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RESEARCH PAPER

School Indoor Air Pollutants: In Relation to Allergy and Respiratory Symptoms among School Children in Urban Areas

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Abstract

Indoor air pollutants affect children's health and previous research mostly focuses on respiratory and allergic diseases. However, little is known about the risks among school children in East Malaysia. Therefore, we studied associations between school children's respiratory and allergic symptoms and indoor air pollutants in schools in Sabah, Malaysia. We randomly selected 332 school children (14 years old) from 24 classrooms in 6 secondary schools in Kota Kinabalu, Sabah. Information on personal characteristics, respiratory and allergic symptoms were gathered by using a standard questionnaire. The skin prick test was used to characterize their atopy. In each classroom, the indoor concentrations of particulate matter (PM_{10} and $PM_{2.5}$), nitrogen dioxide (NO_2), formaldehyde, total volatile organic compounds (TVOC), carbon dioxide (CO_2) temperature and relative humidity were monitored. Overall, 11.7% reported doctor-diagnosed asthma, 14.8% wheezing, 17.5% day-time breathlessness, 37.0% breathlessness after exercise, 13.0% breathlessness at night-time, 55.1% rhinitis and 10.8% skin allergic in the last 12 months. Regression analysis showed that the onset of wheezing was common in doctor-diagnosed asthma (OR= 8.29, 95% CI= 3.70-16.10) and with parental asthma/allergy (OR= 2.13, 95% CI= 1.10-4.15), and associated with concentrations of NO_2 (OR= 1.03, 95% CI= 1.01-1.21) and CO_2 (OR= 1.01, 95% CI= 1.01-1.11). Day-time breathlessness was associated with indoor NO_2 (OR=1.02, 95% CI= 1.02-1.35) and TVOC (OR= 1.30, 95% CI= 1.10-1.52). The indoor concentrations of NO_2, CO_2, TVOC and $PM_{2.5}$ as well as parental asthma/allergy, and parental smoking were risk factors to the health outcome of respiratory and allergic symptoms.

Keywords: Children, School, Indoor air quality, Respiratory symptoms, Allergic symptoms

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INTRODUCTION

Indoor air pollutants exposure in children is associated with various disease conditions, especially allergic respiratory diseases such as asthma, respiratory infections and chronic obstructive pulmonary diseases (COPD). Several epidemiological studies have demonstrated a relationship between indoor air pollutants in the school micro-environment with development and exacerbation of asthma among school children (Fan et al., 2017; Gaffin et al., 2018; Sasso et al., 2019; Suhaimi et al., 2020). Moreover, the indoor school environment has been influenced by the local outdoor air, building characteristics (design, ventilation system, maintenance) and occupant behaviors (Śmiełowska et al., 2017). Particularly, particulate matter of varying sizes (PM_{10}, $PM_{2.5}$), nitrogen dioxide (NO_2), sulphur dioxide (SO_2), carbon monoxide (CO) and ozone (O_3) identified inside the classrooms are mainly related to the combustion of fossil fuels and road traffic emission (Gabriel et al., 2021). Children are far more vulnerable to the adverse effects of indoor air pollutants than adults due to their higher breathing rates relative to body weights, breathe air nearer to the ground, and immaturity of immune system and lungs (Goldizen et al., 2016).

Furthermore, the extant literature suggests that personal attributes, changing lifestyle, urbanization together with environmental characteristics are associated with the prevalence of asthma (Benedictis and Bush, 2007; Nyenhuis et al., 2017). Common symptoms associated with asthma are wheezing, breathlessness, chest tightness and coughing, and these symptoms severity vary from person to person (Aalderen, 2012). Several previous studies demonstrated that air pollutants (PM_{10}, NO_2, SO_2, O_3) measured inside the classrooms were related to the onset of wheezing, attacks of breathlessness, rhinitis (Deng et al., 2016; Li et al., 2019; Madureira et al., 2015; Mann et al., 2010; Velická et al., 2015). Additionally, a review has summarized that the short-term exposure of air particulate and respiratory symptoms in children are not homogenous across studies, possibly due to differences in the inflammatory response to a different composition of particulate and various sources of indoor pollutants in households and schools (Liu et al., 2018). Therefore, investigation of the interrelationship between indoor air parameters and respiratory outcomes among the vulnerable group, especially children is important (Suhaimi et al., 2020).

We have previously reported studies conducted in Peninsular Malaysia (Penang, Johor Bahru, Kuala Terengganu, and Hulu Langat) and found that the prevalence of doctor-diagnosed asthma among school children aged 14 years old was increasing. We also found a variation in the pattern of associations between indoor air pollutants and respiratory symptoms. Therefore, we decided to conduct this study because of these observations and no previous study reported from East Malaysia. The main objective of this study was to assess the associations between the onset of respiratory and allergic symptoms among school children with indoor air pollutants in the school micro-environment in Sabah, Malaysia.

