RELATIONSHIPS BETWEEN RESPIRATORY SYMPTOMS, AIRWAY INFLAMMATION, SICK BUILDING SYNDROME AND ALLERGIES WITH INDOOR OFFICE ENVIRONMENT AMONG WORKERS IN A MALAYSIAN UNIVERSITY

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By

LIM FANG LEE

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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Chair : Professor Zailina Hashim, PhD
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Introduction: Office workers are important workforce in this modern society. However, there are only few office studies on respiratory symptoms and sick building syndrome (SBS) including clinical measurements for atopy and airway inflammation. **Objective:** The objective is to study the associations between indoor office environment, allergies, respiratory symptoms and SBS among office workers. **Methodology:** A cross sectional study was conducted among 695 office workers from 40 offices in a public university in Klang Valley. Health data were collected using a questionnaire (n=695), skin prick test (SPT) (n=463) and airway inflammation measurement [fractional of exhaled nitric oxide (FeNO) as biomarker] (n=460). Settled dust from the offices was vacuumed and analyzed for endotoxin, (1,3)-β-glucan and house dust mite (HDM) allergens namely *Dermatophagoides pteronyssinus* (Der p 1) and *Dermatophagoides farinae* (Der f 1). Indoor office temperature, relative air humidity (RH), carbon monoxide (CO) and carbon dioxide (CO_2) were measured using direct reading instruments. Associations were studied using two-level linear mixed model, two-level multiple logistic regression, stratified analysis and adjustment for personal and home environment factors using Statistical Package for the Social Sciences (SPSS) and STATA statistical package. **Result:** The prevalence of *D. pteronyssinus*, *D. farinae* and cat allergy among office workers were 50.3%, 49.0% and 25.5% respectively. A total of 9.6% had doctor-diagnosed asthma and 53.0% had current rhinitis. For SBS symptoms, 11.9% had weekly dermal symptoms, 16.0% had weekly mucosal symptoms and 23.0% had weekly general symptoms. One-fourth (25.5%) of the office workers had elevated FeNO levels (>25 ppb). Respiratory symptoms were associated with atopy (allergy to HDM or cat) ($p<0.05$) and elevated FeNO levels ($p<0.05$). Male gender ($p<0.001$), currently smoking ($p=0.037$), height ($p<0.001$) and atopy ($p<0.001$) were associated with FeNO levels. In particular, individuals with combination of atopy and elevated FeNO levels were associated with respiratory symptoms ($p<0.050$) and SBS symptoms [dermal ($p=0.002$), mucosal ($p<0.001$) and general symptoms ($p=0.05$)]. After adjusting for personal and home environment factors using two-level multiple logistic regressions, endotoxin level in office dust ($p<0.05$) and RH

(p=0.010) were associated with respiratory symptoms whereas (1,3)-β-glucan level in office dust (p=0.044), room temperature (p=0.016) and CO_2 (p=0.036) were inversely associated with respiratory symptoms. The amount of sieved dust in the offices was associated with FeNO among atopic subjects (p=0.009). Der f 1 level in dust was associated with SBS (p<0.05) symptoms, especially among those with allergy to *D. farinae* (p<0.010). Office-related symptoms were associated with Der f 1 levels in office dust (p=0.02), low relative air humidity (p=0.04) and high office temperature (p=0.05). **Conclusion:** HDM and cat allergies can be risk factors for respiratory symptoms and elevated FeNO levels. A combination of allergy to cat or HDM and high FeNO can be a risk factor for respiratory and 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. Endotoxin levels in settled dust and low room temperature could be the risk factors for rhinitis among workers who worked in mechanical ventilated air-conditioning offices in a tropical country.

Keywords: Respiratory symptoms; Allergy; Sick building syndrome; Fractional exhaled nitric oxide; House dust mites; Endotoxin; Office; Tropical country

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PERHUBUNGAN ANTARA SIMPTOM PERNAFASAN, KERADANGAN SALUR PERNAFASAN, SINDROM BANGUNAN SAKIT DAN ALAHAN DENGAN PERSEKITARAN DALAMAN PEJABAT DI KALANGAN PEKERJA DI SEBUAH UNIVERSITI MALAYSIA

