



Sick building syndrome (SBS) among office workers in a Malaysian university – Associations with atopy, fractional exhaled nitric oxide (FeNO) and the office environment

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HIGHLIGHTS

- Atopy and elevated FeNO show strong association with SBS symptoms.
- Combined atopy and elevated FeNO levels strongly associated with SBS symptoms.
- Transient symptoms were associated with room temperature and relative air humidity.
- Der f1 levels in dust associated to SBS and transient symptoms
- Der f1 levels in dust associated to SBS symptoms of workers who are allergic to *D. farinae*

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ABSTRACT

There are few studies on sick building syndrome (SBS) including clinical measurements for atopy and fractional exhaled nitric oxide (FeNO). Our aim was to study associations between SBS symptoms, selected personal factors, office characteristics and indoor office exposures among office workers from a university in Malaysia. Health data were collected by a questionnaire ($n = 695$), skin prick test (SPT) ($n = 463$) and FeNO test ($n = 460$). Office settled dust was vacuumed and analyzed for endotoxin, (1,3)- β -glucan and house dust mites (HDM) allergens group 1 namely *Dermatophagoides pteronyssinus* (Der p 1) and *Dermatophagoides farinae* (Der f 1). Office indoor temperature, relative air humidity (RH), carbon monoxide (CO) and carbon dioxide (CO₂) were measured by a direct reading instrument. Associations were studied by two-levels multiple logistic regression with mutual adjustment and stratified analysis. The prevalence of weekly dermal, mucosal and general symptoms was 11.9%, 16.0% and 23.0% respectively. A combination of SPT positivity (allergy to HDM or cat) and high FeNO level (≥ 25 ppb) was associated with dermal ($p = 0.002$), mucosal ($p < 0.001$) and general symptoms ($p = 0.05$). Der f1 level in dust was associated with dermal ($p < 0.001$), mucosal ($p < 0.001$) and general ($p = 0.02$) symptoms. Among those with allergy to *D. farinae*, associations were found between Der f 1 levels in dust and dermal ($p = 0.003$), mucosal ($p = 0.001$) and general symptoms ($p = 0.007$). Office-related symptoms were associated with Der f 1 levels in dust ($p = 0.02$), low relative air humidity ($p = 0.04$) and high office temperature ($p = 0.05$). In conclusion, a combination of allergy to cat or HDM and high FeNO is a risk factor for SBS symptoms. Der f 1 allergen in dust can be a risk factor for SBS in the office environment, particularly among those sensitized to Der f 1 allergen.

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1. Introduction

Indoor air quality is an important issue since people in industrialized countries spend most of their time in indoor environments. The World Health Organization (WHO) defined the concept of sick building

syndrome (SBS) in 1983 as certain medical symptoms experienced by occupants in buildings with indoor environment problems (World Health Organization, 1983). SBS was initially studied among office workers, and include symptoms from eyes, upper airways, facial skin, headache and tiredness. SBS is a group phenomenon and not a syndrome as normally defined in medicine and individual diagnostic is difficult (Norbäck, 2009).

SBS studies have been carried out in different indoor environment but mostly among office workers (Apter et al., 1994). A number of risk factors for SBS have been identified (Andersson, 1998; Apter et al., 1994; Norbäck, 2009), including personal factors, psychosocial work environment and indoor environment factors. Female gender (Brasche et al., 2001; Stenberg and Wall, 1995), allergy (Björnsson et al., 1998; Sahlberg et al., 2012), personality traits (Runeson et al., 2004) and lower sense of coherence (Runeson et al., 2003) were reported to be associated with SBS. Moreover, unbalanced psychosocial work environment (Marmot et al., 2006; Runeson et al., 2006) and occupational stress (Azuma et al., 2014; Bakke et al., 2007) have been shown to be related to SBS symptoms. Indoor environmental factors associated with SBS include room temperature (Bakke et al., 2008), relative air humidity (Wolkoff, 2008), building dampness (Mendell et al., 2011; Park et al., 2008), ventilation flow (Seppänen and Fisk, 2004; Sundell et al., 2011), microbial exposure such as molds and bacteria (WHO, 2009), microbial volatile organic compounds (MVOC) (Araki et al., 2010; Sahlberg et al., 2013) and volatile organic compounds (VOC) (Takigawa et al., 2012).

SBS symptoms can be related to building dampness and indoor mold growth (World Health Organization, 2009). In damp buildings, mold and bacteria compounds are found in settled dust. Endotoxin is a compound found in the outer cell membrane of gram-negative bacteria (Gehring et al., 2008), while (1,3)- β -glucan is found in the cell-walls of mold (Iossifova et al., 2007). Endotoxin and (1,3)- β -glucan has pro-inflammatory effects. However, few studies have been carried out to study associations between these environmental microbial compounds and SBS symptoms among office workers. Previously, endotoxin exposure has been related to SBS in office buildings (Teeuw et al., 1994), high number of reported symptoms (Reynolds et al., 2001), upper respiratory symptoms and headache in office workers (Park et al., 2006). A study in water-damaged offices found that endotoxin exposure was positively associated with nasal inflammatory markers (eosinophilic cationic protein and interleukin-8) among office workers (Akpınar-Elci et al., 2013). An office study in Taiwan showed an association between (1,3)- β -glucan and fatigue in office workers (Wan and Li, 1999). Park et al. (2006) reported an interaction effect between endotoxin and fungal exposure among office workers from a water-damaged office building in United State (Park et al., 2006). House dust mites (HDM) contain allergens and HDM allergy is common globally (Milián and Díaz, 2004). HDM allergens are mainly studied in homes but can also be found in the office environment. Menzies and coworkers reported that respiratory symptoms in workers were associated with HDM levels in office dust (Menzies et al., 1998). However, Brunetto et al. (2009) did not find any association between nasal and skin symptoms in employees and HDM levels in office dust possible due to a low number of dust samples with HDM allergens (Brunetto et al., 2009).