METHODOLOGY

Kota Kinabalu, Sabah (East Malaysia) is located in the northern part of the island Borneo, with approximately 527,600 total populations recorded in the year 2019 (DOSM, 2020). Kota Kinabalu is the capital city of the state of Sabah, which experiences a typical equatorial humid climate with high humidity (average 79-85%) and considerable rainfall (average 2,075 mm), and small variation of temperature (annual range of 30-32°C) throughout the year (Tating et al., 2015). Many regions of Kota Kinabalu have seen fast urbanization.

A total of 332 school children aged 14 years old were randomly selected from six secondary schools in Kota Kinabalu. They were chosen at random from four classrooms in each school (Figure 1). School children, who have been attending the same school since January 2018 (or

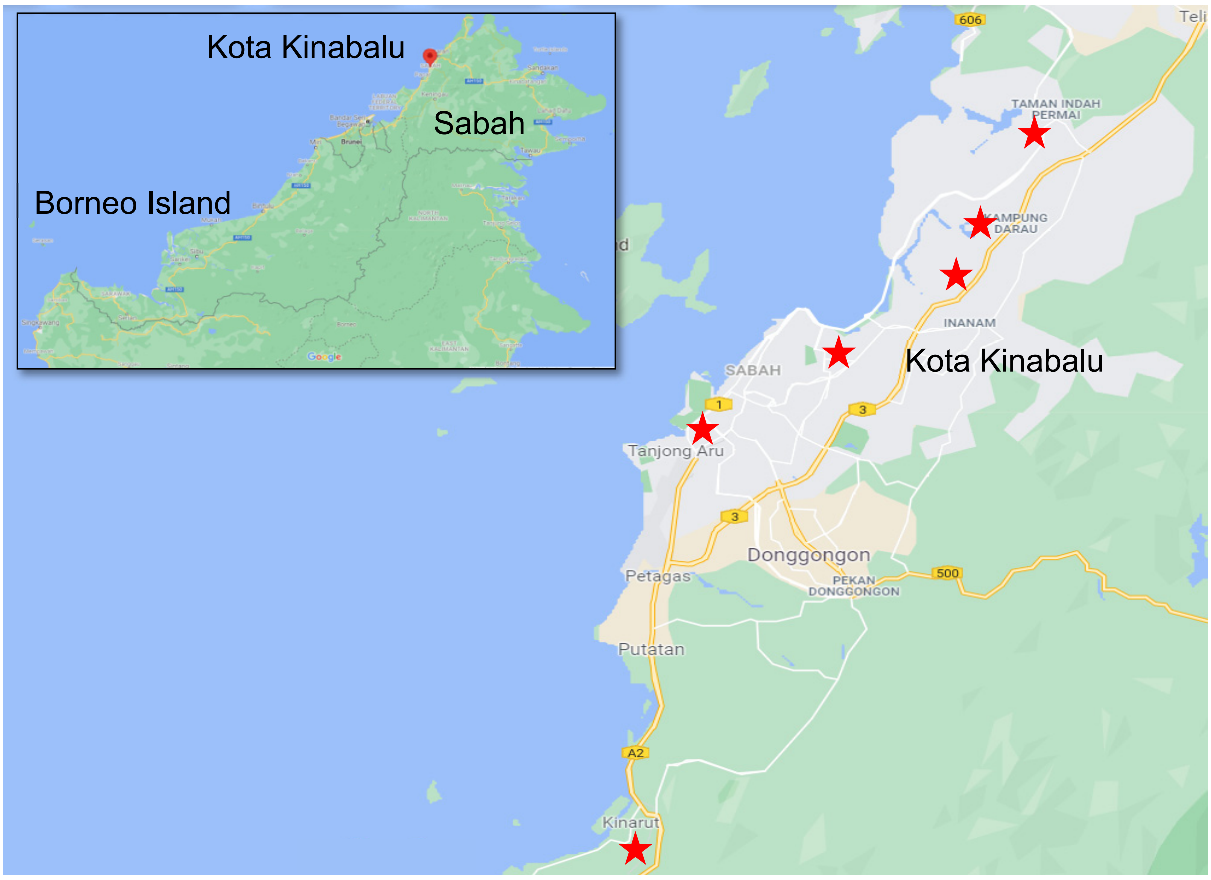

Fig. 1. Map of Kota Kinabalu, Sabah, Malaysia (study area) and location of six selected schools (red stars) (the map was adapted from Google).

more than 18 months) and have acquired written consent from their guardians, as well as their assent, were included as participants. Conversely, school children with concomitant heart diseases and severe asthma conditions were excluded.