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Pengenalan: Baru-baru ini, beberapa bangunan di Malaysia terpaksa ditutup untuk pengubahsuaian disebabkan masalah kualiti udara dalaman (IAQ). Walau bagaimanapun, terdapat kekurangan kajian IAQ di kalangan pekerja pejabat yang mengkaji tentang simptom pernafasan dan sindrom bangunan sakit (SBS) yang melibatkan pengukuran klinikal untuk atopi dan keradangan salur pernafasan. **Objektif:** Objektif kajian ini adalah untuk mengkaji hubungan antara persekitaran dalaman pejabat, simpton pernafasan, keradangan salur pernafasan, SBS dan alahan di kalangan pekerja pejabat. **Methodologi:** Satu kajian keratan rentas dijalankan di kalangan 695 pekerja pejabat daripada 40 pejabat di sebuah universiti awam, Lembah Klang. Data kesihatan dikumpul dengan mengguna kajian soal selidik (n=695), ujian cucuk kulit (SPT) (n=463) dan pengukuran keradangan salur pernafasan [menggunakan pecahan oksida nitrik dalam hembusan (FeNO) sebagai penanda-bio] (n=460). Debu mendapan dalam pejabat divakum dan dianalisis untuk endotoksin, (1-3)-β-glucan dan alergen hama rumah (HDM) bernama *Dermatophagoides pteronyssinus* (Der p 1) dan *Dermatophagoides farinae* (Der f 1). Suhu dalam pejabat, kelembapan udara relatif (RH), kepekatan karbon monoksida (CO) dan karbon dioksida (CO_2) diukur dengan mengguna peralatan bacaan terus. Perhubungan telah dikaji dengan menggunakan pakej statistik untuk sains sosial (SPSS) dan pakej statistik STATA untuk dua peringkat linear model campuran, dua peringkat regresi logistik pelbagai dan analisis berstata, dengan menyelaras untuk faktor individu dan persekitaran rumah. **Keputusan:** Kelaziman alahan untuk *D. pteronyssinus*, *D. farina*e dan kucing di kalangan pekerja pejabat adalah 50.3%, 49.0% dan 25.5% masing-masing. Sebanyak 9.6% ada asma yang dikenal pasti oleh doktor dan 53.0% ada rhinitis semasa. Untuk simptom SBS mingguan, 11.9% ada simptom kulit, 16.0% ada simptom mukosa dan 23.0% ada simptom umum. Satu per empat (25.5%) daripada pekerja pejabat menpunyai aras FeNO yang tinggi (≥25 ppb). Simptom pernafasan mempunyai hubungan dengan atopi (alergi kepada HDM atau kucing) ($p<0.05$) dan aras FeNO yang tinggi ($p<0.05$). Jantina lelaki ($p<0.001$), merokok semasa ($p=0.037$), ketinggian ($p<0.001$) dan

atopi ($p<0.001$) mempunyai hubungan dengan aras FeNO. Khususnya, individu yang mempunyai kombinasi atopi dan aras FeNO yang tinggi mempunyai hubungan dengan simptom pernafasan ($p<0.050$) dan simptom SBS. Aras endotoksin dalam debu pejabat dan RH ($p=0.010$) mempunyai hubungan dengan simptom pernafasan manakala aras (1,3)-β-glucan dalam debu pejabat ($p=0.044$), suhu bilik ($p=0.016$) dan CO_2 ($p=0.036$) adalah berhubungan songsang dengan simptom pernafasan. Jumlah debu pejabat yang disaring mempunyai hubungan dengan FeNO di kalangan responden yang atopi ($p=0.009$). Aras Der f 1 dalam debu mempunyai hubungan dengan simptom SBS ($p<0.05$). Simptom yang berkait dengan pejabat didapati mempunyai hubungan dengan aras Der f 1 dalam debu pejabat ($p=0.02$), RH yang rendah ($p=0.040$) dan suhu pejabat yang tinggi ($p=0.050$). **Kesimpulan:** Alergi HDM dan kucing boleh jadi faktor risiko kepada simptom pernafasan dan aras FeNO yang tinggi. Kombinasi alergi kucing atau HDM dan aras FeNO yang tinggi, boleh jadi faktor risiko kepada simptom pernafasan dan simptom SBS. Alergen Der f 1 dalam debu pejabat boleh jadi faktor risiko kepada SBS di pejabat, khususnya di kalangan mereka yang alergi alergen Der f 1. Endotoksin dalam debu pejabat dan suhu bilik yang rendah boleh jadi faktor risiko kepada rinitis di kalangan pekerja yang berkerja dalam pejabat yang berhawa dingin di sebuah negara tropika.