Tropical countries have warm and humid climate which provide favorable conditions for microbial growth. Some studies on SBS among office workers have been carried out in tropical countries, such as in Turkey (Gül et al., 2007), Brazil (Costa and Brickus, 2000; Graudenz et al., 2002, 2005; Rios et al., 2009), Mauritius (Bholah and Subratty, 2002), Taiwan (Wan and Li, 1999) and Singapore (Ooi et al., 1998; Ooi and Goh, 1997). However, only a few office studies on SBS among office workers have been published from Malaysia. Zamani et al. (2013) reported that one old office building had higher prevalence of SBS than a new office building. Prevalence of SBS was associated with carbon dioxide (CO₂), total VOC (TVOC), particulate matter 10 (PM₁₀), particulate matter 2.5 (PM_{2.5}) and ultrafine particles (UFP) levels in the

offices (Zamani et al., 2013). Fadilah and Juliana (2012) found a higher prevalence of nasal symptoms in workers from new office buildings (Fadilah and Juliana, 2012). Another office study found no association between prevalence of *Penicillium* specific IgE among office workers and prevalence of eyes or nasal symptoms (Goh et al., 2007). None of these office studies from Malaysia have included clinical data or biomarkers except the study from Goh and coworkers.

SBS is important to study since it can lead to poor productivity and absenteeism among workers (Singh, 2005). However, there is lack of office studies on associations between SBS symptoms and levels of micro-organisms and allergens in tropical countries, especially in Malaysia. Moreover, we found that no study investigated associations between SBS symptoms and fractional exhaled nitric oxide (FeNO), a biomarker of T-helper 2 driven lower airway inflammation. Thus, the overall aim was to study SBS symptoms among office workers in a university in Malaysia and investigate associations between the office environment and selected personal factors, including FeNO and atopy, and these symptoms. The first aim was to study associations between SBS symptoms and age, gender, allergy (skin prick test positivity to HDM or cat), current smoking and fraction of exhaled nitric oxide (FeNO). The second aim was to study the associations between SBS symptoms and selected office characteristics and measured indoor exposures.

2. Materials and methods

2.1. Study population

The study population consisted of office workers in a major academic institution, Malaysia. The registrar office of the academic institution was contacted to get a list of all offices and number of employees in each office. Totally, there were 61 offices in the academic institution. The inclusion criterion for selection of offices was that they should be administrative offices equipped with air-conditioning mechanical ventilation system and have at least 15 office workers. Initially, 50 offices fulfilled the inclusion criteria, however, 4 offices were excluded because the workers had mainly work tasks different from ordinary office work. Letters were sent to the top management level of the 46 offices for permission and 40 out of 46 offices gave verbal or written consent.

Totally, 2192 office workers were employed in these 40 offices. All administrative office workers were invited to participate through email, announcement and face-to-face invitation. Totally 701 out of 2192 office workers agreed to participate (32.0%). Six office workers were excluded because of pregnancy leaving 695 to be included. Among these 695 respondents, 465 agreed to participate in skin prick test. However, two were excluded due to recent severe asthma leaving 463 respondents. Among these 463 respondents, 460 of them participated in both skin prick test (SPT) and fraction of exhaled nitric oxide (FeNO) test. Researchers distributed a self-administered questionnaire to the respondents which was collected on the same day or the following days. The questionnaires were answered by the respondents within two weeks from the environmental measurements. After collecting the questionnaire, the researchers went through it and face-to-face interviewed the respondents to clarify uncertainties in the answers or missing data.

The study was approved by the Ethics Committee for Research Involving Human Subjects at Universiti Putra Malaysia (UPM) before the field data collection. All participants gave informed consent. They gave written consent after being informed on the objective of the study and procedures.

2.2. Questionnaire

The respondents were given a self-administrative questionnaire to collect data about demographic information, home environment, office characteristics and SBS symptoms. The questions were adapted from Indoor Air Quality and Work Symptoms Survey, NIOSH (National Institute

Occupational Safety and Health) Indoor Environmental Quality Survey (1991) and a previous SBS study (Zhang et al., 2011). Home environment questions included any home dampness and indoor home painting during the last 12 months. Office characteristics questions included yes/no questions on new furniture in office and office wall painted during the past three months. A question on number of airway infections during the last three months was included in the questionnaire. For SBS symptoms, there were 16 questions which were grouped into three different groups (dermal, mucosal and general symptoms). Dermal symptoms included questions for rashes on hands or forearms, rashes on the face or throat, eczema, itching in the face or on the throat and itches on hands or forearms. Mucosal symptoms included questions on eye irritation, swollen eyelids, runny nose or nasal catarrh, nasal obstruction/blocked nose, throat dryness, sore throat and irritative cough. At last, general symptoms included headache, nausea, sensation of catching a cold, feeling tired and out of sort. Each of the SBS question had four alternative answers for their frequency of occurrence during the past three months. 'No, never' or 'Yes, sometimes 1–3 times per month' coded as 0 and 'Yes, often 1–4 times per week' or 'Yes, everyday' coded as 1. For office-related symptoms (transient symptoms), there was a question asking is any of the SBS symptoms improved when being away from the workplace.

2.3. Skin prick test (SPT) and fraction of exhaled nitric oxide (FeNO) test

One week before the SPT, respondents were informed about the test procedures and avoid using antihistamine drugs or drugs specified in a list that have antihistamine activity. SPT was performed by experienced hospital nurses. ALK-Abello skin prick test kits for *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and *Felis domesticus* were used. Normal saline solution and histamine were used as negative and positive controls. After 20 min, mean wheal diameter for each control and allergens were calculated. The test result was considered as positive if the mean wheal diameter was ≥ 3 mm.