The study protocol (JKEUPM-2018-189) was approved by the Ethics Committee for Research Involving Human Subjects University Putra Malaysia (JKEUPM). All school children were informed about the study procedures (questionnaire and clinical assessment) and given a formal consent form for the guardian's approval before this study have started.

Information on demographic characteristics, current asthma information, doctor-diagnosed asthma, respiratory symptoms, and allergic symptoms were collected by self-administrative questionnaire. We repeated the distribution of a standard questionnaire adapted from the International Study of Asthma and Allergies in Childhood (ISAAC), the European Community Respiratory Health Survey (ECRHS) and already used in our previous school studies (Cai et al. 2011; Ma'pol et al. 2019; Norbäck, et al. 2017). There were questions (yes/no) on doctor-diagnosed asthma, any asthma attack in the last 12 months, asthma medication, wheezing or whistling in the chest in the last 12 months, breathlessness attack at daytime, after exercise and at night-time, and respiratory infections during the last 3 months. Also, there were questions on the smoking status and parental asthma/allergy. This information was verified during a face-to-face interview and telephone calls with the children's respective guardians.

Allergic sensitizations were defined using allergy skin prick test (SPT) on five common allergens, including house dust mites *(Dermatophagoides pteronyssinus* (Derp1), *Dermatophagoides farina* (Derf1)), fungi (*Cladosporium herbarium*, *Alternaria alternate*), and cat (*Felis domesticus*) (ALK-

Abelló, Madrid, Spain). Histamine (10 mg/mL) and glycerol-saline were used as the positive and negative controls, respectively. The procedures of this test were performed strictly according to the Australasian Society of Clinical Immunology and Allergy guidelines (ASCIA, 2016). A wheal reaction of > 3 mm was considered as a positive result and atopy was defined as a significant positive SPT test to at least one of the applied allergens (ASCIA, 2016). The clinical assessment and indoor air monitoring were carried out at the same time from February until March 2019.

The concentration of PM_{10}, $PM_{2.5}$, NO_2, CO_2, TVOC, formaldehyde, temperature and relative humidity were collected from classrooms of participating school children. Indoor temperature (°C), relative humidity (%), the concentration of TVOC (ppm) and CO_2 (ppm) were monitored by smart plug-in probes VelociCalc® Multi-function Ventilation Meter (Model TSI 9565-P TSI Incorporated, Shoreview, Minnesota, USA) with the average log interval values over one minute. A portable TSI Dust-Trak DRX monitor (Model 8534 TSI Incorporated, Shoreview, Minnesota, USA) was used for the assessment of PM_{10} and $PM_{2.5}$ concentrations with the measuring range of 0.001-150 mg/m^3 and accuracy of ±0.001 mg/m^3. The concentration of formaldehyde was monitored by using MultiRae Lite (Model PGM 6208 Rae Systems, San Jose, California, USA). The measuring range of MultiRae Lite for formaldehyde is 0-10 ppm with an accuracy of ±0.05 ppm. All of these instruments were installed no closer than one meter to a wall, window, floor, door and school children. They were set to continuously measure during the learning session for at least four hours in each school and has been previously described (Kamaruddin et al., 2016; Mohd Isa et al., 2020b; Norbäck et al., 2014; Suhaimi et al., 2017).

The average concentration of NO_2 in the air for a week was measured using passive monitoring using the IVL diffusion samplers (IVL, Goteborg, Sweden) with the limit of detection (LOD) of 0.5 µg/m^3 and 10.0% of measurement uncertainty (Foldvary et al., 2017).

Characteristics of the school children are expressed with descriptive statistics and analyzed by Chi-square test using Package for the Social Sciences (SPSS) 25.0. To evaluate the association between respiratory and allergic symptoms, personal characteristics, and indoor air pollutants exposure, we computed using 2-Level Hierarchic Multiple Logistic Regression (school and children). Then, the final risk prediction models were generated by taking in significantly associated predictors in the primary analysis steps by 2-Level Hierarchic Multiple Logistic Regressions. Regression analysis was performed with the STATA 14.0 statistical package using a two-tailed test and a 5% significant level.

RESULTS AND DISCUSSION

A total of 332 school children including 193 (58.1%) female and 139 (41.9) male were recruited in this study. The majority of them were Bajau (35.5%) and Kadazan-Dusun (14.8%), the indigenous ethnic of Sabah, while Malay and other indigenous ethnic (Murut, Bugis, Kedayan, Suluk, and others) constitute about 12.7% and 37.3%, respectively. Based on the questionnaire, the prevalence of doctor-diagnosed asthma was 11.7%, while 27.7% declared either their father or mother having asthma or allergies. A total of 69.9% reported that their parents are cigarette smokers. Moreover, the prevalence of atopy were more common among female school children and doctor-diagnosed asthma group with values of 50.8% (OR = 2.22, 95% CI= 0.28-0.71) and 89.7% (OR = 7.27, 95% CI= 2.52-20.99), respectively.