Kata kunci: Simptom pernafasan; Alergi; Sindrom bangunan sakit; Hembusan pecahan oksida nitrik; Hama rumah; Endotoksin; Pejabat; Negara tropika

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

ATS	American Thoracic Society
AEHP	Associated environmental health problems
BMI	Body mass index
BASE	Building Assessment and Survey Evaluation
BRI	Building related illness
CO_2	Carbon dioxide
CO	Carbon monoxide
DOSH	Department of Occupational Safety and Health
Der f	*Dermatophagoides farinae* allergen
Der p	*Dermatophagoides pteronyssinus* allergen
D. farinae	*Dermatophagoides farinae* species
D. pteronyssinus	*Dermatophagoides pteronyssinus* species
DMSO	Dimethyl sulfoxide
eNOS or NOS III	Endothelial NOS
ELISA	Enzyme linked immune sorbant assay
EOS	Eosinophil counts
ECP	Eosinophilic cationic protein
ECRHS	European Community Respiratory Health Survey
FeNO	Fractional exhaled nitric oxide
GINA	Global Initiative for Asthma
GM	Geometric mean
GSD	Geometric standard deviation
HVAC	Heating and ventilated air conditioning
HEPA	High efficiency particulate arrestance
HCRP	High resolution C reactive protein
HEP	Histamine equivalent prick
HDM	House dust mite
IgE	Immunoglobulin E
IAQ	Indoor air quality
iNOS or NOS III	inducible nitric oxide synthase
ICOPIAQ	Industrial code of practice on indoor air quality
IFN-γ	Interferon γ
IL	Interleukin
ISAAC	International Study of Asthma and Allergies in Childhood
LAL	Limulus ameobocyte lysate

LRW	Limulus reagent water
LPS	Lipopolysaccharide
MAB	Monoclonal antibody
MVAC	Mechanical ventilated air conditioning
MVOC	Microbial volatile organic compounds
MW	Molecular weight
MPO	Myeloperoxide
NHMS	National Health and Morbidity Survey
nNOS or NOS I	Neuronal NOS
NO	Nitric oxide
NOS	Nitric oxide synthase
PM10	Particulate matter 10
PM2.5	Particulate matter 2.5
PAMPs	Pathogen associated molecular patterns
PBS-T	Phosphate-buffer saline with Tween
RH	Relative air humidity
SBS	Sick building syndrome
SPT	Skin prick test
NaOH	Sodium hydroxide
SPSS	Statistical Package for the Social Sciences
TH2	T-helper cell type 2
TH1	T-helper cell type 1
TLR	Toll-like receptor
TVOC	Total volatile organic compounds
UFP	Ultrafine particles
US	United States
UPM	Universiti Putra Malaysia
VOC	Volatile organic compound
WHR	Waist hip ratio
WHO	World Health Organization
8-OHdG	8-hydroxydeoxyguanosine

CHAPTER 1

INTRODUCTION

Indoor air quality (IAQ) is recognized as an important public health problem in developed and developing countries at home, schools, institutions or offices. According to World Health Organization (WHO) (2009), energy conservation measures that are not properly implemented; urbanization; climate change; globalization; quality of building materials and components; construction concepts and techniques have contributed to conditions associated with increased exposure to dampness and mould (WHO, 2009). Indoor air quality may be a public health issue since the health of people who live or work in these environments is affected (Mitchell et al., 2007).

Most of the office buildings nowadays are equipped with mechanical ventilated air conditioning (MVAC) systems to provide good indoor air quality (IAQ) through control of air temperature, humidity, ventilation rate, and particulate concentration (Wong, Mui, Hui, Chan & Law., 2008). There are more than 240 million air-conditioning devices installed worldwide (Santamouris & Wouters, 2006). Malaysia is a tropical country with hot and humid climate which favours the development of office buildings with mechanical air-conditioning systems. Airtight buildings' enveloped system affects buildings' energy use and transports contaminants between indoor and outdoor air. It is almost always desirable to increase air tightness from an energy standpoint alone, however it will result in indoor air quality problem if the outdoor air flow rate is too low (Santamouris & Wouters, 2006).

Building occupants might experience a variety of health symptoms due to improper maintenance of MVAC system, inadequate housekeeping and fault building design. Sick building syndrome (SBS) is a term to describe a range of common symptoms that can be associated with the indoor environment in a particular building. The symptoms of SBS can be divided into mucous membrane symptoms related to eyes, nose and throat; dry skin; general symptoms of headache and lethargy (Crook & Burton, 2010; Burge, 2004). The mucosal symptoms are such as eye irritation, swollen eyelids, irritating cough, throat dryness, sore throat, and nasal obstruction (Zhang et al., 2012).