FeNO level was measured by a portable device (NIOX-MINO, Aerocrine AB, Stockholm, Sweden). The device is equipped with a NO filter that removes ambient NO to avoid any influence from ambient NO. Respondents were advised to avoid nitrate rich food three hours and avoid strenuous exercise one hour before the measurement. Before performing the FeNO test, a video demonstration was shown and the test procedure was described. The participants were required to empty their lungs by complete expiration followed by inhalation of NO-free air through the disposable filter to their maximum lung capacity. Then, they were required to exhale air constantly into the machine at an exhalation rate of 50 ± 5 ml/s without a nose clip. One FeNO measurement was collected for each respondent. Twenty five ppb was used as cutoff point of the FeNO level (Dweik et al., 2011). FeNO readings < 25 ppb was categorized as low level, whereas ≥ 25 ppb was categorized as elevated (high level) in this study.

2.4. Building assessment and climate measurement

Twenty five out of 40 offices were randomly selected for the office environment study, which included building inspection, dust sample collection, indoor and outdoor climate measurement. Fifteen offices (60%) were selected from 25 offices with 15 to 55 office workers and 10 offices (66%) were selected from 15 offices with more than 55 office workers. In each of these 25 offices, one to five administrative rooms were included in the office environment measurement, depending on the size of the office. Signs of dampness such as water leakage, indoor mold growth, information on the building materials and floor furnish were recorded. Q-trak indoor air quality monitor 7565 (TSI Incorporated, St. Paul, MN, USA) was used to measure indoor temperature ($^{\circ}\text{C}$), relative air humidity (RH) (%), carbon dioxide (CO_2) concentration (ppm) and carbon monoxide (CO) (ppm) during normal activities in

the center of room at height 1–1.5 m above the floor level and about 1 m from the workers for 50–70 min by logging average values per minute (Zhao et al., 2008). Each office room with dust sample collection had one Q-trak measurement except two larger offices which had two Q-trak measurements. The outdoor climate was measured by a Q-trak instrument outside of the office building on the same day after the dust collection was completed.

2.5. Dust collection

In each of these 25 offices, 2–10 dust samples were collected from one to five administrative rooms, depending on the size of the office (totally 35 office rooms). Each room was divided into two parts (entrance side half and window side half) and a dust sample was collected from each part (Zhang et al., 2011). A 1800 W electric power vacuum cleaner (Model PVC-31A, Pensonic, Malaysia) equipped with a special dust collector fitted with a Millipore filter (pore size $6 \mu\text{m}$) (ALK Abello, Copenhagen, Denmark) was used to vacuum the settled dust. All dust samples were collected by vacuum cleaning off office floors (4 min) and of tables and chairs (4 min). The settled dust samples were sieved (particle diameter $< 400 \mu\text{m}$) to obtain fine dust (Zhao et al., 2008). The sieved dust samples was weighted and stored at -20°C until extraction (Zhang et al., 2011). A total of four office rooms had only one dust samples since the amount of dust on each of the dust filters was inadequate for individual analysis of microbial compounds. The two dust samples from each of these four office rooms were mixed homogenously before used for analysis. A total of 70 dust samples were collected from 35 office rooms for analysis.

2.6. Extraction and analysis of microbial

For extraction of house dust mite allergens, 2 ml of phosphate-buffer saline with Tween (PBS-T) was added into each fine dust sample (100 ± 5 mg) in a centrifuge tube. The centrifuge tubes were shaken for 2 h at room temperature and centrifuged for 10 min at 3000 rpm (Prester et al., 2007). Then, the supernatants were transferred into Eppendorf tube and stored at -20°C until analysis of dust mites. Two-site monoclonal antibody (MAB) sandwich ELISAs (Indoor Biotechnologies, Inc., Charlottesville, VA) were used to analyze for Der p 1 and Der f 1. Analysis were performed according to the manufacturer's protocols with the exception that Streptavidin–horseradish peroxidase was obtained from Nacalai Tesque, Inc., Kyoto, Japan. All units were expressed as ng/g (Zhao et al., 2006). The detection limit for HDM allergens was 10 ng/g.

For extraction of endotoxin, 10 mg of dust from each sample was weighted, transferred into a depyrogenated test tube and suspended in 1 ml of 0.5 N NaOH solution. The samples were vortexed and shaken on a rotary shaker for 2.5 h (Johnson et al., 2010). The tubes were left to let the particles to settle and the supernatant were transferred into another depyrogenated tube. They were stored at -20°C until analysis. To extract (1,3)- β -glucan, 1 mg of dust sample was suspended in 50 μl of dimethyl sulfoxide (DMSO) solution for 30 min at room temperature. The dust suspension was sonicated for 4 h with vigorous vortexing every 30 min (Young et al., 2011). The extracts were stored at -20°C until analysis. Endotoxin and (1,3)- β -glucan were determined using the Limulus amoebocyte lysate (LAL) chromogenic method (Pyrotell®-T kinetic turbidimetric endotoxin testing) (Associates of Cape Cod, Falmouth, MA, USA) and Glucate kit (Associates of Cape Cod, Falmouth, MA, USA) according to the manufacturer's instructions. Certified depyrogenated test tubes (Associates of Cape Cod, Falmouth, MA, USA) were used for all endotoxin and (1,3)- β -glucan testing. Other glassware, forceps and aluminium foil that used for samples preparation were depyrogenated by dry heat at 180°C for 12 h (Johnson et al., 2010).

2.7. Statistical analysis

Basic characteristics of office workers between genders were compared using Chi-square test and independent t-test. Comparisons of the prevalence of SBS symptoms between groups was analyzed by Chi-square test and comparisons between office rooms with age less than 10 years and 10 years or more was analyzed by Mann–Whitney U test. Associations between SBS symptoms, personal factors (age, gender and current smoking) and the combined variable of SPT and FeNO were analyzed by two-levels (individual level and office level) multiple logistic regression. Associations between SBS symptoms and office exposures (office characteristics and office measurement) were analyzed by two-levels multiple logistic regressions, with each model adjusted for personal factors and home environment factors (any sign of home dampness and indoor home painting). Then, two-levels logistic regression were used to analyze the associations between office-related symptoms and personal factors as well as associations between office measurement and office-related symptoms, adjusting for personal factors. Finally, stratified analysis with respect to *D. farinae* sensitization was performed. Odds ratio (OR) with 95% confidence interval (95% CI) was calculated. All data analysis was conducted using Statistical Package for the Social Sciences (SPSS) 21.0 or the STATA statistical package 11.0, using two-tailed tests at a 5% significance level.