Table 1 also provides the data on the prevalence of respiratory and allergic symptoms. A total of 14.8% or 49 school children had wheezing in the last 12 months, 17.5% had day-time breathlessness, and 37.0% have had breathlessness after exercise, while breathlessness attacks at night-time were less common at 13.0%. For allergic symptoms, about 55.1% and 10.8% of the school students had onset of rhinitis and skin allergic in the last 12 months, respectively. Furthermore, 75.5% of school children with atopy reported wheezing in the past 12 months (OR= 2.44, 95% CI= 1.22-4.87). This present study showed that the prevalence of doctor-

Table 1. Prevalence of respiratory symptoms and infections among atopic and non-atopic school children in Sabah

Personal factors and symptoms	Overall (%)	Atopic	Non-atopic	*p*	OR	95% CI
Personal factors						
Female	58.1	98 (50.8)	95 (49.2)	<0.001**	2.22	0.28-0.71
Doctor-diagnosed asthma	11.7	35 (89.7)	4 (10.3)	<0.001**	7.27	2.52-20.99
Parental asthma/allergy	27.7	58 (63.0)	34 (37.0)	0.323	1.28	0.78-2.10
Parental/sibling smoking	69.6	140 (60.6)	91 (39.4)	0.295	1.29	0.80-2.06
Respiratory symptoms						
Wheezing symptom in last 12 months	14.8	37 (75.5)	12 (24.5)	0.010*	2.44	1.22-4.87
Day-time breathlessness	17.5	34 (58.6)	24 (41.4)	0.984	0.99	0.56-1.77
Breathlessness after exercise	37.0	74 (60.2)	49 (39.8)	0.685	1.10	0.70-1.73
Night-time breathlessness	13.0	28 (65.1)	15 (34.9)	0.362	1.36	0.70-2.66
Allergic symptoms						
Rhinitis in the past 12 months	55.1	114 (62.3)	69 (37.7)	0.144	1.39	0.89-2.15
Skin allergic in the past 12 months	10.8	21 (58.3)	15 (41.7)	0.922	0.97	0.48-1.95

* p-value < 0.05; ** p < 0.001
OR = Odd ratio; CI = Confidence interval

Table 2. The allergy skin prick test results among doctor-diagnosed asthma (N= 332)

Allergen Tested		Doctor-diagnosed asthma			
		Overall (%)	Yes (%)	No (%)	*p*
House dust Mites	Derp1	45.5	26 (17.2)	125 (82.8)	0.005*
House dust Mites	Derf1	50.3	29 (17.4)	138 (82.6)	0.001*
Fungi	*C. herbarium*	13.9	11 (23.9)	35 (76.1)	0.006*
Fungi	*A. alternate*	4.5	4 (26.7)	11 (73.3)	0.154
Cat	*D. farina*	15.4	13 (25.5)	38 (74.5)	<0.001*
Mix house dust mites	Derp1 & Derf1	54.8	30 (16.5)	152 (83.5)	0.003*

* p-value < 0.05

diagnosed asthma was higher than the previous studies recorded among school children aged 13 to 14 years old in Peninsular of Malaysia, which was conducted in Selangor (10.6%) (Mohd Isa et al., 2020b), Terengganu (8.4%) (Ma'pol et al., 2019), and Penang (10.3%) (Norbäck, et al., 2017). Moreover, the prevalence of doctor-diagnosed asthma among school children from Sabah was the highest recorded compared with a recent study conducted in Indonesia (8.8%) (Soegiarto et al., 2019), Singapore (10.0%) (Goh et al., 2021), and Thailand (8.8%) (Chinratanapisit et al., 2019). According to the recent reviews, the trends in the prevalence of asthma varies by country, in certain regions of the world, prevalence is rising while in others it is declining (Asher et al., 2020; Stern et al., 2020).

Furthermore, our results show that 58.7% of school children were positive to at least one of the allergens tested, with 54.8% being positive to house dust mites (Derp1 and Derf1), and 15.4% of them sensitized towards the cat. The majority of the doctor-diagnostic asthma school children (25.5%) were tested positive towards cat allergen, followed by *C. herbarium* allergen (23.9%) (Table 2). Likewise, the prevalence of atopy seen in this study was higher than previously reported in Selangor (57.7%) (Mohd Isa et al., 2020a), Indonesia (29.0%) (Soegiarto et al., 2019) and Taiwan (57.3%) (Wu et al., 2021). Furthermore, the bivariate analysis revealed that doctor-diagnosed asthma was associated with the atopy; this was particularly true as the majority of them were sensitized to house dust mites (76.9%). In fact, atopy was considered the strongest predisposing factor for the development and exacerbation of asthma (Moustaki et al., 2017).

