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Indoor Air Pollutants Exposure and the Respiratory Inflammation (FeNO) among Preschool children in Hulu Langat, Selangor

[1]Nur Aida Aziz, [2]Juliana Jalaludin, [1]Suhaili Abu Bakar

[1]*Universiti Putra Malaysia, Department of Environmental and Occupational Health, Faculty of Medicine and Health Sciences, 43300 Serdang, Malaysia*
[2]*Universiti Putra Malaysia, Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, 43300 Serdang, Malaysia*

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ABSTRACT

Background: Children's increased risk of respiratory diseases is possibly due to exposure to indoor air pollutants since they spend much of their time indoors. This study aims to determine the association between indoor air pollutants (PM10, PM2.5, and NO2) and respiratory inflammation among preschool children. **Methods:** A cross sectional comparative study was conducted among healthy preschool children selected from urban (n=129) and rural (n=141) area preschools in Hulu Langat District. Questionnaires were used to determine respiratory symptoms reported among respondents. Indoor exposure to PM2.5 and PM10 was measured using Dustrak DRX Aerosol Monitor, while LaMotte Air Sampler was used to monitor NO2 in class. Fractional exhaled Nitric Oxide (FeNO) was measured by instructing respondents to exhale directly into the NIOX MINO device ('online' technique). **Result:** The median (interquartile range) concentration of PM2.5 (63.0 (32) µg/m3) and PM10 (68.2 (31) µg/m3) in preschools in urban area were slightly higher compared to the preschools in rural area (PM2.5= 55(37) µg/m3; PM10 = 62 (35) µg/m3). A significant difference was found in NO2 ($p<0.01$) measurements between the two areas. NO2 was found to be significantly associated with Fractional exhaled Nitric Oxide (FeNO) measured in rural area ($p<0.05$). **Conclusion:** It was suggested that preschool children in urban area are highly exposed to indoor air particles compared to those from the rural area. The exposure to NO2 was associated with Fractional exhaled Nitric Oxide in rural area suggesting that greater exposure may later influence children's respiratory health causing, particularly, inflammatory airways.

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INTRODUCTION

Indoor air pollution has been identified as one of the more serious global environmental issues that affect billions of people. Women and children, especially, are regularly exposed to high levels of indoor air pollution that exceeds what is considered to be the acceptable limit [1]. World Health Organization (WHO) in their World Health Report 2002 reported that 2.7% of worldwide global burden diseases were caused by the effects of indoor air pollution [2]. The indoor air pollutants issue has caught the attention of many researchers and people worldwide. However, this is not a relatively new issue and it is be worst in developing countries. WHO also reported that 72% of Malaysians, in year 2010, are living in rapidly developing urban areas in Malaysia [3]. Studies have found that the concentrations of several pollutants can be much higher indoors compared to outdoors. Furthermore, the pollutants originate from a variety of sources and processes whether it is from indoors or outdoors.

Many studies suggest that children are affected more by indoor air pollution than ambient air. Children spend over 85% [4] of their total time in a day indoors, such as, in institutional buildings like schools and homes. Children are among the most vulnerable group of air pollutants. They are particularly vulnerable because of the continued maturation of their respiratory system, their low immune system and their evolving defence mechanisms. They also inhale a higher volume of air per body weight with respect to adults [5]. With extensive and strenuous activities that they are involved in everyday, the effects of air pollution exposures can be worst. Since exposures to these microenvironments are likely to contribute to daily personal exposure, a good indoor

Corresponding Author: Juliana Jalaludin, Universiti Putra Malaysia, Department of Environmental and Occupational Health, Medicine and Health Sciences Faculty, 43400 Serdang, Malaysia.
Tel: +60389472401, E-mail: juliana@upm.edu.my

air quality is crucial for them. Air quality at classrooms is particularly important to children because they are present at school almost every day from morning and up until late in the afternoon.