3. Results

Among the 695 respondents, 62.6% were females and mean age was 34.2 years (range 18–59 years) (Table 1). The majority of the current smokers were men. The prevalence of atopy, elevated FeNO level and combination of atopy and elevated FeNO level were significantly higher in men compared to women. No gender differences were found for age, signs of dampness in the office, new furniture in the office recently, office walls painted recently or wall-to-wall carpet in the office. The prevalence of SBS symptoms are shown in Table 2. Among the 463 respondents who participated in the SPT, 50.3% were allergic to *Dermatophagoides pteronyssinus*, 49.0% were allergic to *D. farinae*, 25.4% were allergic to *F. domesticus*, 54.4% had any allergy (to cat or HDM) and 25.9% had elevated FeNO levels (≥ 25 ppb). Tiredness was the most common SBS symptoms, followed by headache and nasal symptoms. There were no significant gender differences for most SBS symptoms or office-related symptoms, except for dermal symptoms which were more common in women. The prevalence of dermal, mucosal symptoms and a sensation of catching cold was higher among those with atopy. FeNO level was higher among those with mucosal, general symptoms and itches in the face or on neck.

Associations between SBS symptoms, office-related symptoms and personal risk factors analyzed by multiple logistic regressions are shown in Table 3. Atopy and high FeNO level were associated with dermal and mucosal symptoms, with a border line significance for general symptoms ($p = 0.054$). General symptoms were inversely associated with age. Associations between number of airway infections and log FeNO were analyzed using Spearman's rank correlation test. Significant association ($p = 0.023$, ρ (rho) = 0.106) was found between these two variables.

Among the 35 office rooms with office environment measurement, 20 office rooms had split unit air conditioning system, seven had centralized conditioning system and eight had both centralized and split unit air conditioning system. Seven office rooms had visible signs of water leakage and three had visible indoor mold growth. Seven office rooms had either water leakage or mold problem. In total, 15 office rooms had wall-to-wall carpet, 17 had stone tiles, two had PVC (Polyvinyl chloride) plastic floors and one had wooden tile floor material. Comparisons of indoor office measurements in 35 office rooms with age less than 10 years and 10 years or more is presented in Table 4. Indoor RH in office rooms with age less than 10 years were significantly higher than office rooms with age 10 years or more. The concentration of endotoxin ($p = 0.034$) and amount of sieved dust ($p = 0.003$) were significantly higher in office rooms with age 10 years or more. Indoor room temperature was higher in office rooms with age 10 years or more (borderline significance $p = 0.050$). However, the age of the office rooms was not significantly associated with FeNO level or any weekly dermal, mucosal and general symptoms. Associations between the environmental parameters and office age as a continuous variable were analyzed using Spearman's rank correlation test. Building age was correlated with concentration of endotoxin ($p = 0.001$, $\rho = 0.405$) and amount of sieved dust ($p < 0.001$, $\rho = 0.493$), but not correlated with other indoor measured indoor environment factors.

As a next step, associations between weekly SBS symptoms and office-related symptoms and office characteristics and indoor office measurements were analyzed (Table 5). New furniture in the office was associated with dermal symptoms. RH was negatively associated with mucosal symptoms while Der f1 level was associated with dermal, mucosal, general and office-related symptoms. As a next step, we analyzed significant associations using two levels logistic regression with further adjustment for the combined variable of SPT and FeNO. New furniture in the office rooms was no longer significantly associated with dermal symptoms (OR = 2.04, 95% CI = 0.90–4.60, $p = 0.086$) after adjusting for personal factors (age, gender, current smoker, the combined variable of SPT and FeNO level) and home environment factors (any home dampness and any recent indoor home painting).

Table 1
Basic characteristics of office workers stratified by gender (N = 695).

Variables	Men (N = 232)	Women (N = 463)	p-Value	Total (N = 695)
Age, years (Mean $\pm$ Standard Deviation) ^a	34.4 (9.6)	34.2 (9.2)	0.790	34.2 (9.3)
Current smoker, n (%)	70 (30.2)	2 (0.4)	<0.001***	72 (10.4)
Atopy, n (%) ^{b,c}	113 (65.7)	139 (47.8)	<0.001***	252 (36.3)
Elevated FeNO level, n (%) ^{d,e}	57 (33.1)	62 (21.5)	0.008**	119 (17.1)
Atopy and elevated FeNO level, n (%) ^d	52 (30.2)	50 (17.4)	0.002**	102 (22.17)
Signs of dampness in the office, n (%) ^{f,g}	44 (23.7)	69 (20.6)	0.438	113 (16.3)
New furniture in office in the last three months, n (%)	34 (14.7)	44 (9.5)	0.055	78 (11.2)
Office walls painted in the last three months, n (%)	23 (9.9)	30 (6.5)	0.129	53 (7.6)
Wall-to-wall carpet in the office, n (%)	56 (24.1)	141 (30.5)	0.090	197 (28.3)

^a Missing data = 4.

^b n = 463.

^c Allergic to *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* or *Felis domesticus*.

^d n = 460.

^e Equal or more than 25 ppb.

^f Missing data = 174.

^g Signs of water leakage or mold growth observed in the office.

** $p < 0.01$.

*** $p < 0.001$.

Table 2

Prevalence of weekly sick building syndrome (SBS) symptoms stratified by gender, atopy and FeNO level among office workers.