Table 3. Summary statistics of indoor air parameters in classrooms (n = 24)

Parameter	Minimum	Maximum	Median	IQR	Reference
CO_2 (ppm)	408	746	459.0	121	< 1000[a,b,c,d]
NO_2 ($\mu g/m^3$)	2.9	26.0	18.0	5.5	200[b], 100 ppb[c], 75[d]
PM_{10} ($\mu g/m^3$)	18.0	52.0	31.0	16.0	50[b], 150[c], 120[d]
$PM_{2.5}$ ($\mu g/m^3$)	16.0	40.0	23.5	11.0	25[b], 35[c], 50[d]
TVOC (ppm)	0.4	8.2	0.6	0.2	3[a]
Formaldehyde (ppm)	0.001	0.050	0.006	0.024	0.1[b,d]
Temperature (°C)	23.7	32.1	26.3	4.4	23-26[a]
Relative Humidity (%)	58.9	77.4	66.3	4.8	40-70[a]

IQR = Interquartile range

[a] Industrial Code of Practice on Indoor Air Quality (ICOP-IAQ) 2010

[b] World Health Organization (WHO) guideline

[c] The National Ambient Air Quality Standard by USEPA

[d] The new Malaysian Ambient Air Quality Standard 2018 Interim Target-2

The summary of indoor air measurements taken from 24 classrooms is presented in Table 3. The concentration of indoor CO_2 and NO_2 were ranged widely with the median values of 459 ppm (range 408-746) and 18 $\mu g/m^3$ (range 2.9-26.0), respectively. The median concentrations of PM_{10} and $PM_{2.5}$ during learning in sessions were 31.0 $\mu g/m^3$ (range 18.0-52.0) and 23.5 $\mu g/m^3$ (range 16.0-40.0), respectively. The median concentrations of formaldehyde and TVOC in indoor air were 0.006 ppm (range 0.001-0.050) and 0.6 ppm (range 0.4-8.2), respectively. Overall, the mean concentrations of all parameters is much lower than the recommended values established by World Health Organization (WHO) guideline, The National Ambient Air Quality Standard by USEPA, the Industrial Code of Practice on Indoor Air Quality (ICOP-IAQ) 2010 and The new Malaysian Ambient Air Quality Standard 2018 Interim Target-2. Comparison of the indoor parameters across previous studies can be difficult due to differences in sampling times, devices, geographical characteristics and climate conditions (Madureira et al., 2015). Generally, classrooms in Malaysia are naturally ventilated. Considering the classroom design, natural ventilation system, wide jalousie window panes on both sides of the walls and enough ceiling fans (majority 3 units) significantly improve the thermal comfort and concentrations of indoor pollutants (Schibuola et al., 2016; Stabile et al., 2017).

The indoor concentrations of PM_{10} and $PM_{2.5}$ might be generated by the occupants, resulting from their activities, and resuspension of deposited particles, as well as from the outdoor traffic and industrial emissions (Askariyeh et al., 2020; Othman et al., 2019). Similarly, NO_2 may be produced as a byproduct of fossil-fuel combustion, biomass burning and agricultural activities (Hua, 2018). According to Madureira et al. (2016) and Salthammer (2019), formaldehyde and total VOC are ubiquitously found indoor and might be originated from paints, adhesives, sealants, consumer products, furniture, plywood and textile. Indeed, most school buildings in Malaysia are situated nearby heavy traffic roads, which have a significant impact on indoor air quality. Furthermore, indoor air quality in classrooms is much affected by the indoor sources and infiltration of outdoor sources, such as traffic emission, industrial and construction activities, urbanization and natural sources (Bennett et al., 2018). Thus, the detrimental health impacts are more prominent to the school children in urban and suburban areas compared to rural (Del-Rio-Navarro et al., 2020; Paciência & Rufo, 2020). Therefore, findings from this current study suggest that the indoor concentrations of PM_{10}, $PM_{2.5}$, NO_2 and TVOC need to be addressed with certain abatement techniques, such as improved air exchange rate, application of air cleaners, improving the cleaning routine, use of ultra-low-emitting volatile organic compounds (VOCs) furniture and finishing products to reduce the exposure of school children to various sources

Table 4. Personal factors related to respiratory symptoms among the school students.

