NATIONAL INSTITUTE OF ENVIRONMENTAL MEDICINE
Unit of Lung and Allergy Research
Karolinska Institutet, Stockholm, Sweden

PREVALENCE AND DETERMINANTS OF ASTHMA, COPD AND ALLERGY TO COMMON AIRBORNE ALLERGENS IN NORTHERN VIETNAM

Hoàng Thị Lâm

Stockholm 2011

To my husband,
and my sons: Kiên and Phú

ABSTRACT

Introduction: While a large amount of data about the epidemiology of asthma, allergy, COPD, chronic bronchitis and respiratory symptoms are available from developed countries, the information about these diseases and conditions in developing countries in south-east Asia are scarce. There are, however, several reports indicating an increase in asthma and allergy parallel to urbanization in developing countries. The proportion of smoking men in south-east Asia including Vietnam is large.

Aim: The aim of this thesis was to assess the prevalence of obstructive airway diseases and symptoms and their relation with demographic data including smoking habits among adults in rural and urban Vietnam. Special interest was paid to asthma, rhinitis, allergic sensitization and COPD.

Methods: The study was conducted in two parts. A random sample of subjects aged 21 -70 years were invited; 3008 subjects living in an inner city area of Hanoi, Hoankiem, and 4000 in a rural area of Bavi in northern Vietnam. An internationally used questionnaire was delivered by field workers to the study subjects. From the questionnaire responders, a randomly selected sample of 750 subjects from each of the two areas was invited to the second part of the study. The second part consisted of clinical examinations including structured interview, dynamic spirometry, skin prick testing (SPT) and bronchial provocation testing with methacholine. The SPT panel included ten common indoor and outdoor allergens. For the structured interview a modified GA^2LEN study questionnaire was used. The spirometry followed the American Thoracic Society guidelines and East Asian reference values were used. COPD was defined by using the fixed ratio of FEV1/FVC < 0.7.

Results: The response rate to the questionnaire was 92% in Bavi and 70% in Hoankiem. Of men in Bavi 67.8% (Hoankiem 49.7%; p < 0.001) were smokers, while of women 4.2% were smokers in Hoankiem (Bavi 1.2%; p < 0.001). The prevalence of ever having had asthma was in Hoankiem 5.6% (Bavi 3.9%; p $= 0.003$) with no major gender difference. The most common symptom was longstanding cough (Hoankiem 18.1%, Bavi 12.0%; p < 0.001) followed by sputum production, while the prevalence of symptoms common in asthma was considerably lower. Respiratory symptoms were slightly more common in men than women. Allergic rhinitis ever or chronic nasal symptoms were reported by 50.2%. The prevalence of allergic rhinitis was considerably higher in the urban area compared to the rural, 29.6% vs. 10.0% (p<0.001). Allergic rhinitis ever and chronic nasal symptoms were both significantly associated with asthma and respiratory symptoms (p<0.001). Exposure to gas, dust or fumes at work was significantly associated with all rhinitis conditions. No major gender differences were found, and smoking was not significantly associated with the nasal conditions.
The participation rate in the clinical part was 46%. The representativeness of the participants was good as no statistical difference in prevalence of symptoms was found between the participants and all responders in the questionnaire survey. Of men 36.9% and of women 31.0% (n.s.) had positive SPT to at least one allergen. The

most common sensitizer was the storage mite, *Blomia tropicalis* (men 27.7%; women 18.7%, p = 0.013). Sensitization to mites and cockroach were common (26.1%; 13.2%), and was strongly associated with allergic rhinitis. Young age, male sex and occupational exposure to gas, dust and fumes were risk factors for allergic sensitization to mites or cockroach. A significant positive association between the number of positive SPT reactions and airway hyper-reactivity was found.

The overall prevalence of COPD was 7.1% (men 10.9%; women 3.9%), and the prevalence increased considerably by age. The distribution of COPD by disease severity was 12.5% severe or very severe COPD (FEV1<50% of predicted), 40% moderate COPD (50≤ FEV1 <80% of pred.) and 47.5% mild COPD (FEV1≥80% of pred.). Among men with COPD all but one was current or ex-smokers, while the women with COPD were all never smokers. Among men, COPD was strongly related to the number of pack-years of tobacco consumption and a half of smokers aged ≥60 years had developed COPD.

Conclusions: The prevalence of asthma in adults may have increased in both urban and rural Vietnam, as the few previous estimates have found 2% of adults having asthma. The majority of men were smokers versus a few percent of women. A half of the studied population had rhinitis conditions with allergic rhinitis being more common in the urban area, however, a disparity in the knowledge about what allergy is may have contributed to this urban-rural difference. The pattern and prevalence of allergic sensitizers conforms to results from other areas with a similar climate. Taking into account the young population of Vietnam, the prevalence of COPD must be considered as high particularly among smoking men. Except increasing age and a previous history of asthma, no other risk factors for COPD among women could be demonstrated.

