022)**	4.26 (1.97–9.18) **(p <0.001)**	2.77 (1.08–7.13) **(p = 0.035)**	2.26 (1.25–3.81) **(p = 0.013)**	2.18 (1.25–3.81) **(p = 0.006)**	3.13 (1.67–5.86) **(p < 0.001)**

Keeping gender, ethnicity, current smoking, ETS at home, reported allergy (pollen, cat or seafood allergy) and categorized FeNO in all models (one model per health variable).
Significance for bold values is $p < 0.05$.

0.006), wheeze (p = 0.031), current asthma (p = 0.019) and weekly eye symptoms (p = 0.013) and weekly rhinitis (p = 0.28) were associated with FeNO (Table S2).

Then, we divided FeNO into three groups. In total, 54.0% had low FeNO (<20 ppb), 18.4% had intermediate FeNO (20–35 ppb) and 27.6% had high FeNO (>35 ppb). Boys (p = 0.003) and those reporting any allergy (p = 0.003) had more often high FeNO (Table S3). If stratifying FeNO by ethnicity, prevalence of high FeNO (<35 ppb) was 27.6% in Malay, 20.8% in Chinese and 30.9% in Indian students (data given in text only). Then, we analysed associations between selected health variables and the categorised FeNO variable in multilevel logistic regression models, using normal FeNO (<20 ppb) as the reference category. Wheeze (p = 0.008) and current respiratory infections (p = 0.023) were associated with intermediate FeNO. Diagnosed asthma (p = 0.022), wheeze (p < 0.001), current asthma (p = 0.035), weekly ocular symptoms (p = 0.013), weekly rhinitis (p = 0.006) and current respiratory infections (p < 0.001) were all associated with high FeNO (Table 4).

Moreover, we analysed associations between prevalent home environment factors (>20% prevalence) and wheeze, ocular symptoms, rhinitis and current respiratory infections. Cat keeping was associated with rhinitis (p = 0.041) and current respiratory infections (p = 0.008). No associations

Table 5. Associations between selected home environment variables (>20% prevalence) and current wheeze, ocular symptoms, rhinitis and respiratory infections (N = 620).

Home environment variable	Wheeze OR (95% CI)	p-value	Ocular symptoms OR (95% CI)	p-value	Rhinitis OR (95% CI)	p-value	Respiratory infection OR (95% CI)	p-value
Apartment building	0.78 (0.45–1.36)	0.377	1.35 (0.83–2.20)	0.225	0.76 (0.51–1.14)	0.186	0.83 (0.49–1.41)	0.495
Wooden house	1.58 (0.90–2.58)	0.114	0.77 (0.45–1.31)	0.335	1.11 (0.73–1.69)	0.617	1.16 (0.62–2.20)	0.641
ETS at home	1.19 (0.71–1.99)	0.513	0.95 (0.59–1.55)	0.850	1.14 (0.78–1.67)	0.505	1.06 (0.64–1.77)	0.813
Cat keeping	1.01 (0.55-1.86)	0.972	0.92 (0.52–1.64)	0.784	1.57 (1.02–2.43)	**0.041**	2.29 (1.24–4.25)	**0.008**
Any dampness, water leakage or mould[a]	1.72 (1.03–2.87)	**0.038**	1.03 (0.63–1.66)	0.916	1.18 (0.81–1.73)	0.383	1.47 (0.89–2.43)	0.129
Indoor painting last 12 months	0.84 (0.50–1.41)	0.501	0.88 (0.54–1.42)	0.596	1.13 (0.77–1.64)	0.542	0.95 (0.56–1.60)	0.839

Associations analysed by two-level (classroom, student) multilevel logistic regression models, keeping gender, ethnicity, current smoking, parental asthma/allergy reported allergy (pollen or cat or seafood allergy) in all models
[a]Water leakage or flooding, signs of floor dampness, visible indoor mould or mould odour in the last 12 months and/or water leakage, dampness or mould in the last 5 years
Significance for bold values is $p < 0.05$.

Table 6. Stratified analysis of associations between selected home environment variables and current wheeze, rhinitis and respiratory infections by two-level (classroom, student) multilevel logistic regression[a].