Personal characteristics	Respiratory symptoms				Allergic symptoms	
	Wheezing symptom in last 12 months OR (95% CI)	Day-time breathlessness OR (95% CI)	Breathlessness after exercise OR (95% CI)	Night-time breathlessness OR (95% CI)	Rhinitis in the past 12 months OR (95% CI)	Skin allergy in last 3 months OR (95% CI)
Female	1.07 (0.55-2.06)	1.56 (0.84-2.87)	1.492 (0.93-2.38)	2.33 (1.08-5.03)*	0.67 (0.42-1.08)	1.01 (0.44-2.09)
Atopic	1.67 (0.78-3.57)	0.92 (0.51-1.67)	1.088 (0.68-1.75)	1.24 (0.58-2.63)	1.27 (0.79-2.02)	1.06 (0.53-2.12)
Doctor- diagnosed asthma	5.98 (2.78-12.88)*	2.03 (0.88-4.68)	1.579 (0.78-3.21)	3.05 (1.37-6.77)*	1.07 (0.52-2.19)	0.34 (0.06-1.78)
Parental asthma/allergy	2.01 (1.03-3.90)*	1.02 (0.54-1.93)	1.205 (0.73-2.00)	1.62 (0.81-3.23)	1.12 (0.68-1.87)	1.71 (0.77-3.80)
Parental/sibling smoking	1.56 (0.73-3.32)	2.04 (1.01-4.12)*	1.131 (0.69-1.85)	2.90 (1.12-7.47)*	1.04 (0.65-1.67)	1.12 (0.51-2.46)

*p-value <0.05; OR = Odd ratio; CI = Confidence interval

OR was calculated by 2-Level Hierarchic Multiple Logistic Regression of air pollution (Fsadni et al., 2018). Besides, a periodic awareness program organized by the school management and professional bodies can help to empower the staff and school children on the awareness of health.

Table 4 shows the 2-Level Hierarchic Multiple Logistic Regression models (school and children) between the personal characteristics and symptoms. Significant associations between onset of wheezing with doctor-diagnosed asthma (OR= 5.98, 95% CI= 2.78-12.88) and parental asthma/allergy (OR= 2.01, 95% CI= 1.03-3.90) were observed in school children. The onset of day-time breathlessness was associated with parental/sibling smoking (OR= 2.04, 95% CI= 1.01-4.12). Similarly, the onset of night-time breathlessness was common among female (OR= 2.33, 95% CI= 1.08-5.03) and associated with doctor-diagnosed asthma (OR= 3.05, 95% CI= 1.37-6.77), and parental/sibling smoking (OR= 2.90, 95% CI= 1.12-7.47). No associations were found between the personal characteristics with the onset of breathlessness after exercise, and allergic symptoms.

Following that, we use the same analysis technique to determine the associations between indoor pollutants exposure against respiratory and allergic symptoms while controlling personal attributes. The onset of wheezing was associated with concentrations of CO_2 (OR= 3.23, 95% CI= 1.42-8.90) and NO_2 (OR= 5.00, 95% CI= 1.07-3.54). In addition, higher concentration of NO_2, PM_{10}, $PM_{2.5}$ and TVOC increased the odd of day-time breathlessness among school children with the values of OR= 2.70 (95% CI= 1.16-1.89), OR= 12.5 (95% CI= 2.01-9.78), OR= 20.44 (95% CI= 1.11-37.5) and OR= 6.32 (95% CI= 1.03-8.89), respectively. The onset of breathlessness after exercise was associated with a concentration of TVOC (OR= 5.19, 95% CI= 1.04-25.97). We found there was no significant association between indoor pollutants against night-time breathlessness and rhinitis symptom (Table 5). We observed the concentration of $PM_{2.5}$ was significantly associated with the onset of skin allergy in the past 3 month (OR= 1.38, 95% CI= 1.02-1.88).

We further analyzed the significant variables in the previous analysis using the 2-Level Hierarchic Multiple Logistic Regression models (school and children) to determine the association between respiratory symptoms (wheezing and day-time breathlessness) against personal factors and indoor pollutants (Table 6). The analysis showed that the onset of wheezing was more common among doctor-diagnosed asthma (OR= 8.29, 95% CI= 3.70-16.10) and school children with parental asthma/allergy (OR= 2.13, 95% CI= 1.10-4.15) ($p < 0.05$). The same model also showed that the concentration of CO_2 and NO_2 were also significantly associated with the onset of wheezing ($p < 0.05$). Furthermore, in this final model, only the concentration of NO_2 and TVOC were positively associated with the onset of day-time breathlessness ($p < 0.05$).

In the final regression analysis, we found that school children with conditions of doctor-diagnosed asthma and parental asthma/allergy were more likely to experience the onset of wheezing. These findings are in agreement with our previous study conducted in Selangor and Penang, Malaysia (Mohd Isa et al., 2020b; Norbäck et al., 2017b) as well recently reported by Cao et al. (2020) among children in Lanzhou, China. This was anticipated, as genetic disposition is known to be a major factor for asthma development (Holst et al., 2020). In the same regression model, we found that indoor concentrations of NO_2 and CO_2 were associated with the onset of wheezing. This also accords with the findings of some studies (Enkh-Undraa et al., 2019; Fraga et al., 2008; Olaniyan et al., 2020). Additionally, in northern Portugal, school children exposed to more than 4.6 $\mu g/m^3$ of NO_2 concentration had significantly increased odds of wheezing (OR = 1.62, 95% CI= 1.09-2.43) (Branco et al., 2020). Remarkably, we found clear evidence that doctor-diagnosed asthma school children with parental asthma/allergy and exposure to indoor NO_2 and CO_2 were associated with the onset of wheezing indicating a potential genetic-environmental interaction.