Weekly SBS symptoms	Gender (n = 695)			Atopy status ^a (n = 463)			FeNO (n = 460)			Total (n = 695)
	Men (n = 232)	Women (n = 463)	p-value	No atopy (n = 211)	Atopy (n = 252)	p-value	<25 ppb (n = 341)	≥25 ppb (n = 119)	p-value	
<i>Dermal</i>										
Rashes on hands or forearms	4 (1.7)	21 (4.5)	0.082	5 (2.4)	9 (3.6)	0.589	8 (2.3)	6 (5.0)	0.140	25 (3.6)
Rashes on the face or neck	5 (2.2)	8 (1.7)	0.695	4 (1.9)	7 (2.8)	0.761	8 (2.3)	3 (2.5)	0.914	13 (1.9)
Eczema	9 (3.9)	28 (6.0)	0.284	7 (3.3)	16 (6.3)	0.197	14 (4.1)	9 (7.6)	0.146	37 (5.3)
Itches in the face or on the neck	12 (5.2)	26 (5.6)	0.862	9 (4.3)	25 (9.9)	0.021*	20 (5.9)	14 (11.8)	0.042*	38 (5.5)
Itches on hands or forearms	7 (3.0)	35 (7.6)	0.018*	8 (3.8)	20 (7.9)	0.078	17 (5.0)	11 (9.2)	0.117	42 (6.0)
Any weekly dermal symptoms	18 (7.8)	65 (14.0)	0.016*	19 (9.0)	40 (15.9)	0.035*	80 (23.5)	38 (31.9)	0.087	83 (11.9)
<i>Mucosal</i>										
Eye irritation	12 (5.2)	39 (8.4)	0.164	7 (3.3)	36 (14.3)	<0.001***	22 (6.5)	21 (17.6)	0.001**	51 (7.3)
Swollen eyelids	3 (1.3)	12 (2.6)	0.407	4 (1.9)	8 (3.2)	0.559	8 (2.3)	4 (3.4)	0.517	15 (2.2)
Runny nose/nasal catarrh	13 (5.6)	30 (6.5)	0.740	12 (5.7)	25 (9.9)	0.121	21 (6.2)	16 (13.4)	0.018*	43 (6.2)
Nasal obstruction/ blocked nose	21 (9.1)	43 (9.3)	1.000	15 (7.1)	36 (14.3)	0.017*	28 (8.2)	22 (18.5)	0.003**	64 (9.2)
Throat dryness	18 (7.8)	37 (8.0)	1.000	14 (6.6)	27 (10.7)	0.141	24 (7.0)	16 (13.4)	0.038*	55 (7.9)
Sore throat	10 (4.3)	21 (4.5)	1.000	5 (2.4)	19 (7.5)	0.019*	13 (3.8)	11 (9.2)	0.030*	31 (4.5)
Irritative cough	6 (2.6)	12 (2.6)	1.000	4 (1.9)	11 (4.4)	0.188	9 (2.6)	6 (5.0)	0.204	18 (2.6)
Any weekly mucosal symptoms	36 (15.5)	75 (16.2)	0.913	23 (10.9)	62 (24.6)	<0.001***	46 (13.5)	37 (31.1)	<0.001***	111 (16.0)
<i>General</i>										
Headache	24 (10.3)	66 (14.3)	0.153	28 (13.3)	38 (15.1)	0.596	43 (12.6)	23 (18.5)	0.127	90 (12.9)
Nausea	10 (4.3)	25 (5.4)	0.587	12 (5.7)	17 (6.7)	0.703	19 (5.6)	10 (8.4)	0.278	35 (5.0)
Sensation of catching a cold	15 (6.5)	44 (9.5)	0.196	14 (6.6)	32 (12.7)	0.042*	25 (7.3)	19 (16.0)	0.010*	59 (8.5)
Feeling tired and out of sort	23 (9.9)	69 (14.9)	0.075	31 (14.8)	41 (16.3)	0.700	48 (14.1)	22 (18.5)	0.299	92 (13.3)
Any general symptoms	46 (19.8)	114 (24.6)	0.181	49 (23.2)	71 (28.2)	0.243	36 (10.6)	23 (19.3)	0.017*	160 (23.0)
Office-related symptoms	14 (6.0)	40 (8.6)	0.293	13 (6.2)	24 (9.5)	0.229	28 (8.2)	9 (7.6)	1.000	54 (7.8)

^a Skin prick test result positive to either *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* or *Felis Domesticus*.

* p<0.05.

** p<0.01.

*** p<0.001.

(n = 461). RH was no longer associated with mucosal symptoms (OR = 0.66, 95% CI = 0.40–1.08, p = 0.099) after adjusting for personal and home environment factors. Der f 1 level was no longer associated with office-related symptoms (OR = 1.09, 95% CI = 0.98–1.20, p = 0.101) after adjusting for personal and home environment factors. However, associations between Der f 1 level and dermal symptoms (OR = 1.21, 95% CI = 1.08–1.36, p = 0.001), mucosal symptoms (OR = 1.23, 95% CI = 1.10–1.38, p < 0.001) and general symptoms (OR = 1.15, 95% CI = 1.02–1.30, p = 0.021) remain significant after adjusting for personal and home environment factors (n = 371).

As a next step, a stratified analysis was performed with respect to *D. farinae* allergy. Significant associations were found between Der f 1 level in dust and dermal symptoms (OR = 1.23; 95% CI = 1.07–1.40; p = 0.003), mucosal symptoms (OR = 1.25; 95% CI = 1.09–1.44; p =

0.001) and general symptoms (OR = 1.21; 95% CI = 1.05–1.38; p = 0.007) among those with *D. farinae* allergy. However, among those with no *D. farinae* allergy, no significant associations between Der f 1 level with dermal symptoms (OR = 1.16; 95% CI = 0.93–1.43; p = 0.183), mucosal symptoms (OR = 1.15; 95% CI = 0.94–1.39; p = 0.171) and general symptoms (OR = 1.04; 95% CI = 0.84–1.28; p = 0.742) were found. In the logistic regression models, OR was calculated for 1000 ng/g increase of the Der f1 level.