There is a lack of evidence in order to estimate the risk of developing asthma or airway inflammation diseases among young children. It has been determined that the prevalence of asthma and allergic diseases among children living in the urban areas in economically developing countries is increasing. It can be due to air pollution, indoor or outdoor, that may play an important role in the development of diseases. Fractional exhaled Nitric Oxide (FeNO) was the recommended biomarker to suggest a subclinical inflammation even in the absence of signs and symptoms measured across all ages [6]. Several classes of pulmonary cells produced nitric oxide can be easily detected in the exhaled air. It can be produced by several pulmonary cells including inflammatory endothelial and airway epithelial cells. Endogenous NO is synthesised from L-arginine by isoenzymes known as inducible NO Synthethase [7]. Inducible NO synthethase is present in the bronchial epithelial cells responsible for raised nitric oxide in response to proinflammatory cytokines and oxidants [8]. FeNO was the first useful non-invasive marker of airway inflammation in asthmatic patients that can be potentially useful to evaluate the effects of air pollution on the inflammatory state of airways in either healthy or asthmatic children. In fact, several previous studies have found that air pollution is associated with FeNO in asthmatic or healthy children and adults [5.9]. The mechanisms involved in this bronchial inflammation and pollution exposure are not yet fully clarified as they still depend on types of pollutant [5].

In this study, in order to better understand the association of indoor air exposure and FeNO, FeNO was used as biomarker to detect the pro-inflammatory effects among healthy children. Several air pollutants, such as PM_{10}, $PM_{2.5}$ and $NO_{2,}$ determined to be commonly related with indoor air pollutions from several sources inside preschools were measured. These pollutants have the potential to increase the susceptibility of subjects via an inflammatory effect on the airway and airway reactivity [10]. Besides, there is evidence that indoor air pollutants may have elevated the level of FeNO in children, but this previous study was focused particularly on students with asthma and allergies. Thus, the aim of the study was to correlate FeNO level among healthy preschool children with the measured concentrations of exposure to indoor air pollutants ($PM_{2.5}$, PM_{10} and NO_2) in these preschools. This correlation was then compared between preschools in urban and rural areas.

MATERIALS AND METHODS

Study design and location:

This study was conducted in several urban and rural area preschools in the Hulu Langat district. A list of preschools from both urban (Ampang) and rural (Hulu Langat) areas were obtained from KEMAS state office. Permission was obtained from KEMAS state and district offices before the study was carried out. The definition of urban areas nowadays in Malaysia is ‘gazzetted area with 10000 or more inhabitants’ [11]. Extensive criteria obtained from the Department of Statistics stated that the minimum gross density of population is 50-60 people per hectare and at least 60% of the 15 years old above population were involved in non-agricultural activity [12]. Meanwhile, the criteria for rural area were vice versa and more straightforward which is, not a city or non-metropolitan area. Overall, 13 preschools were selected to represent preschools in urban area and 9 to represent preschools in rural area. This is a cross sectional comparative study as it measures exposure variables, which are pollutants exposure and health effects (FeNO) at the same time while comparing them between the two areas; urban and rural (Figure 1).

Study sample:

Only those preschool children who fulfilled the inclusion criteria were selected in this study. The purpose of the study was explained to the parents; consent letters were obtained from the parents for permission to allow their children to participate in this study. For those who agreed to participate, they were asked to answer a set of questionnaire and return them to the class teacher once they were filled in completely. The recruited children (those who fulfilled inclusion criteria) were then randomly sampled based on simple random method. Inclusion criteria included children who have not had asthma, fully enrolled and were present at the preschool for not less than 6 months.

Questionnaire:

A standardised set of questionnaire adopted from ATS-DLC-78-C WHO [13] was used to collect the data on respiratory symptoms and home exposures. A part of the questionnaire is from the International Study of Asthma and Allergies in childhood (ISAAC) questionnaire [14] that comprises questions on asthma and allergies among the subjects. This questionnaire was in Malay language mainly to be easily answered by parents. Besides, instruction and contact numbers of the researchers were given for further inquiries.

Indoor concentration levels of $PM_{2.5}$& PM_{10}& NO_2 monitoring:

Monitoring of indoor air and concentration levels were conducted in each of the selected preschool during class period (8.30a.m-12.30pm). It included the monitoring of particles ($PM_{2.5}$& PM_{10}) and nitrogen dioxide. Measurements were taken from September until November 2013. Air sampling tool (Dustrak DRX Aerosol Monitor 8534) was used to measure aerosol particle size limit of 10 µm ($PM_{2.5}$ and PM_{10}), while LaMotte air sampling with calorimetric reading was used to obtain the NO_2 measurement. During the monitoring session, both instruments were placed on the desk within the children's breathing zone at the back of the classroom [15] away from the doors and windows. This was to ensure the instruments were far from air pollution sources, safely located and out of reach of children.