	Stratification variable groups	Wheeze OR (95% CI)	Interaction *p*-value	Rhinitis OR (95% CI)	Interaction *p*-value	Current respiratory infections OR (95% CI)	Interaction *p*-value
Home exposure variable							
Cats at home	Normal FeNO	3.46 (0.64–18.6) p = 0.148	**0.026**	2.32 (0.98–5.52) p = 0.056	0.945	2.75 (1.08–7.03) **p = 0.034**	0.769
Cats at home	Elevated FeNO	0.51 (0.14–1.78) p = 0.290		1.62 (0.63–4.18) p = 0.322		2.44 (0.90–6.65) p = 0.081	
Home exposure variable							
Dampness/mould[b]	Normal FeNO	2.11 (0.60–7.36) p = 0.242	0.634	1.22 (0.60–2.46) p = 0.584	0.476	1.21 (0.55–2.63) p = 0.638	0.171
Dampness/mould[b]	Elevated FeNO	3.44 (1.43–8.27) **p = 0.006**		1.71 (0.78–3.75) p = 0.183		2.48 (1.11–5.53) **p = 0.026**	
Home exposure variable							
Dampness/mould[b]	Concrete construction	0.91 (0.46–1.80) p = 0.796	**0.042**	1.21 (0.74–1.99) p = 0.441	0.416	1.22 (0.68–2.20) p = 0.498	**0.088**
Dampness/mould[b]	Wooden construction	5.54 (2.10–14.6) **p = 0.001**		1.04 (0.54–1.99) p = 0.911		2.96 (0.94–9.32) p = 0.064	
Home exposure variable							
Dampness/mould[b]	No cats at home	1.62 (0.89–2.94)¨ p = 0.112	0.467	1.11 (0.71–1.75) p = 0.64	0.658	1.67 (0.94–2.97) p = 0.08	0.541
Dampness/mould[b]	Cats at home	4.01 (0.98–16.4) **p = 0.053**		1.32 (0.63–2.77) p = 0.46		1.06 (0.36–3.15) p = 0.91	

[a]Adjusting for gender, ethnicity, current smoking, parental asthma/allergy reported allergy (pollen or cat or seafood allergy) in all models.
[b]Water leakage or flooding, signs of floor dampness, visible indoor mould or mould odour in the last 12 months and/or water leakage, dampness or mould in the last 5 years
Significance for bold values is $p < 0.05$ for association p-values and $p < 0.1$ for interaction p-values.

were found between any home environment variable and ocular symptoms (Table 5). Sensitivity analysis was performed for home environment factors with $p < 0.2$ in Table 5, stratifying by normal (less than 20 ppb) v.s. elevated (20 ppb or higher) FeNO (Table 6). Cat keeping was associated with symptoms in the group with normal FeNO, significant for current respiratory infections ($p = 0.034$). Moreover, there were associations between the dampness variable and wheeze ($p = 0.006$) and current respiratory infections ($p = 0.026$) in the group with elevated FeNO, only. Living in a wooden house was not associated with any health variable, neither in the group with normal nor with elevated FeNO (data shown in text only).

Finally, we analysed interaction between home environment factors with $p < 0.2$ in Table 5. The associations between the dampness variable and respiratory symptoms were significant only among children living in a wooden house ($p = 0.001$ for wheeze and $p = 0.064$ (borderline significance) for current respiratory infections). An association between the dampness variable and wheeze was found only among children with cats at home ($p = 0.053$). Significant interaction terms ($p < 0.1$) were found for interaction by FeNO on the association between cat keeping and wheeze (interaction $p = 0.026$). Interaction by type of construction (wood v.s. concrete) was found for the association between the dampness variable and wheeze (interaction $p = 0.042$) and for the association between the dampness variable and respiratory infections (interaction $p = 0.088$) (Table 6).