Different studies on SBS among office workers have been conducted since 1980s in different countries. Work-related mucosal symptoms and general symptoms were found significantly associated with gender, job category and work activities of the office workers such as working with video display terminals, handling with carbonless paper and photocopying (Skov, Valbjørn & DISG, 1987). Other risk factors of SBS reported in large IAQ studies include personal factors such as atopy and photosensitive skin (Stenberg, Eriksson, Höög, Sundell & Wall, 1994), psychosocial factors (Azuma, Ikeda, Kagi, Yanagi & Osawa, 2014; Stenberg et al., 1994), indoor physical environment (Apte, Fisk

& Daisey, 2000), indoor chemical pollutants (Bluyssen et al., 2016), indoor microbes (Reynolds et al., 2001) and heating, ventilating, and air-conditioning (HVAC) characteristics such as poor maintenance of HVAC system (Mendell, Lei-Gomez, Mirer, Seppänen & Brunner, 2008).

On the other hand, building related illness (BRI) are well defined diseases that can be caused by indoor factors. Symptoms of BRI include respiratory, immunologic, and neurologic symptoms that are associated with water damaged buildings (Rea et al., 2003; Wolff, 2011) and indoor toxic molds exposure (Pestka, Yike, Dearborn, Ward, & Harkema, 2008). Humidifier fever and legionnaire's disease are examples of infectious diseases which are related to BRI (Crook & Burton, 2010; Gül, Issever, Ayraz & Güngör, 2007). Previous study reported that building related illness was highly correlated with levels of exposure to toxic mold (Rea et al., 2003). Recent researches have shown that dampness and mold exposure can cause respiratory symptoms and respiratory infection such as asthma, allergic rhinitis, allergic bronchopulmonary aspergillosis, sinusitis and hypersensitivity pnuemonitis (WHO, 2009; Bush, Portnoy, Saxon, Terr, & Wood, 2006; Institute of Medicine, 2004).

1.1 Problem Statement

Indoor air quality issues such as inadequate ventilation, high levels of total volatile organic compounds (TVOC), carbon dioxide, microorganism and humidity are the major causes which lead to IAQ issues in 77% of the non-industrial workplace in Malaysia (Deros, Ismail, Khamis, Yusof, & Ismail, 2012; Ismail, Deros, & Leman, 2010; Zamani, Jalaludin, & Shaharom, 2013). In years 2004 to 2008, there were at least six hospitals in Malaysia which faced temporary closure due to problematic hospital projects or severe IAQ issues (Tay, 2011).

Hospital Sultan Ismail in Johor had to be closed temporarily after two months of opening in year 2004 due to extensive visible fungus infestion throughout the entire ten storeys hospital (Kumar, Satish, & White, 2006). The widespread fungus growth was believed to occur due to faulty air-conditioning ducts and leaking pipes in the hospital (Edwards, 2008). Besides fungus growth, overflowing faeces from toilet, leaking sewage pipes, and leaking of sterilization network in operating theatres were other problems that caused Ampang Hospital, Sultan Abdul Halim Hospital in Kedah, and Hospital Universiti Kebangsaan Malaysia forced to be closed temporarily for renovation (Edwards, 2008). Other than hospitals, Public Service Department office in Cyberjaya was also reported to be infested by fungus in September 2011 ("Fungus attacks," 2011). A series of indoor environmental quality (IEQ) problems due to quality issues in building design, construction, and maintenance caused Malaysian Public Work Department to initiate and publish a guidance document to reduce IEQ issues in year 2013*, Guideline on IEQ for Government Office Builings* (Public Work Department of Malaysia, 2013).

Microbial contamination can occur due to poor construction quality or building management. Poor maintenance of humidification system and less frequent cleaning of cooling coils and drain pans were significantly associated with an increase in upper respiratory symptoms, eye symptoms, fatigue/ difficulty concentrating, headache and skin symptoms (Mendell et al., 2008). Moreover, building factors such as energy-efficient buildings with high indoor temperatures and high humidity can facilitate the growth of bacteria and mold which could increase the risk of exposure to allergen, allergic reactions and symptoms of asthma and allergy (Arshad, 2010).