LIST OF PUBLICATIONS

I. Hoàng Thị Lâm, Eva Rönmark, Nguyễn Văn Tường, Linda Ekerljung, Nguyễn Thị Kim Chúc and Bo Lundbäck
    Increase in asthma and a high prevalence of bronchitis: Results from a population study among adults in urban and rural Vietnam
    Respir Med, 2011 Feb; 105 (2) 177-185

II. Hoàng Thị Lâm, Nguyễn Văn Tường, Linda Ekerljung, Eva Rönmark and Bo Lundbäck
    Allergic rhinitis in northern Vietnam: increased risk of urban living according to a large population survey
    Clin and Transl Allergy, 2011, 1:7. E-pub: 11 August 2011
    (http://www.ctajournal.com/content/1/1/7)

III. Hoàng Thị Lâm, Nguyễn Văn Tường, Bo Lundbäck and Eva Rönmark
    Allergic sensitization to common airborne allergens among adults –
    A population survey in northern Vietnam.
    Submitted for publication

IV. Hoàng Thị Lâm, Linda Ekerljung, Nguyễn Văn Tường, Eva Rönmark, Kjell Larsson and Bo Lundbäck
    Prevalence of COPD by disease severity in men and women in relation to smoking in northern Vietnam
    Submitted for publication

CONTENTS

LIST OF ABBREVIATIONS

AHR	Airway hyper-responsiveness
AR	Allergic rhinitis
ARIA	Allergic rhinitis and its Impact on Asthma
ASEAN	Association of South East Asian Nations
ATS	American Thoracic Society
BHR	Bronchial hyper-reactivity
BTS	British Thoracic Society
CO2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
DEPs	Diesel exhaust particles
EAACI	European Academy of Allergy and Clinical Immunology
ECRHS	European Community Respiratory Health Survey
ERS	European Respiratory Society
FEV1	Forced expired volume in 1 second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for chronic Obstructive Lung Disease
ICU	Intensive care unit
ISAAC	International Study of Asthma and Allergies in Childhood
NO2	Nitrogen dioxide
OLD	Obstructive of lung disease
OLIN	Obstructive Lung disease In Northern of Sweden
	In Swedish: Obstruktiv Lungsjukdom i Norrbotten
PM-10	Particulate matter ≤ 10 µg
SES	Socio economic status
SOB	Shortness of breath
SPT	Skin prick testing
TBC	Tuberculosis
WHO	World Health Organization
n.s.	Not significant
pred.	Predicted value

INTRODUCTION

Asthma, allergic rhinitis (AR) and COPD (Chronic Obstructive Pulmonary Disease) represent significant health problems throughout the world. These diseases cause a significant economic burden on health care systems and the society as a whole, and they all affect quality of life. Approximately 300 million people worldwide currently have asthma, and its prevalence increases by 50% every decade particularly in developing countries parallel to urbanization (GINA, 2010). Allergic disease is the fifth leading chronic disease in the United States among all ages (Ebert & Pillsbury, 2011). By 2020, COPD will be the third leading cause of death and the fifth leading cause of disability adjusted life years in the world (GOLD, 2010). Asthma, rhinitis and COPD are multi-factorial processes and caused by a complex combination of hereditary and environmental factors.

Among the data of respiratory and allergic diseases in the world, the information from Vietnam is rare, and this is true especially for adults in the northern part of the country. With the exception of one abstract from the European Respiratory Society´s annual congress in 2010 (Phan et al., 2010)**,** there are actually no reference to data of adult asthma, rhinitis or COPD from northern Vietnam published in international scientific journals. Data about these diseases based on population studies are lacking also in domestic journals. Thus there was a need of a well-designed population study to obtain clear information of respiratory and allergic diseases among adults in the northern part of Vietnam.

Vietnam is a developing country. From a renovation in 1986, the economy has developed quickly. As a consequence, the quality of life of the population is increasing, but the development has also side effects in terms of increasing air pollution. I myself am a physician working at the Allergy & Clinical Immunology Department, Bachmai Hospital, Hanoi. At the hospital, we have frequent contacts with asthma and COPD patients. Most of them seek for aid from health care only during exacerbations. This creates an impact not only for the health care system but also for social life. When I read the papers of the study about asthma and COPD in northern Sweden, I got an idea of a similar study in Vietnam. Thru the co-operation between Hanoi Medical University and Karolinska Institutet this study could be realised. It has been an interesting journey to face possibilities and difficulties in performing the study using methods in my country that are used in developed countries. Now I am very happy to present the results of my study in this book.