Discussion

The outdoor concentration of NO_2 outside the schools was low and similar at all schools (15.9–22.9 $\mu g/m^3$) indicating low levels of traffic-related air pollution in the area. However, almost half (46.0%) of the students had elevated FeNO (18.4% intermediate and 27.6% high values) according to established normal values (Dweik et al. 2011). The overall GM was 19.9 ppb, similar as in two other school studies in Malaysia. They reported a GM of 15.7 ppb in Terengganu children (Ma'Pol et al. 2020) and 19.5 ppb in schools in Melaka and Putrajaya (Adman et al. 2020). Malay children tended to have higher FeNO than Chinese children, in agreement with another study from Malaysia, reporting that Malay children had more asthma than Chinese (Norback et al. 2021). We found that boys and students with allergies had higher mean FeNO, which is consistent with previous studies (Alving and Malinovschi 2010). Our finding that cat allergy and seafood allergy are determinants of FeNO is in agreement with a previous study in school children in Terengganu, Malaysia (Ma'Pol et al. 2020). Reports on seafood allergy were common in our study (14.4%). We had no information on allergy to house dust mites (HDM) in our study, but the Terengganu study found that 39.4% of the children had skin prick positivity to HDM (39.4%) in school children in Malaysia (Ma'Pol et al. 2020). Moreover, other studies have demonstrated a cross-reactivity between seafood allergy and HDM allergy (Boquete et al. 2011; Rosenfield et al. 2017). Thus, our finding of an association between seafood allergy and FeNO may be related to cross-reactivity with HDM allergy.

Doctor diagnosed asthma and current asthma were associated with FeNO. This is in agreement with previous studies from China (Zhao et al. 2013) and Malaysia (Ma'Pol et al. 2020). Moreover, wheeze was consistently associated with FeNO in our study, even in the group with intermediate FeNO level (20–35 ppb). These are similar results as found in a previous school study in Chinese students (Zhao et al. 2013). Moreover, we found that ocular and nasal symptoms were associated with FeNO, indicating that these two questions can be related to airway inflammation. Similar results were found in a school study from Thailand (Prapamontol et al., 2022). FeNO is mainly a marker of allergic (TH2 driven) asthma (Alving and Malinovschi 2010) but in our study the association between asthma and FeNO was strong even in students not reporting any allergy. Previous population studies have reported a high prevalence of HDM allergy in Malaysian population (40–50%) (Lim et al. 2016; Ma'Pol et al. 2020), but we had no information on HDM allergy in our study. Thus, it is likely that in the group not reporting any allergies, many had HDM allergy which could trigger asthma and elevated FeNO.

About one-fourth of the students reported respiratory infections within the week before the FeNO test was performed. We found a consistent association between recent respiratory infection and FeNO. Respiratory infections by rhinoviruses can cause elevated FeNO, but infections by respiratory syncytial virus (RSV) or influenza virus tend to be associated with reductions rather than increases in FeNO. Moreover, there is no evidence that bacterial respiratory infections influence FeNO (Malinovschi et al. 2015). We performed our study during the dry months, and it is possible that rhinovirus infections were common during that period.

FeNO level was lower among students with ETS at home. Nicotine can decrease production of NO on the cellular level (Alving and Malinovschi 2010) and one large study from the USA, assessing ETS exposure by measuring cotinine in blood, reported that ETS exposure reduced FeNO (Merianos et al. 2021). Thus, we conclude that the degree of ETS exposure in the homes in Penang was sufficiently high to reduce FeNO levels in the students.

Dampness, water leakage and indoor mould were common and increased the risk of current wheeze, in agreement with conclusions from previous reviews (e.g. Quansah et al. 2012). However, our study is one of the few studies on this topic from a tropical country. FeNO was not associated with dampness or mould, but FeNO modified the association between the dampness variable and respiratory illness. In the group with elevated FeNO (20 ppb or higher) dampness was associated with current wheeze and respiratory infections, but we found no such associations among children with normal FeNO. To our knowledge, our study is the first on interaction of FeNO on the association between dampness and respiratory symptoms. We conclude that children with Th2 driven airway inflammation are more sensitive to dampness related indoor exposure. Previous studies in school children in Taiwan have demonstrated gene-environment interaction between dampness exposure at home and genetic disposition for inflammation, detected by specific SNPs (Tsai et al. 2011; Su et al. 2012).

We found that cat keeping was associated with rhinitis and current respiratory infections. Cats produce allergens (e.g. Fel d1) and 8.3% of the children reported cat allergy, which was associated with higher FeNO. However, a stratified analysis showed that cat keeping was a significant risk factor for rhinitis and respiratory infections only in the group with normal FeNO. This suggests that the association between cat keeping and respiratory symptoms was not mediated by a Th2 driven allergic airway inflammation. Cat keeping can increase microbial exposure indoors, including endotoxin (Chen et al. 2012) and beta-1,3-glucan, a fungal cell wall compound (Tischer et al. 2015). Moreover, we found that cat keeping modified the respiratory effects of dampness and indoor mould. Children in homes with cats had a significant association between dampness and wheeze, while children in homes without cats had a significant association between dampness and respiratory infections. One possible explanation could be that microbial exposure associated with cat keeping can cause respiratory symptoms by other mechanisms than Th2 driven airway inflammation, and that microbial exposure linked to cat keeping can modify respiratory effects of dampness and indoor mould.