Endotoxins are part of the outer cell membrane of Gram negative bacteria which are commonly present in the environment and occupation settings. It is commonly used as surrogate microbial load in studies (Simpson & Martinez, 2010). Endotoxins have strong proinflammatory and immune stimulatory properties (Douwes, Pearce, & Heederik, 2002). A large number of occupational epidemiology studies showed that endotoxins exposure increases the likelihood of organic dust toxic syndrome, chronic bronchitis and asthma-like syndrome (Radon, 2006). In contrast to endotoxin, (1,3)-β-glucan is the cell wall components of most fungi (Douglas, 2001). Exposure to (1,3)-β-glucan were found to be associated with airway inflammation and symptoms in observational and experimental studies (Douwes, 2005).

Other than bacteria and fungi, house dust mite (HDM) allergens are dominant indoor allergens that are associated with asthma and other allergic conditions globally (Milián & Díaz, 2004). HDM allergy is the most prevalent type of sensitization among Asian community (Lâm, Ekerljung, Bjerg, Văn Tường, Lundbäck et al., 2014; Li et al., 2009; Daengsuwan et al., 2003; Liam, Loo, Wong, Lim, & Lee, 2002) and it is associated with asthma and/ or respiratory symptoms (Lâm et al., 2014; Li et al., 2009; Liam et al., 2002). HDM allergens interact with airway epithelium and mediate development of airway inflammation, asthma and allergic sensitization (Gandhi, Davidson, Asaduzzaman, Nahirney, & Vliagoftis, 2013).

Asthma and allergic rhinitis can cause psychological stress, reduced activity days and reduced quality of life (Ampon, Williamson, Correll, & Marks., 2005). Significant fatigue and mood changes (Marshall, O'Hara, & Steinberg, 2002), depression and anxiety (Sansone & Sansone, 2011) and impairment of cognitive function (Kremer, den Hartoq, & Jolles, 2002) can affect work performance and subsequently quality of life. Besides quality of life, poor IAQ in offices can also have economic consequences since many days of work can be lost through absenteeism, lack of concentration or employees falling sick. A significant amount of absenteeism is attributed by SBS, BRI and associated environmental health problems (AEHP), which can lead to low work morale and affect the ability to concentrate, produce eye strain and poor productivity (Singh, 2005).

According to Sahakian, Park, and Cox-Ganser (2009) it is estimated that an annual cost of US$1.4 billion for excess respiratory related sick leave among

office workers with workplace dampness. It is estimated that the total cost of asthma due to mortality, cost of medical care, losf of work or school days in U.S. for 2004 is approximately $17 billion dollars a year. Out of this $17 billion dollars, it is estimated that approximately $3.5 billion dollars annual asthma cost is due to exposure to dampness and mold (Mudarri & Fisk, 2007). Respiratory problems and work-related symptoms among office workers can cause sickness absence, loss of work time and decreased health related quality of life which have important public health and economic implications (Cox-Ganser et al., 2005).

1.2 Importance of the Study

A large proportion of the working population does office work in the post-industrial society. There was a focus on building occupants' health effects due to indoor environment issues since 1980's in USA (Repace, 1982; Weschler, 2009) and Europe (Skov et al., 1987) especially for non-specific symptoms including the sick building syndrome (World Health Organization, 1983). Healthy workplace is an important concern as the environmental exposures in the office will influence health, well-being and productivity of the employees (Jaakkola & Jaakkola, 2007). Nevertheless, there is lack of studies studied on associations between indoor office environment with asthma and rhinitis (Akpinar-Elci et al., 2008). Moreover, few epidemiological studies are available from offices in the tropical countries (Li, Hsu, & Lu, 1997; Li, Hsu, & Tai, 1997; Ooi, Goh, Phoon, Foo, & Yap, 1998; Wan & Li, 1999a). Thus, IAQ research among office workers in tropical country is crucial since different climate and environmental exposure might have different effects on human health.

Malaysia is a tropical country with warm and humid environment, which can facilitate microbial growth. However, there is lack of epidemiological studies on exposure to house dust mite allergens, endotoxin and (1,3)-β-glucan in settled dust in office and most of these studies are from temperate climate countries (Akpinar-Elci et al., 2013; Cho, Park, Kreiss, & Cox-Ganser, 2011; Fishwick et al., 2002; Park, Cox-Ganser, Rao, & Kreiss, 2006; Park, Kreiss, & Cox-Ganser, 2012; Teeuw, Vandenbroucke-Grauls, & Verhoef, 1994; Wan & Li, 1999b). We found no previous epidemiological study on associations between house dust mite allergens, endotoxin and (1,3)-β-glucan levels in offices with the prevalence of respiratory symptoms and SBS among office workers in tropical countries.