BACKGROUND

Vietnam - socio-economic and environmental aspects

Since 1986, Vietnam has been involved in a renovation process *(đổi mới)* in order to promote socio-economic development and closer integration with the rest of the world. The market forces freed by the renovation process have produced a very strong economic growth in Vietnam during the 1990s. Market principles are now accepted as the basis for remunerating labour, for determining land use and also for determining public-sector accountability. The household economy is thriving, rural production is becoming more diversified and better rewarded, and more and better housing is being produced in the cities. Vietnam has opened its economy to trade and foreign investments and opened its borders to flows of people: tourists, people involved in business, students and scholars. Through trade and diplomacy, Vietnam has become increasingly involved in the region, and has successfully joined the Association of South East Asian Nations (ASEAN).

Figure 1. Air pollution on the streets of Hanoi is partly caused by motorbike fuel

The extremely fast development, growth, and increased energy consumption during the last decades has contributed significantly to improve the living standard of people in Vietnam. However, the development has put considerable pressure on environment, mainly thru air pollution. This pollution is mainly in the form of emissions, dust, water, waste and sewage.

The air in Hanoi contains high levels of benzene, sulphur dioxide and microscopic dust known as PM-10 (Particulate matter $\leq 10\mu g$), which is one of the most dangerous pollutants. Levels of PM-10 of about 80 micrograms per m^3 has been

measured in Hanoi, which is twice as high compared to the current level in Bangkok and well above the guideline of 20 micrograms per m^3 set by the World Health Organization (WHO) (Fuller, 2007). Air pollution can be seen, smelt and felt in Hanoi (figure 1). The abundant dirt comes from mainly from vehicles including motorbikes and cars, visible garbage, drainage systems, untreated sewage and burning of waste, all contribute to poor air quality. Adding to these dangers, high humidity and low awareness of proper sanitation has created favourable conditions for bacteria to bind with dust, which is one way diseases can spread.

Although there have been positive developments regarding the environment, the level of the awareness of environmental protection in the general public and even in some enterprises needs to improve further. Many local authorities and enterprises pay insufficient attention to implement important decisions that have been made in order to improve the environment, but instead they are waiting for support and subsidies from the central government.

Asthma, allergic diseases and COPD

Prevalence trends of asthma, allergic diseases and COPD

The Global Initiative for Asthma (GINA) reports adult asthma prevalence ranging from 5-18% in the world (GINA, 2010). It is estimated that asthma affects as many as 300 million people worldwide, and this is expected to increase to 400 million by 2025 (GINA, 2010). AR is even more common than asthma with estimates of prevalence of 10-20%, and it is expected to affect 500 million people worldwide (Ebert & Pillsbury, 2011). AR is the most common allergic disease at least in the Western part of the world (Bauchau & Durham, 2004).

The increase in prevalence of asthma in developed countries may have levelled off. Two studies performed 10 and 18 years apart in Sweden found that the prevalence of asthma had probably not increased, while the prevalence of most respiratory symptoms had decreased (Ekerljung et al., 2010a; Lotvall et al., 2009). In England, the incidence rate of asthma has decreased particularly in children below the age of five years, and a decrease in the lifetime prevalence of asthma was also noticed (Simpson & Sheikh, 2010). In Denmark, the prevalence of asthma and bronchial hyperactivity among schoolchildren did not change over a ten year period (Zilmer et al., 2011).

In contrast to particularly Australia and some European countries, the prevalence of asthma and allergic diseases seems to be increasing in several developing countries (Asher et al., 2006). In order to determine the time trends of childhood asthma in Taiwan, data from two nationwide ISAAC (International Study of Asthma and Allergies in Childhood) surveys were compared. The results showed a general tendency towards an increase in lifetime prevalence of physician-diagnosed asthma and asthma symptoms and the increase was more marked among girls than boys (Lee et al., 2007). Another study conducted in Morocco

using the ISAAC questionnaire also found an increase of allergic symptoms over a five-year period (Bouayad et al., 2006).

In Vietnam, the prevalence of asthma or asthma-like symptoms in the southern part was 2.4% in ages more than five years in 2004 (Sy et al., 2007). In contrast, a study among children and teenagers following the ISAAC protocol in Hanoi, Vietnam, found the prevalence of ever wheeze, ever asthma and ever having had hay fever to be 24.9%, 12.1%, and 7.8%, respectively (Nga et al., 2003).