Traditionally homes in Malaysia were made of wood, but nowadays most are concrete buildings. Our interaction analysis showed that living in wooden homes significantly enhanced the effects of dampness and indoor mould on wheeze and respiratory infections. To our knowledge, this is a new finding. However, since tropical countries have high air humidity and heavy rains in wet season, wood can be affected by rot fungi and mould. Moreover, wooden chip board material can emit formaldehyde and some types of wood emit terpenes, chemical compounds associated with respiratory illness (Norbäck et al. 1995). Few studies have investigated how types of construction (wood versus concrete buildings) modify health effects of other indoor exposures. In a recent study from Japan, school children living in wooden homes had a higher risk of rhinitis if the home was recently painted indoors. In contrast, the risk of rhinitis associated with window pane condensation was lower in wooden homes as compared to concrete buildings (Takaoka et al. 2022). Window pane condensation is a sign of high air humidity and poor ventilation in a cold climate. In conclusion, more epidemiological studies are needed on interaction between different indoor exposures.

Our study has a number of strengths. FeNO is an objective marker of airway inflammation, and our study is one of the few on FeNO and the home environment in the tropics. Selection bias can be a problem in epidemiology, but our participants were randomly selected. The participation rate was not very high (58%) but since 52.9% of the participants were girls there was no evidence of gender-related selection bias. Moreover, since the proportion of students with diagnosed asthma was similar as in previous studies Malaysian studies, there was no evidence of asthma-related selection bias.

Our study had some limitations. One limitation is that the study was performed in one part of Malaysia (State of Penang) only. Moreover, data on the home were questionnaire data only, and there were no indoor environment measurements or inspections of the homes. Finally, since the study was cross-sectional, we cannot draw clear conclusions on causality.

Conclusions

The high prevalence of elevated FeNO level indicates a high prevalence of undiagnosed asthma among students in Penang. Rhinitis, ocular and respiratory symptoms among school children in this area of Malaysia can be due to Th2 driven respiratory inflammation. Cat keeping can be a risk factor for rhinitis and respiratory infections. Th2 driven respiratory inflammation, as indicated by elevated FeNO, can enhance the association between dampness and mould and respiratory symptoms such as wheeze and respiratory infections. Moreover, living in a wooden home and keeping cats can enhance the risk of having wheeze when exposed to dampness or mould at home. Measures are needed to reduce FeNO and improve the home environment in order to improve respiratory health in school children in Malaysia.

Disclosure statement

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ORCID

Dan Norbäck http://orcid.org/0000-0002-5174-6668
Jamal Hisham Hashim http://orcid.org/0000-0001-8154-5069

References

Adman MA, Hashim JH, Manaf MRA, Norback D. 2020. Associations between air pollutants and peak expiratory flow and fractional exhaled nitric oxide in students. Int J Tuberc Lung Dis. 24:189–195. doi:10.5588/ijtld.19.0096.

Alving K, Malinovschi A. 2010. Basic aspects of exhaled nitric oxide. In: Horvath I de Jongste J, editors. Exhaled biomarkers. Plymouth: European Respiratory Society. pp. 1–32.

Asher MI, Montefort S, Björkstén B, Lai CKW, Strachan DP, Weiland SK, Williams H, ISAAC Phase Three Study Group. 2006. 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. 368:733–743. doi:10.1016/S0140-6736(06)69283-0.

Boquete M, Iraola V, Morales M, Pinto H, Francisco C, Carballas C, Carnes J. 2011. Seafood hypersensitivity in mite sensitized individuals: is tropomyosin the only responsible allergen. Ann Allergy Asthma Immunol. 106:223–229. doi:10.1016/j.anai.2010.11.014.

Cai GH, Hashim JH, Hashim Z, Bloom E, Larsson L, Lampa E, Norbäck D, Norbäck D. 2011. Fungal DNA, allergens, mycotoxins and associations with asthmatic symptoms among pupils in schools from Johor Bahru, Malaysia. Pediatr Allergy Immunol. 22:290–297. doi:10.1111/j.1399-3038.2010.01127.x.