Besides that, epidemiology studies on respiratory health in tropical countries usually use self-report respiratory symptoms questionnaire and seldom apply clinical methods to assess respiratory health status of the study respondents. Fractional exhaled nitric oxide (FeNO) is a new emerging non-invasive method to measure lower airway inflammation level in recent years. However, there are a few studies on associations between indoor environment exposure in offices and respiratory health using FeNO measurement. We found only one study from United States measuring the FeNO in office workers (Akpinar-Elci et al., 2008) but none from tropical and subtropical countries. In the study, no associations were found between FeNO and doctor-diagnosed asthma or respiratory symptoms.

Respiratory symptoms and SBS could be due to indoor environmental exposures or influenced by personal factors. Earlier studies reported that different personal characteristics such as age, gender, smoking status, people with atopy or chronic respiratory diseases were associated with respiratory symptoms (Antó et al., 2010; Lâm et al., 2014; Sonomjamts et al., 2014) or SBS (Antó et al., 2010; Brasche, Bullinger, Morfeld, Gebhardi, & Bischof, 2001). Besides, exposures to indoor biological contaminants are associated with respiratory diseases such as upper respiratory symptoms, cough, wheeze, asthma and allergy symptoms (Institute of Medicine, 2004; WHO, 2009). Therefore, symptoms due to personal factors or indoor environmental exposures need to be determined first before investigating relationships between environmental exposures with respiratory health in the study subjects.

Building characteristics such as type of floor furnishing, furniture and mechanical ventilation system and occupants' activities such as smoking activity, are factors which can influence indoor environment pollutants' concentration. Building Assessment and Survey Evaluation (BASE) study in US office reported building characteristics were significantly associated with upper respiratory symptoms, eyes symptoms, fatigue or difficulty concentrating, headache and skin symptoms (Mendell et al., 2008). However, there is a lack of indoor air quality research in Asia which relates human respiratory health with office characteristics. The building designs and material used in tropical countries can be different compared to temperate and subtropical countries. Therefore, one of the objectives in this study was to study the associations between office characteristics with respiratory symptoms, FeNO and SBS.

1.3 Study Objectives

1.3.1 General Objective

The general objective of this study was to determine the prevalence of respiratory symptoms, elevated airway inflammation level, sick building syndrome (SBS) and allergies among office workers and determine their relationships with indoor office environmental factors [endotoxin, (1,3)-β-glucan, house dust mites allergens (Der p 1 and Der f 1), temperature, relative air humidity, carbon dioxide and carbon monoxide].

1.3.2 Specific Objectives

The specific objectives were:

i. To determine the prevalence of respiratory symptoms, elevated airway inflammation level, SBS symptoms and allergies among the office workers.
ii. To determine the levels of indoor office environmental parameters (endotoxin, (1,3)-β-glucan, Der p 1, Der f 1, amount of sieved dust, temperature, relative air humidity, carbon monoxide and carbon dioxide) in the office.
iii. To study associations between respiratory symptoms, airway inflammation level and SBS symptoms with allergies among the office workers.
iv. To determine the associations between potential personal risk factors with respiratory symptoms, elevated airway inflammation level and SBS symptoms among the office workers.
v. To study associations between respiratory symptoms, airway inflammation level and SBS among the office workers with indoor office environmental parameters and office characteristics.

1.4 Study Hypothesis

i. There are significant associations between respiratory symptoms, airway inflammation and SBS with allergies among the office workers.
ii. Age, gender, smoking status, allergies, body mass index and height are significantly associated with personal risk factors for respiratory symptoms, elevated airway inflammation level and SBS.
iii. There are significant associations between respiratory symptoms, elevated airway inflammation level and SBS among the office workers with indoor office environmental parameters and office characteristics.