A total of 7.8% of the office workers reported office-related symptoms that were improved when being away from the office. Associations between having any office-related symptoms, personal factors and indoor office environment factors were analyzed by two-levels multiple logistic regressions. None of the personal factors (age, gender, smoking status and combine variable of atopy status and FeNO level)

Table 3

Multilevel logistic regression analysis of associations between personal factors and self-reported weekly symptoms (n = 460).

	Weekly dermal symptoms		Weekly mucosal symptoms		Weekly general symptoms		Office-related symptoms	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Age ^a	0.98 (0.95–1.02)	0.343	0.97 (0.93–1.00)	0.033*	0.62 (0.46–0.82)	<0.001***	0.99 (0.95–1.03)	0.644
Gender	2.17 (1.04–4.54)	0.040*	1.38 (0.74–2.59)	0.309	1.63 (0.94–2.84)	0.087	1.89 (0.79–4.52)	0.153
Current smoker	1.19 (0.38–3.74)	0.765	0.95 (0.37–2.49)	0.922	0.81 (0.34–1.94)	0.641	0.63 (0.13–3.16)	0.574
Combined variable of SPT and FeNO								
SPT negative and low FeNO level ^b	1		1		1		1	
SPT negative and high FeNO level ^c	1.56 (0.31–7.72)	0.588	2.26 (0.56–9.16)	0.253	1.22 (0.35–4.28)	0.761	0.98 (0.12–8.08)	0.983
SPT positive and low FeNO level ^d	1.66 (0.81–3.38)	0.165	1.84 (0.95–3.55)	0.070	1.12 (0.65–1.93)	0.684	2.02 (0.92–4.45)	0.081
SPT positive and high FeNO level ^e	3.12 (1.51–6.48)	0.002**	4.80 (2.44–9.43)	<0.001***	1.78 (1.00–3.17)	0.054	1.45 (0.56–3.75)	0.440

Each model consists of age, gender, current smoker and combine variable of SPT and FeNO.

^a (OR calculated for 10 years increase in age).^b n = 194 (Reference group).^c n = 17.^d n = 147.^e n = 102.

* p<0.05.

** p<0.01.

*** p<0.001.

Table 4
Office indoor environment measurements.

Environmental parameters	Office age < 10 years (n = 8) Median (IQR)	Office age ≥ 10 years (n = 29) Median (IQR)	p-Value	Total material (n = 37) Median (IQR)
Indoor room temperature (°C)	22.8 (22.6–24.4)	24.4 (23.1–26.3)	0.050	23.9 (22.8–25.7)
Indoor relative air humidity (%)	62.3 (53.1–75.2)	56.5 (47.6–60.4)	0.022*	57.1 (49.5–61.5)
Indoor carbon monoxide (ppm)	0.3 (0.13–0.5)	0.4 (0.2–0.7)	0.241	0.3 (0.2–0.7)
Indoor carbon dioxide (ppm)	512.5 (438.0–758.0)	559.0 (474.0–741.0)	0.658	543.0 (474.0–741.0)
Endotoxin (EU/mg)	8.8 (3.3–11.9)	12.3 (7.5–21.1)	0.034*	11.3 (7.0–19.2)
(1,3)-β-glucan (ng/g)	55.6 (49.0–70.8)	65.7 (47.0–87.3)	0.400	62.9 (48.3–85.2)
Der p1 (ng/g)	543.7 (366.3–577.8)	557.8 (376.2–581.8)	0.657	556.2 (376.2–581.2)
Der f1 (ng/g)	442.5 (322.5–1921.3)	725.8 (434.1–1114.8)	0.543	658.0 (421.3–1135.8)
Amount of sieved dust (g/sample)	0.7 (0.3–0.8)	1.0 (0.6–1.3)	0.003**	1.0 (0.6–1.2)

N = 70 for endotoxin, (1,3)-β-glucan, Der p 1, Der f 1 and amount of sieved dust and N = 37 for air measurement from 35 office rooms.

Air and dust measurements (n = 37) were from 35 office rooms of the 25 offices selected for environmental measurements.

* p<0.05.

** p<0.01.

were significantly associated with office-related symptoms. RH (OR = 0.57, 95% CI = 0.34–0.97, p = 0.037), Der f 1 allergen level (OR = 1.13, 95% CI = 1.02–1.26, p = 0.020) in office settled dust and high indoor office temperature (OR = 1.22, 95% CI = 1.00–1.48, p = 0.050) were significantly associated with office-related symptoms after adjusting for age, gender and smoking. The range values of RH and temperature were 39.8%–79.1% and 20.9 °C–27.5 °C respectively.

4. Discussion

Weekly SBS symptoms were common among the office workers, especially eye, nose and throat symptoms, headache and tiredness. Similar results were found in other studies (Bakke et al., 2008; Rios et al., 2009; Runeson et al., 2006). A high prevalence of weekly ocular (21%), nasal (21%) and laryngeal (17%) symptoms were found among university staff (Bakke et al., 2008). Rios and coworkers found that upper airways

symptoms, eye symptoms, tiredness and headache were common (range 27.1–58.5%) among office workers in Brazil (Rios et al., 2009). General symptoms (headache, fatigue and sensation of getting cold) were most common among the Swedish workforce (range 10–25%) followed by mucosal symptoms (range 10–20%) (Runeson et al., 2006). Moreover, we found that atopy and elevated level of FeNO, a marker of allergic lower airway inflammation, were associated with both mucosal and dermal symptoms, and borderline significant with general symptoms. A combination of skin prick test positivity to cat or house dust mite (HDM) allergens and elevated levels of HDM allergen (Der f 1) in office dust were associated with SBS symptoms especially among those sensitized to Der f 1 allergen.