Casas L, Tischer C, Wouters IM, Torrent M, Gehring U, Garcia-Esteban R, Thiering E, Postma DS, de Jongste J, Smit HA, et al. 2013. Early life microbial exposure and fractional exhaled nitric oxide in school-age children: a prospective birth cohort study. Environ Health. 12:103. doi:10.1186/1476-069X-12-103.

Chen CM, Thiering E, Doekes G, Zock JP, Bakolis I, Norbäck D, Sunyer J, Villani S, Verlato G, Täubel M, et al. 2012. Geographic variation and the determinants of domestic endotoxin levels in mattress dust in Europe. Indoor Air. 22:24–32. doi:10.1111/j.1600-0668.2011.00740.x.

Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, Olin AC, Plummer AL, Taylor DR. 2011. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med. 184:602–615. doi:10.1164/rccm.9120-11ST.

Janson C, Anto J, Burney P, Chinn S, de Marco R, Heinrich J, Jarvis D, Kuenzli N, Leynaert B, Luczynska C, et al.2001. The European Community Respiratory Health Survey: what are the main results so far? European Community Respiratory Health Survey II. Eur Respir J. 18:598–611. doi:10.1183/09031936.01.00205801.

Johansson E, Reponen T, Vesper S, Levin L, Lockey J, Ryan P, Bernstein DI, Villareal M, Khurana Hershey GK, Schaffer C, et al. 2013. Microbial content of household dust associated with exhaled NO in asthmatic children. Environ Int. 59:141–147. doi:10.1016/j.envint.2013.05.011.

Leung R, Ho P. 1994. Asthma, allergy, and atopy in three south-east Asian populations. Thorax. 49:1205–1210. doi:10.1136/thx.49.12.1205.

Lim FL, Hashim Z, Md Said S, Than LT, Hashim JH, Norbäck D. 2016. Fractional exhaled nitric oxide (FeNO) among office workers in an academic institution Malaysia - associations with asthma, allergies and office environment. J Asthma. 53:353–361. doi:10.3109/02770903.2015.1077861.

Lu C, Liu Z, Liao H, Yang W, Li Q, Liu Q. 2022a. Effects of early life exposure to home environmental factors on childhood allergic rhinitis: modifications by outdoor air pollution and temperature. Ecotoxicol Environ Saf. 244:114075. doi:10.1016/j.ecoenv.2022.114076.

Lu C, Yang W, Liu Z, Liao H, Li Q, Liu Q. 2022b. Effect of preconceptional, prenatal and postnatal exposure to home environmental factors on childhood pneumonia: sA role in early life exposure. Environ Res. 214:114098. doi:10.1016/j.envres.2022.114098.

Malinovschi A, Ludviksdottir D, Tufvesson E, Rolla G, Bjermer L, Alving K, Diamant Z. 2015. Application of nitric oxide measurements in clinical conditions beyond asthma. Eur Clin Respir J. 2:28517.

Ma'Pol A, Hashim JH, Norbäck D, Weislander G, Hashim Z, Isa ZM. 2020. FeNO level and allergy status among school children in Terengganu, Malaysia. J Asthma. 57:842–849. doi:10.1080/02770903.2019.1614614.

Merianos AL, Jandarov RA, Cataletto M, Mahabee-Gittens EM. 2021. Tobacco smoke exposure and fractional exhaled nitric oxide levels among U.S. adolescents. Nitric Oxide. 117:53–59. doi:10.1016/j.niox.2021.10.004.

Mohd Isa KN, Jalaudin J, Mohd Elias S, Mohamed N, Hashim JH, Hashim Z. 2022. Evaluation of the relationship between fractional exhaled nitric oxide (FeNO) with indoor PM_{10}, $PM_{2.5}$ and NO_2 in suburban and urban schools. Int J Environ Res Public Health. 19:4580. doi:10.3390/ijerph19084580.

Norbäck D, Björnsson E, Janson C, Widström J, Boman G. 1995. Asthmatic symptoms and volatile organic compounds, formaldehyde, and carbon dioxide in dwellings. Occup Environ Med. 52:388–395. doi:10.1136/oem.52.6.388.