1.5 Definition of Variables

1.5.1 Conceptual Definitions

i. Respiratory Symptoms

Respiratory system is a group of organs and tissues, which includes airways; lungs and blood vessels; muscles and bones, which function together for breathing (American Lung Association, 2016). An example of cronic lung disease is asthma which inflames and narrows the airways (National Heart, Lung, and Blood Institute, 2014). Wheeze, shortness of breath, chest tightness, and cough are typical respiratory symptoms for asthma that vary over time and in intensity (Reddel et al., 2015).

ii. Airway Inflammation

Airway consists of upper airway and lower airway which include nose, sinuses, and lungs (World Allergy Organization, 2016b). Airway inflammation is an interaction of inflammatory cells and multiple mediators with airway epithelial cells which ultimately results in bronchial inflammation, airway hyperresponsiveness, airflow limitation and lead to recurrent episodes of cough,

wheeze, and breathlessness (U.S. Department of Health and Human Services, 2007).

iii. Sick Building Syndrome

Sick building syndrome is a group of symptoms which is experienced by the building occupants when they are in the building and the symptoms will diminish when they leave the building (U.S. Environmetal Protection Agency, 2015).

iv. Allergy

Allergy refer to hypersensitivity reactions which is due to immunological mechanisms, which could be antibody- or cell-mediated allergy. Typical type of antibody-mediated allergy is IgE-mediated allergy which is triggered by IgE isotype. Allergic contact dermatitis is an example of cell-mediated allergy which is mediated by lymphocytes, a type of white blood cell (World Allergy Organization, 2016a).

1.5.2 Operational Definitions

i. Respiratory symptoms

Respiratory symptoms include airway symptoms (wheeze, wheeze with breathlessness, wheeze without a cold, waking with tightness in the chest, daytime attacks of breathlessness, and waking with breathlessness); asthma symptoms (ever asthma, doctor's diagnosed asthma, and attack of asthma), and nasal allergies symptoms (Zhao et al., 2006; European Community Respiratory Health Survey, 1996)

ii. Airway inflammation

Excess levels of nitric oxide (NO) are produced from epithelial cells of the airway if eosinophilic airway inflammation occur (Taylor, Pijnenburg, Smith, & De Jongste, 2006). Thus, fractional exhaled nitric oxide (FeNO) in exhaled breath is a noninvasive biomarker that is used to measure airway inflammation and assess airway disease (Dweik et al., 2011). Low FeNO level (< 25 ppb) indicates no airway inflammation or noneosinophilic whereas intermediate (25 – 50 ppb) and high (> 50 ppb) FeNO level implies eosinophilic airway inflammation but the results need to be interpreted cautiously with reference with clinical context (Dweik et al., 2011).

iii. Sick building syndrome

Sick building syndrome symptoms are dermal, mucous or general symptoms which are experienced by the building occupants everyday or one to four times per week (Zhang et al., 2011). Dermal symptoms refers to rashes on hands or forearms, rashes on the face or neck, eczema, itchiness in the face or on the neck, and itchiness on hands or forearms (Runeson-Broberg & Norbäck, 2013). Mucous symptoms include eye irritation, swollen eye lids, runny nose, nasal obstruction, throat dryness, sore throat, and irritative cough (Runeson-Broberg & Norbäck, 2013). General symptoms include headache, nausea, sensation of catching cold, and feeling tired (Zhang et al., 2011).

iv. Allergies

IgE mediated allergy can be diagnosed using allergy testing such as skin prick test (SPT) and intradermal testing (Australasian Society of Clinical Immunology and Allergy, 2013). In this study, individuals who are allergic or atopic refer to individuals with SPT positive result towards environmental allergens such as house dust mite allergens (*Dermatophagoides pteronyssinnus* and *Dermatophagoides farinae*) and cat allergen (*Felis domesticus*).

1.6 Conceptual Framework

The indoor air quality in a building can be affected by factors such as building characteristics, mechanical ventilated air conditioning (MVAC) system and their condition (Mendell et al., 2008); building occupants and their activities inside the building; besides outdoor environment of the building such as topography and meteorology.

Chemical, physical and biological parameters are the main groups of indoor air quality parameters (Department of Occupational Safety and Health, 2010). These parameters can influence the comfort and health of building occupants through inhalation and direct contact. However, only carbon monoxide (CO), carbon dioxide (CO_2), temperature, relative humidity, endotoxin, (1,3)-β-glucan and HDM are the indoor parameters that were investigated in this study. Indoor air parameters such as carbon dioxide, temperature and dampness in building are related with the concentrations of indoor microbes and allergens (WHO, 2009). These allergens could cause inflammation (Beijer, Thorn, & Rylander, 2002), provoke immune response (Andiappan et al., 2014; Bakolis et al., 2014) in humans and lead to airway inflammation, asthma, respiratory symptoms, and SBS.