Fractional exhaled Nitric Oxide (FeNO):

Children recruited underwent single-breath FeNO analysis after they had been selected (simple random) and ensured they were not absent on the day of sampling. FeNO was determined with an on-line method by using NIOX MINO (Aerocrine, Stockholm, Sweden) analyser. This analyser with its compact size and portability used electrochemical method. After comfortably seated, children made an inspiration of exhaled NO via a connected mouthpiece immediately followed by full exhalation at a constant rate of 50mL/sec for at least 6 seconds according to ATS/ERS [16]. However no repetition of analysis was made among children. The measured value of 20 ppb or more were considered elevated values in children, according to ATS/ERS [16]. The measurements was carried out one hour after heavy physical activity (if any) while consumption of nitrate-rich food and caffeine among respondents was discouraged.

Statistical analysis:

Comparison between groups of study for population characteristics, pollution distribution and FeNO value was tested with Mann-Whitney U test for continuous variables and the Chi-square(χ^2) test or exact Fisher test for categorical variables. Paired t-test was used for comparison within each group. The associations between the FeNO value and different variables were tested using Spearman correlation. The p-value of less than 0.05 was considered statistically significant and all analyses were carried out using Statistical Package of Social Sciences (SPSS) version 20.

Results:

A total of 550 questionnaires were distributed to the preschools that were selected to be involved in this study in both areas. However, only 340 of the questionnaires were returned back and only 328 of which were completely filled in and were acceptable. Healthy children (reported without "ever asthma", any respiratory diseases or allergic diseases) for both areas underwent the next analysis test (FeNO) of this study. The final sample included 129 children from 13 preschools in Ampang and 141 children from 9 preschools from Dusun Tua. Statistical results show that there were no significant difference between those two groups of respondents for age, sex, races and weight and height.

The prevalence of respiratory symptoms was obtained from questionnaires according to what have been reported by the parents. The percentage of reported cough was 6.2% from urban area children and 3.5% from rural area children. The prevalence of reported phlegm was 2.3% from urban area children and 2.1% from rural area children. Prevalence for chest tightness in urban area children was 0.8% and in rural area children was 0.7%. Meanwhile, prevalence for wheezing was 3.1% and 6.4% for urban and rural area children respectively. In short, children from preschools in urban area showed higher prevalence for cough, phlegm and chest tightness.

Results shown in Table 1 indicate that all the pollutants ($PM_{2.5}$, PM_{10} and NO_3) concentrations measured were high in urban area. It also indicates that there is significant difference ($p<0.05$) between urban and rural areas. All the concentrations were taken from 4 hours measurement during the class session. Besides, the FeNO values (Table 1) measured were elevated in those children from urban area compared to those who were from rural area. The median (IQR) among 51 urban preschool children who underwent the FeNO test was 11(7.0) ppb while the median for 84 rural children was 9.0(4.8) ppb. However, no significant difference was found for FeNO value between these two groups of study.

The correlation test showed that an insignificant relationship was obtained between FeNO value and pollutants measured among respondents in both areas (Table 2).However, only NO_2 had any significant association with elevated level of FeNO among preschool children in rural areas as well as total number of children studied [17]. The mean of each FeNO value obtained from each of the area studied was considered to be normal which is less than 20 ppb. Any reading above this value is considered as elevated value in children [16].

Table 1: Comparison of socio-demographic, respiratory symptoms, pollutants concentrations and FeNO value among respondents.