Furthermore, our result is also consistent with those previously reported that the indoor concentration of NO_2 was associated with the onset of day-time breathlessness among school children (Mentz et al., 2018; Patel et al., 2010; Prieto-parra et al., 2017; Yeatts et al., 2012). Interestingly, Patel et al. (2010) found that multiple lags of NO_2 exposure (2-5 days) were

Table 5. The association between indoor air and respiratory symptoms of school students.

Indoor air parameters	Respiratory symptoms				Allergic symptoms	
	Wheezing symptom in last 12 months OR (95% CI)	Day-time breathlessness OR (95% CI)	Breathlessness after exercise OR (95% CI)	Night-time breathlessness OR (95% CI)	Rhinitis in the past 12 months OR (95% CI)	Skin allergy in last 3 months OR (95% CI)
CO_2 (ppm)	3.23	0.42	0.95	0.94	1.02	0.98
	(1.42-8.90)*	(0.17-1.08)	(0.50-1.80)	(0.37-2.38)	(0.99-1.05)	(0.98-1.02)
NO_2 (μg/m^3)	5.00	2.70	0.75	0.76	1.03	1.08
	(1.07-3.54)*	(1.16-1.89)*	(0.38-1.47)	(0.27-2.10)	(0.96-1.10)	(0.95-1.07)
PM_{10} (μg/m^3)	0.18	12.5	0.59	0.51	0.97	0.79
	(0.02-1.53)	(2.01-9.78)*	(0.13-2.72)	(0.06-4.09)	(0.85-1.11)	(0.62-0.99)
$PM_{2.5}$ (μg/m^3)	6.19	20.44	1.60	1.87	1.02	1.38
	(0.36-105.7)	(1.11-37.5)*	(0.21-11.99)	(0.13-27.12)	(0.83-1.21)	(1.02-1.88)*
TVOC (ppm)	5.42	6.32	5.19	3.43	1.09	1.04
	(0.66-44.59)	(1.03-8.89)*	(1.04-25.97)*	(0.53-22.26)	(0.92-1.27)	(0.85-1.27)
Formaldehyde (ppm)	1.12	3.72	3.84	5.91	0.01	0.02
	(8.91-1.41)	(-8.07-1.71)	(-4.8-3.07)	(-1.1-3.12)	(0.02-1.12)	(0.09-2.41)

*p-value <0.05; OR = Odd ratio; CI = Confidence interval
OR calculated for 100 ppm increase in the concentration of CO_2
OR calculated for 10 mg/m^3 increase in the concentration of NO_2
OR calculated for 10 μg/m^3 increase in the concentration of PM_{10} and $PM_{2.5}$
OR calculated for 10 mg/m^3 increase in the concentration of TVOC
OR calculated for 10 mg/m^3 increase in the concentration of formaldehyde
OR was calculated by 2-Level Hierarchic Multiple Logistic Regression

Table 6. The final model of the association between respiratory symptoms and allergies among secondary students

Respiratory symptoms	OR (95% CI)	*p*
Wheezing symptom in last 12 months		
Doctor's diagnosed asthma	8.29 (3.70-16.10)	<0.001**
Parental asthma/allergy	2.13 (1.10-4.15)	0.026*
CO_2 (ppm)	1.01 (1.01-1.11)	<0.001**
NO_2 (μg/m^3)	1.03 (1.01-1.21)	0.028*
Day-time breathlessness		
Parental/sibling smoking	1.65 (0.81-3.38)	0.171
NO_2 (μg/m^3)	1.02 (1.02-1.35)	0.044*
PM_{10} (μg/m^3)	1.03 (0.76-1.06)	0.206
$PM_{2.5}$ (μg/m^3)	2.25 (0.26-19.51)	0.459
TVOC (ppm)	1.30 (1.10-1.52)	0.002*
Breathlessness after exercise		
TVOC (ppm)	5.19 (1.04-25.97)*	0.038*
Night-time breathlessness		
Female	2.33 (1.08-5.03)*	0.028*
Doctor's diagnosed asthma	3.05 (1.37-6.77)*	0.002*
Parental/sibling smoking	2.90 (1.12-7.47)*	0.014*
Skin allergy in the last 3 months		
$PM_{2.5}$ (μg/m^3)	1.38 (1.02-1.88)*	0.035*