Gender differences were found for dermal symptoms only. This is in agreement with other studies reporting a higher prevalence of SBS symptoms among women. The causes of gender differences for SBS are not well understood. A general excess of psychosomatic symptoms

Table 5
Associations between office characteristics, office measurement and any weekly dermal, mucosal, general and office-related symptoms reported by office workers.

	Any weekly dermal symptoms		Any weekly mucosal symptoms		Any weekly general symptoms		Office-related symptoms	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
<i>Office characteristics (N = 691)</i>								
Observed office dampness ^{a,b}	0.85 (0.40–1.78)	0.659	0.80 (0.40–1.61)	0.539	0.85 (0.42–1.71)	0.640	0.54 (0.21–1.35)	0.187
New furniture in the office	2.25 (1.19–4.25)	0.012*	1.46 (0.79–2.69)	0.224	1.25 (0.71–2.23)	0.441	0.52 (0.15–1.74)	0.287
Office wall painted	1.43 (0.62–3.29)	0.400	1.38 (0.65–2.91)	0.394	1.45 (0.73–2.89)	0.289	0.47 (0.11–2.08)	0.321
Wall-to-wall carpet in office	1.26 (0.73–2.20)	0.405	1.27 (0.75–2.15)	0.381	1.03 (0.59–1.79)	0.923	0.78 (0.38–1.61)	0.496
<i>Office measurement</i>								
Temperature ^b	0.91 (0.75–1.10)	0.334	0.99 (0.83–1.17)	0.872	0.90 (0.76–1.08)	0.274	1.22 (1.00–1.49)	0.050
Relative air humidity ^b	0.75 (0.46–1.23)	0.251	0.66 (0.44–0.99)	0.046*	0.87 (0.57–1.33)	0.532	0.57 (0.34–0.97)	0.037*
Carbon monoxide ^b	0.73 (0.28–1.89)	0.515	0.80 (0.35–1.82)	0.594	1.35 (0.55–3.27)	0.512	0.67 (0.23–1.92)	0.455
Carbon dioxide ^b	0.93 (0.74–1.16)	0.504	1.04 (0.87–1.25)	0.633	1.11 (0.92–1.33)	0.283	1.05 (0.84–1.30)	0.688
Endotoxin ^c	0.93 (0.64–1.35)	0.690	1.30 (0.96–1.75)	0.088	0.97 (0.68–1.38)	0.851	1.27 (0.90–1.78)	0.168
(1,3)-β-glucan ^c	1.02 (0.91–1.14)	0.737	0.98 (0.88–1.08)	0.660	1.05 (0.95–1.17)	0.318	1.00 (0.89–1.12)	0.965
Der p1 ^b	0.94 (0.68–1.30)	0.693	0.87 (0.65–1.17)	0.344	1.06 (0.79–1.42)	0.706	0.97 (0.70–1.35)	0.865
Der f1 ^b	1.19 (1.09–1.31)	<0.001***	1.19 (1.09–1.30)	<0.001***	1.14 (1.02–1.28)	0.017*	1.13 (1.02–1.26)	0.020*
Amount of dust ^b	1.32 (0.59–2.96)	0.494	1.41 (0.70–2.83)	0.331	1.14 (0.55–2.36)	0.722	1.12 (0.50–2.54)	0.781

Each model was adjusted for age, gender, current smoker, any sign of home dampness, indoor home painting in the last 12 months and offices.

(OR calculated for 10% increase in relative humidity).

(OR calculated for 100 ppm increase in carbon dioxide).

(OR calculated for 10EU/mg dust increase in endotoxin).

(OR calculated for 10 ng/g dust increase in beta-glucan).

(OR calculated for 100 ng/g increase in level of Der p1).

(OR calculated for 1000 ng/g increase in level of Der f1).

^a Signs of water leakage or mold growth in the investigated room.

^b N = 517.

^c N = 510.

* p<0.05.

** p<0.01.

*** p<0.001.

among women has been suggested as one explanation as well as gender differences in life situation, social roles, working condition and indoor exposures (Stenberg and Wall, 1995). Self-reported allergy and smoking were risk factors for SBS in females (Brasche et al., 2001). Younger office workers in this study reported higher prevalence of general symptoms compared to older. There is no consistency between studies with regard to association between age and SBS symptoms in different studies (Eriksson and Stenberg, 2006; Norbäck, 2009; Runeson-Broberg and Norbäck, 2013).

We found that subjects sensitized to cat or HDM had more SBS symptoms. Some office studies have reported a positive association between atopy status and SBS (Björnsson et al., 1998; Malkin et al., 1998; Menzies et al., 1998; Sahlberg et al., 2012), while other studies did not find any association between SBS symptoms and atopy (Bakke et al., 2008; Gomzi et al., 2008). Our data showed that FeNO was associated with SBS symptoms, especially mucosal symptoms. FeNO is a non-invasive biomarker of allergic airway inflammation (eosinophilic airway inflammation) (Barnes and Liew, 1995; Berry et al., 2005). Increased in FeNO indicate local T-helper cell type 2-driven inflammation in the bronchial mucosa (Alving and Malinovski, 2010). We found only one study on SBS symptoms among office workers and FeNO levels and this study found no association between nasal symptoms and FeNO levels (Akpınar-Elci et al., 2008). However, two recent epidemiological studies among school children in China demonstrated that rhinitis is more common at higher FeNO levels (Xu et al., 2011; Zhao et al., 2013).

The highest prevalence of SBS symptoms was found among office workers with a combination of high FeNO and skin prick test positivity. This implies that the SBS symptoms are due to active allergic inflammation. This conclusion is supported by Olin et al. (2004). They found that atopic subjects who had rhinitis or asthma and were allergic to indoor allergens (cat or HDM allergens) had higher FeNO value, while atopic subjects who had rhinitis or asthma and were allergic to seasonal allergens had normal FeNO value (Olin et al., 2004). A SBS cohort study found that respondents with increased eosinophilic markers [eosinophil cationic protein (ECP) and eosinophil counts (EOS)] at baseline data had increased risk of developing general and mucosal symptoms (Sahlberg et al., 2012). Two other studies reported that allergy to HDM was associated with higher exhaled nitric oxide levels (Moody et al., 2000; Olin et al., 2004). Thus, our study indicated that ongoing Th2 driven inflammation can be an important mechanism for the SBS symptoms reported by the office workers in our study.