Norbäck D, Cai GH. 2020. Microbial agents in the indoor environment: associations with health. In: Kishi R, Norbäck D, and Araki A, editors. Indoor environmental quality and health risk toward healthier environment for all. Singapore: Springer press; pp. 179–198.

Norback D, Hashim Z, Ali F, Hashim JH. 2021. Asthma symptoms and respiratory infections in Malaysian students - associations with ethnicity and chemical exposure at home and at school. Environ Res. 197:111061. doi:10.1016/j.envres.2021.111061.

Norbäck D, Hashim JH, Hashim Z, Cai GH, 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. SciTotal Environ. 2017a;577:148–154. doi:10.1016/j.scitotenv.2016.10.148.

Norbäck D, Hashim JH, Hashim Z, Sooria V, Ismail MS, Wieslander G. 2017b. Ocular symptoms and tear film break up time (BUT) among junior high school students in Penang, Malaysia- Associations with fungal DNA in school dust. Int J Hyg Environ Health. 220:697–703. doi:10.1016/j.ijheh.2017.01.016.

Norbäck D, Hashim JH, Markowicz P, Cai GH, Hashim Z, Ali F, Larsson L. 2016. Endotoxin, ergosterol, muramic acid and fungal DNA in dust from schools in Johor Bahru, Malaysia – Associations with rhinitis and sick building syndrome (SBS) in junior high school students. Sci Total Environ. 545-546:95–103. doi:10.1016/j.scitotenv.2015.12.072.

Omar AH. 1990. Respiratory symptoms and asthma in primary school children in Kuala Lumpur. Acta Paediatr Jpn. 32:183–187. doi:10.1111/j.1442-200X.1990.tb00807.x.

Prapamontol T, Norbäck D, Thongjan N, Suwannarin N, Somsunun K, Ponsawansong P, Khuanpan T, Kawichai S, Naksen W. 2022. Fractional exhaled nitric oxide (FeNO) in students in northern Thailand: associations with

respiratory symptoms, diagnosed allergy and the home environment. J Asthma. 59:1787–1795. doi:10.1080/02770903.2021.1968424.
Quansah R, Jaakkola MS, Hugg TT, Heikkinen SA, Jaakkola JJ, Behrens T. 2012. Residential dampness and molds and the risk of developing asthma: a systematic review and meta-analysis. PLoS One. 7:e47526. doi:10.1371/journal.pone.0047526.
Raju S, Siddharthan T, McCorman MC. 2020. Indoor air pollution and respiratory health. Clin Chest Med. 41:825–843. doi:10.1016/j.ccm.2020.08.014.
Rosenfield L, Tsoulis MW, Milio K, Schnittke M, Kim H. 2017. High rate of house dust mite sensitization in a shrimp allergic southern Ontario population. Allergy Asthma ClinImmunol. 13:5.
Su MW, Tung KY, Liang PH, Tsai CH, Kuo NW, Lee YL. 2012. Gene-gene and gene-environmental interactions of childhood asthma: a multifactor dimension reduction approach. PLoS One. 7:e30694.
Takaoka M, Suzuki K, Norback D. 2022. Rhinitis in Japanese students –associations with window pane condensation, recent indoor painting, wooden home and dog allergen at school. Int J Environ Health Res. doi:10.1080/09603123.2022.2104225. .
Tischer C, Zock JP, Valkonen M, Doekes G, Guerra S, Heederik D, Jarvis D, Norbäck D, Olivieri M, Sunyer J, et al. 2015. Predictors of microbial agents in dust and respiratory health in the Ecrhs. BMC Pulm Med. 15:48.
Tsai CH, Tung KY, Chen CH, Lee YL. 2011. Tumour necrosis factor G-308A polymorphism modifies the effect of home dampness on childhood asthma. Occup Environ Med. 68:771–776.
Wang J, Janson C, Malinovschi A, Holm M, Franklin KA, Modig L, Johannesen A, Schlünssen V, Gislason T, Jogi NO, et al. 2022. Asthma, allergic rhinitis and atopic dermatitis in association with home environment. The RHINE study. Sci Total Environ. 853:158639.
Zhao Z, Huang C, Zhang X, Xu F, Kan H, Song W, Wieslander G. 2013. Fractional exhaled nitric oxide in Chinese children with asthma and allergies – a two-city study. Respir Med. 107:161–171.