Atopic people are prone to have moderate or severe immune response when they are exposed to these allergens. Thus, positive reaction towards skin prick test (SPT) is included in this thesis. Gender (Antó et al., 2010), smoking and chronic respiratory disease (An et al., 2015) are associated with SBS and respiratory health.

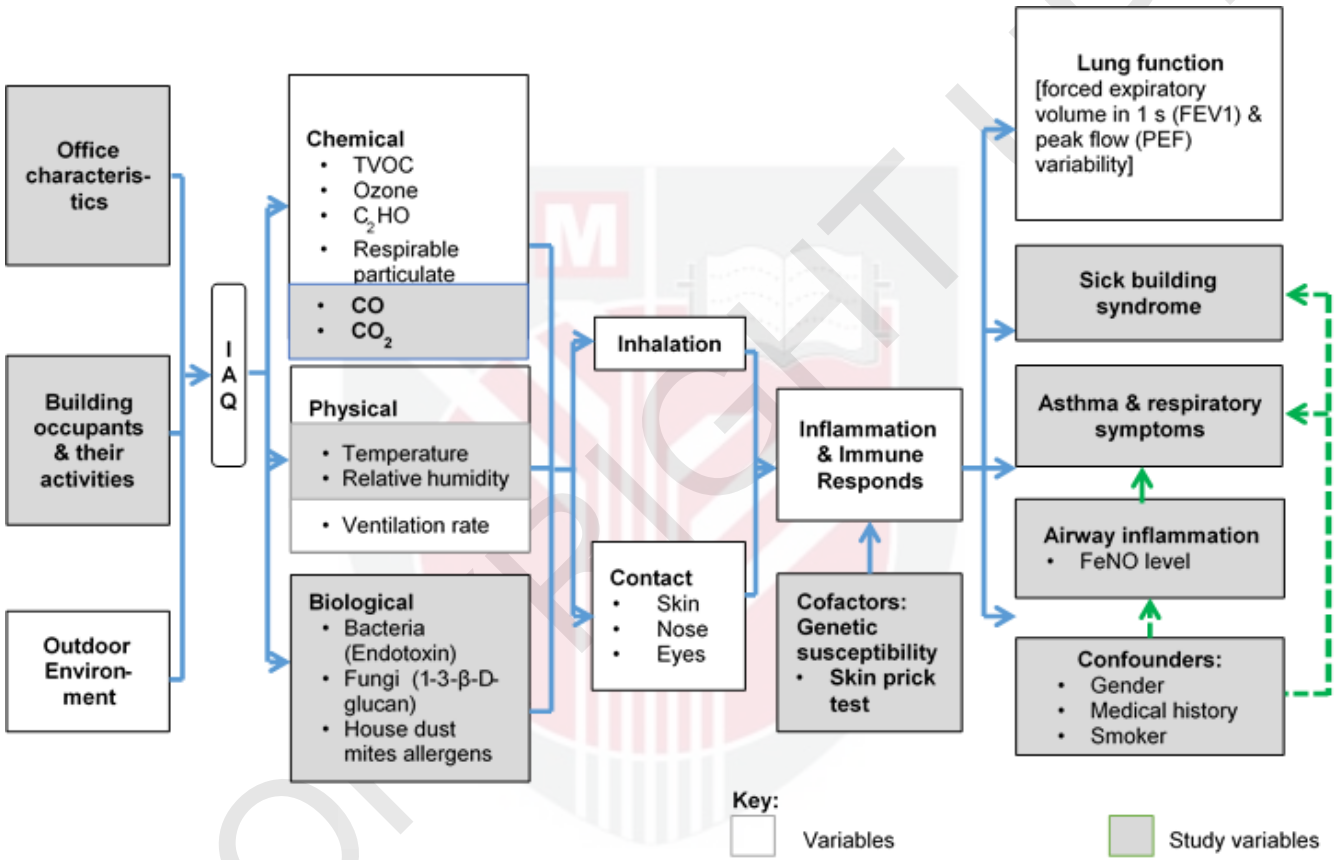

Figure 1.1. Conceptual framework of indoor air quality in offices and its relationships with respiratory symptoms, airway inflammation and SBS among office workers

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Lim, F.L., Zailina, H., Z., Than, L.T.L., Salmiah, M. S., Jamal Hisham, H., Norbäck, D. (2015) Asthma, airway symptoms and rhinitis in office workers in Malaysia: Associations with house dust mite (HDM) allergy, cat allergy and levels of house dust mite allergens in office dust. *PLoS ONE*, *10*(4), e0124905.

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