Most of the office measurement data such as indoor office temperature, RH, CO and CO₂ levels were within acceptable range and limits of indoor air quality guideline (Department of Occupational Safety and Health, 2010) except there were some office rooms had indoor temperature lower than acceptable minimum level, 23 °C. Generally, these variables were not associated with SBS in our study except for office-related symptoms which were more common at higher temperature and lower RH. Some office studies have reported that high room temperature is related to SBS (Fang et al., 2004; Norbäck and Nordström, 2008; Witterseh et al., 2004) and reduced task performance (Lan et al., 2011; Tham, 2004). The mechanisms and cut points for temperature triggered health symptoms in tropical countries is unclear. The mean indoor office temperature in the current study was mostly below thermal comfort temperature suggested by some studies in tropical countries (about 26 °C).

There are some thermal comfort studies available from hot and humid tropical countries. Thermal neutral temperature in an air-conditioned mechanical ventilated office in Malaysia was 26 °C (Daghighi et al., 2009). A large thermal comfort survey of air-conditioned buildings in Thailand proposed 26 °C and 50–60% relative humidity as comfortable environment conditions (Yamtraipat et al., 2005). A thermal comfort field study from south India proposed a mean comfort temperature of 26.4 °C in air-conditioned offices (Indraganti et al., 2014). A thermal comfort office study in Jakarta,

Indonesia, found that the neutral temperatures were 26.4 °C (air temperature), 26.7 °C (operative temperature) and 25.3 °C (equivalent temperature) (Karyono, 2000). Our study indicated that SBS symptoms might be triggered at lower room temperature than the suggested thermal comfort temperature in tropical countries. Two office studies from Singapore found that the workers complained about overcooling (Chen and Chang, 2012; Foo and Phoon, 1987). In study conducted by Foo and Phoon, around 60% of the workers were exposed to air temperatures less than 24 °C and the researchers concluded that an air temperature of 27 °C would be comfortable for more than 80% of the workers (Foo and Phoon, 1987). Although ideal mean temperature recommended by ASHRAE is 24.4 °C, many office workers think this is too cold probably because they are adapted to a tropical environment (Chen and Chang, 2012).

We found that the Der f 1 level in the office dust was strongly associated with SBS symptoms, including office-related symptoms, in particular among those sensitized to *D. farinae*. This is a new finding with regard to one specific HDM exposure and SBS symptoms among office workers. One previous study found associations between HDM allergen levels and SBS symptoms in offices (Menzies et al., 1998). In our study, Der f 1 allergen was detected in most of the office dust samples (93%) and was found at higher levels than Der p 1 levels in the dust samples. It is known that *D. farinae* can survive better than *D. pteronyssinus* in dry conditions (Arlian, 1992; Arlian and Morgan, 2003) and these two mites have different ecology and environmental determinants. Possible sources of HDM allergens in indoor includes soft furniture, carpeted floor and filters in air-conditioning system (Li et al., 2014; Liu et al., 2007; Wang et al., 2014). Further studies on HDM allergies in offices and SBS in tropical areas are needed, including measurement of the tropical storage mite, *Blomia tropicalis*.

There are some strengths and limitation of this study. Epidemiology studies can be influenced by information and selection bias. Potential individual selection bias in this study due to low participation rate has been previously analyzed (Lim et al., 2015). There was no significant difference between participating and non-participating groups with respect to doctor diagnosed asthma, allergic rhinitis, rhinitis and eczema. Moreover, the office workers did not have any information on environmental measurements or the results from the clinical investigation when they answered the questionnaires. The dust samples were analyzed in an arbitrary sequence without any knowledge on the environmental measurement or health status of the respondents by the same person using same laboratory equipment. Reporting bias should not be a critical issue in this study since FeNO, allergy testing and environment measurements are objective measurements that are not influenced by personal attitudes or recall bias. Therefore, we concluded that the study was not seriously influenced by selection bias or information bias.

However, there are some limitations of this study. One limitation is that we did not study job stressors and psychological work environment. These factors are found to be associated with SBS in previous studies (Azuma et al., 2014; Bakke et al., 2007; Marmot et al., 2006; Runeson et al., 2006). However, it is less likely that these factors would be related to clinical parameters such as SPT or FeNO. Another limitation is lack of information on concentrations of allergens and microbial compounds in the home environment. It was practically impossible to sample these compounds in the homes due to time and budget constrain. However, lack of information on these exposures in the home environment would most likely lead to a non-differential misclassification. Another limitation is that we did not perform any clinical investigation of the ocular or nasal mucosa. The NO-instrument which we used can also be used to measure nasal nitric oxide (NO) but nasal NO is related to certain nasal diseases and not related to nasal inflammation. NO has different function in different parts of the body and a high nasal NO concentration is normal in a healthy subject while subjects with certain nasal diseases such as primary ciliary dyskinesia and cystic fibrosis have very low nasal NO (Lundberg, 2008). Finally, one

important limitation of our study is the cross-sectional study design which limits the possibility to draw conclusions on causality.

In conclusion, allergy to cat or HDM as well as elevated FeNO levels can be important risk factors for SBS symptoms and a combination of atopy and elevated FeNO seems to be a strong risk factor for SBS symptoms. Office-related symptoms were associated with high office room temperature and low RH. Der f 1 allergen in dust can be an important risk factor in the office environment in tropical areas. It is recommended to have a thermostat in the air-conditioning system to control room temperature. It is also important to do frequent house cleaning to reduce HDM allergens in the tropical office environment.

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