* *p*-value < 0.05; ** p < 0.001; OR = Odd ratio; CI = Confidence interval
OR calculated for 100 ppm increase in the concentration of CO_2
OR calculated for 10 mg/m^3 increase in the concentration of NO_2
OR calculated for 10 μg/m^3 increase in the concentration of PM_{10} and $PM_{2.5}$
OR calculated for 10 mg/m^3 increase in the concentration of TVOC
OR was calculated by 2-Level Hierarchic Multiple Logistic Regression

significantly associated with the onset of breathlessness among adolescents (13-20 years old) in New York City areas. A recent review summarized the mediate effects of indoor TVOC exposure in pulmonary diseases (Alford and Kumar, 2021) and the most common symptoms documented were mucous membrane irritations, neurotoxic effects, respiratory symptoms (wheezing, cough, shortness of breath), skin symptoms, chemosensory changes and visual disturbance (Baccouche and Sevostianov, 2020). However, we found only two studies reported a significant association between VOCs exposure and breathlessness attack at nocturnal among the elderly (Alford and Kumar, 2021; Bentayeb et al., 2013). Therefore, future research should be undertaken to verify the interrelationship of TVOC exposure and the onset of breathlessness among children.

This study also showed that the onset of night-time breathlessness was more common in female and school children with conditions of doctor-diagnosed asthma and who's parental/ sibling smoking. This result support previous studies conducted among school children in Al-Khobar City, Saudi Arabia (Al-Dawood, 2001), Ukraine (Semotyuk et al., 2018), Juárez, Mexico (Bird and Staines-Orozco, 2016) and Shanxi, China (Li et al., 2019). Nevertheless, other studies found no association between parental/asthma smoking or environmental tobacco smoke (ETS) exposure and the onset of breathlessness (Takaoka et al., 2016; Wang et al., 2021).

This inconsistency finding probably is explained by the dose-response relationship. Studies conducted by Morkjaroenpong et al. (2002) and, Dai and Chan (2020) discovered that children who lived with active smokers who consumed more than 10 and 20 cigarettes/day, respectively had a greater risk of respiratory symptoms manifestation.

Among other indoor pollutants, we found the concentration of $PM_{2.5}$ was significantly associated with the onset of skin allergy in the past 3 months. This result is in line with those of previous studies indicating that $PM_{2.5}$ develop and aggravate the symptoms of skin allergic reactions (Majbauddin et al., 2016; Sugiyama et al., 2020). Recent transcriptome studies suggested that $PM_{2.5}$ induce an inflammatory response in keratinocytes through reactive oxygen species (ROS) signaling (COX-2 or XDH), toll-like receptor signaling, IL6 signaling, aryl hydrocarbon receptor signaling, and NF-κB signaling. These pathophysiological pathways together with alteration of gene expression levels (IL-36γ and CXCL14) eventually affect the skin barrier functions or immune dysregulation (Kim et al., 2017; Liao et al., 2020).

Rhinitis has a complicated etiology. From a clinical perspective, allergic reactions do not affect everyone who is exposed to the same environmental factors, implying that hereditary factors play an important role in allergic manifestation (Song et al., 2015). This factor may be partly explained why we observed no clear associations between rhinitis symptoms with indoor pollutants and personal characteristics. Further exploration on the pathogenesis of rhinitis from different geographical and adopts a longitudinal perspective is therefore suggested.

Some limitations of this study should be noted. First, the nature of this cross-sectional study design, limit the possibility to form causal conclusions. Second, we have no information on the air quality levels outside the classrooms. However, we assumed that the ratios of indoor/outdoor concentrations of all pollutants remain consistent throughout the year. Several studies were undertaken across Malaysia supported this assertion (Abidin et al., 2014; Norbäck et al., 2017a). Finally, the school children may erroneously provide information on respiratory and allergic symptoms in the self-administrative questionnaire that depends on their ability to recall events in the past. The influence of recall bias was minimized with a verification approach through face-to-face- interview following the completion of the questionnaire and telephone call with their respective parents.

CONCLUSIONS

In this study, we have found consistent associations between the onset of wheezing with indoor concentrations of NO_2 and CO_2, which were more common among doctor-diagnosed asthma and whose parents had asthma/allergy. Distinctly, these associations provided further support for the genetic-environmental interaction that influenced the development of respiratory morbidities. Furthermore, this study agrees with the emerging evidence that indoor concentrations of $PM_{2.5}$ were associated with the onset of skin allergy.

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CONFLICT OF INTEREST

The authors declare that there is not any conflict of interests regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/ or falsification, double publication and/or submission, and redundancy has been completely observed by the authors.

LIFE SCIENCE REPORTING

This study was approved by the Ethics Committee for Research Involving Human Subjects Universiti Putra Malaysia (JKEUPM-2018-189). Written informed consents were obtained from the guardians before enrollment in this study, with the addition of the children's assent.

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