Variables	Urban(n=129)	Rural(n=141)	p value
Sex Boy Girl	 59 (45.7%) 70 (54.3%)	 68 (48.2%) 73 (51.8%)	0.68
Age (years) 5 6	 54 (41.9%) 75 (58.1%)	 69 (48.9%) 72 (51.1%)	0.24
Races Malay Non-Malay	 122(94.6%) 7(5.4)	 135 (95.7%) 6(4.3)	0.65
Weight(kg) Height(cm)	21 (2.7) 110 (8)	20.3 (3.8) 113 (8)	0.52 0.07
Cough Phlegm Chest tightness Wheezing	5 (3.9%) 1 (0.8%) 1 (0.8%) 5 (3.1%)	5 (3.5%) 2(1.4%) 2 (1.4%) 8 (6.4%)	0.57# 0.53# 0.53# 0.49
$PM_{2.5}$ (µg/m^3) PM_{10} (µg/m^3) NO_2 (ppm)	63(32) 68.2(30) 0.029(0.0)	55 (37) 62 (35) 0.012 (0.0)	<0.01* <0.01* <0.01*
FeNO (ppb) (urban, n=50;rural,n=86)	11 (7)	9.0 (5)	0.08

FeNO, Fraction of exhaled Nitric Oxide

Data were given as median (interquartile range), absolute numbers (%), respectively. Data were compared by group using Mann-Whitney U-test and Chi-squared tests, respectively. *p value significant <0.05, # Fisher exact test

Table 2: Association between FeNO and concentrations of pollutants measured.

FeNO	Urban(n=50)		Rural(n=86)		Total (N=136)	
	r value	p value	r value	p value	r value	p value
$PM_{2.5}$	0.01	0.93	0.05	0.67	0.08	0.34
PM_{10}	0.02	0.89	0.03	0.76	0.08	0.35
NO_2	0.09	0.53	0.26	0.02*	0.20	0.03*

Spearman Rho's Test was used for correlation between pollutants and FeNO.*p value significant <0.0

Discussions:

According to questionnaires that were returned back, overall response rate was 62% whereby the response rate was lower for Ampang (urban) as compared to Dusun Tua (rural). This was mainly because parents from urban area refused to get involved as they did not have much time to participate in this study as compared to parents from the rural area. Most of the mothers from rural areas are housewives. Results show that these two groups of respondents were matched even for age, sex, races, height and weight.

In this study, self-reported numbers of respiratory symptoms (cough, phlegm, and chest tightness) were higher among urban area children compared to rural area children (Table 1). Only wheezing was reported to be higher among rural area children compared to urban area children. Even though the data collected were only based on questionnaire feedbacks without further carrying out clinical test, parents and teachers were given instructions on how to complete the questionnaire before filling them in. Statistical analysis results show that urban area children experience more respiratory symptoms compared to rural area children. Living near road traffic and construction areas might be related to an increase in prevalence of adverse respiratory health problems. Several local studies carried out in Klang Valley have found that most of the children (5-12years old) living in urban areas also show higher prevalence of chronic cough, phlegm and chest tightness as compared with rural area [17,18]. This might be due to high exposure to gaseous and particles emissions from vehicles and constructions area near their preschool. Besides attending preschools, most of the children stayed at residential areas near the preschools and there are possibilities of increasing their exposure. However, there were lesser traffic and construction areas in rural regions as the greenery is still maintained. In addition, Ampang area is located next to Kuala Lumpur which, in 2009 Department of Environment (DOE) recorded that Kuala Lumpur was among the cities with the highest number of unhealthy days based on Air Pollutants Index (API) from 2001-2009. DOE also suggested that the high level of pollution resulted from the high traffic volumes in those areas [19]. In addition, a study done by Nurul [17] also reported that living near busy roads will result in higher concentrations of $PM_{2.5}$ measured as compared to less busy road. The result obtained shows that $PM_{2.5}$ sources of cooking activity showed significant difference between study areas.

The measurements of air pollutants inside the preschools confirmed that the levels of pollutants were different between these two studied areas (Table 1). A high concentration of pollutants ($PM_{2.5}$, PM_{10} and NO_2) measured can be seen in urban area. In the urban area, source of PM_{10} exposure was from road traffic and also from the demolition of construction site. It might also be generated by the handling, loading and unloading of

dusty materials. A previous research suggests the sources of $PM_{2.5}$ and NO_2 might be from combustion activities especially from motor vehicles and several industries [20]. Construction works and highways present in urban area might contribute to high concentrations of particulate matter and NO_2 in urban area. All the measured pollutants show significant difference between the study areas ($p<0.01$).

In comparison, previous study by Tezara *et al.* [21] found that the concentration of indoor PM_{10} in daycare centres were almost similar for the mean concentration of indoor PM_{10} in areas near the main road and industrial area (69.8 µg/m^3 and 68.8µg/m^3, respectively) and slightly lower in daycare centres in residential area. The study also reported that the reasons for indoor PM_{10} concentration to be higher might be due to building age, floor type, shelf area, dust from fans and presence of curtain in the daycare centre. The findings from this study might be related to the findings from that previous study as most of the preschools involved were present with all the factors mentioned by Tezara *et. al.* [21]. However, both studies did not exceed the permissible limit of 150 µg/m3 stated by Department of Occupational Safety and Health Malaysia [22]. Meanwhile, a study by Mukala *et al*.[23], showed that the NO_2 concentration measured were different from outside and inside of the preschool. This might be resulted from scarce indoor sources of NO_2 such as gas appliances and smoking activities inside the preschool. However, NO_2 sources can be derived from outdoor environment. In this study, a measurement of inside indoor NO_2 was considered low but slightly higher in urban area as compared to rural area.

From the results obtained (Table 1),the mean concentrations of FeNO at both areas (urban =11.3 ppb, rural=9.5ppb) were lower than the standards (20 ppb to 35ppb for children) based on ATS clinical practice guideline for interpretation of FeNO. At low FeNO value (<20ppb), eosinophilic airway inflammation is unlikely to happen; whereas at high FeNO (>35) level, eosinophilic airway is more likely to happen. Besides that, several factors (individual and environmental) were highly related to the increase of FeNO value and they are needed to be investigated further in the multivariate analysis (7). The correlation of indoor air pollutions exposures with FeNO concentration was assessed among healthy children in urban and rural area. Only NO_2 shows a significant association with the elevated level of FeNO ($p<0.05$) (Table 2) in rural area. However, the exposure to NO_2 in this study were lower in both area based on the measurements carried out. When the data of the two study areas were combined, they also show a significant association between NO_2 and FeNO. However, the relationship was not strong (coefficient of 1). This result may be related to individual susceptibility (nutrition status, genetic [5]) instead of pollutants exposure. As previous study by Marion *et al.* [24] shows, there was a significant elevated FeNO level among asthmatic and non- asthmatic children who were exposed to high concentrations of indoor $PM_{2.5}$. Franklin et.al [7] previously explained that FeNO value in children increases until the age of 13 years. Finally, it was suggested that this study can be a preliminary study to relate the indoor air pollutants exposure and FeNO as limited epidemiology study was done before especially in Malaysia.

There may be some information bias such as recall bias as parents or guardians may not well recall the actual experience of their children during when they filled in the questionnaire. However, minimisation of information bias was considered as only those questionnaire completely filled by parents/guardian were accepted. Thus, examination by medical doctor was suggested to confirm the respiratory symptoms complained among those studied subjects. For doubtful cases, the questionnaires were rejected. The measurements taken in this study was done by following the standard procedure and guideline provided to ensure the measurements taken were reliable. Thus, the conclusions drawn were highly reliable. However, cross-sectional study design limits the possibility to draw conclusions about causal relationships.

Conclusions:

This study confirms that classrooms in urban area (Ampang) were exposed to a high amount of indoor air pollutants ($PM_{2.5}$,PM_{10} and NO_2) as compared to the rural area . It also shows that there is a high number of reported respiratory symptoms among them. The FeNO values were also slightly higher among urban preschool children but still under normal range based on ATS classification. This result obtained can be due to multifactorial predictor contributed to the decreased and elevated. It was expected that not just pollutants but multifactor may be contributed to high or low value of FeNO. Therefore, FeNO can be suggested as a non-invasive biomarker for respiratory inflammations in children of preschool age. However, a follow up on the exposure and respiratory inflammation (FeNO test) for a period of time was suggested. It is also suggested that measurements on the exposure to children for a longer period of time or continuously at home should be taken. This, together, can help to determine the causal factors (individual or environmental) that may elevate the value of FeNO among children. For further understanding of indoor air exposure effects and respiratory inflammation, more research on this biomarker should be carried out especially among preschool children.

Ethical considerations:

Ethical issues such as plagiarisms, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, et cetera have been completely observed by the authors.

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