The increase in asthma prevalence has raised concerns for the heavy burden of the disease on patients and society. Increased urbanisation in the developing world may contribute to these trends as a higher prevalence of allergic diseases has been observed in urban compared to rural environments (Platts-Mills et al., 2005). The 'hygiene hypothesis' or the 'microbial exposure hypothesis' can be used to explain the disparities of the prevalence of allergic diseases between developed and developing countries. The hypothesis proposes that a cause of the recent rapid rise in atopic disorders could be a consequence of a lower incidence of early childhood infections. A consensus is probably under development around the view that more fundamental changes in lifestyle have led to decreased exposure to certain microbial or other species, such as helminthic, that are important for the development of immune-regulatory mechanisms (Bloomfield et al., 2006). Factors that may contribute to the diversity include lifestyle changes, climate changes, increasing indoor and outdoor air pollution (GINA, 2010).

COPD is a common disabling disease. The prevalence and mortality of COPD are increasing and COPD has become a serious public health problem worldwide (GOLD, 2010). Unfortunately, although COPD is preventable, it is underdiagnosed for many reasons (GOLD, 2010). Prevalence estimates of COPD differ largely depending on the diagnostic instruments used, study design, and the studied populations (GOLD, 2010). In northern Sweden, the prevalence of COPD was estimated at 7.6%, 14.0%, and 14.1% according to British Thoracic Society (BTS), European Respiratory Society (ERS), and Chronic Obstructive Lung Disease (GOLD) criteria, respectively (Lindberg et al., 2005). A study based on information about smoking habits in 12 Asia Pacific countries and regions indicated that the prevalence of COPD in Vietnam, despite a young population, is the highest of the Asia Pacific countries, 6.7% (Tan et al., 2003).

The burden of asthma, allergic rhinitis and COPD

The economic burden of asthma, AR and COPD includes the costs on the health care system as well as the cost on the society. Direct medical costs include costs of health care, such as hospitalisations, doctor's visits and medications. However, the indirect costs such as loose of work days, absence from school, costs attributed to disability and premature death are as important as direct medical costs. Costs per patient vary across countries because these costs depend on how the health care is provided and paid. In USA the total costs for the medical expenditures of asthma have been estimated at 18 billion USD annually (Sullivan et al., 2011). AR alone was responsible for 3.5 million missed days of work in USA and more than $6 billion was spent on prescriptions of medications for AR in 2000 (Stempel & Woolf, 2002). In European Union, the total direct costs of

4

respiratory diseases have been estimated at about 6% of the total health care budget with COPD accounting for 56% (39 billion Euros) of the costs of respiratory diseases (GOLD, 2010). Following a study in Bangkok, Thailand, the Thai had to pay 7 000 – 10 000 Bht per day for care at an Intensive Care Unit (ICU) for COPD (Saenghirunvattana et al., 2001). In addition to direct and indirect costs, respiratory diseases effect quality of life and activities of daily living including work (GOLD, 2010).

AR and asthma are often associated, and the two diseases interact at various levels. Rhinitis often precedes the development of asthma among adults and can contribute to unsatisfactory asthma control (Bousquet et al., 2008). While not life-threatening, AR has a major impact on quality of life, overall health and daily functioning (Seth et al., 2007). Untreated AR has been associated with fatigue, irritability and restlessness. Sleep disturbance is a serious complication of AR and can reduce ability to concentrate and to learning and may contribute to family dysfunction. The importance of treating AR is magnified by the additional potential benefit of improving other associated co-morbidities (Bousquet et al., 2008).

Allergic sensitization

Mechanism of allergic sensitization

In normal conditions, exposure to non-infectious protein antigens induces tolerance, which is essential to maintain the normal mucosal homeostasis under exposure to environmental antigens.

Allergic sensitization occurs by a failure in the mechanisms of tolerance, leading to allergic sensitization and development of an inflammatory reaction. Allergic reactions can occur as immediate reactions, late-phase reactions, or as a chronic allergic inflammation. Immediate or acute-phase reactions occur within seconds to minutes after allergen exposure (Curotto de Lafaille et al., 2010), so called type I hypersensitivity. The allergic reaction requires first sensitization to a specific allergen, it occurs mostly in genetically predisposed individuals, and the reaction is mediated by IgE antibodies. This class of antibodies binds with a high affinity to Fc-receptors on the surface of the tissue of mast cells and blood basophils. Mast cells and basophils that are coated with IgE are said to be sensitized. Re-exposure to the antigen can then create a cross-linking with these IgE antibodies resulting in release and formation of chemical mediators from the sensitized cells (figure 2).

Allergens and skin prick testing

An allergen is another word for an antigen that causes an allergic reaction. The most important allergens for respiratory diseases are those that are inhaled. Common inhaled allergens include animal dander (skin, saliva), dust mites, cockroach particles, moulds, and pollen. The pattern of different allergens on allergic sensitization and morbidity varies between countries. In so called

developed countries, the most common allergens include animal dander like cat and dog, and pollens (Pallasaho et al., 2006; E. Ronmark et al., 2009a). A recent nationwide survey reported that 55% of the people in the United States were tested positive to an allergic response to one or more allergens (AAAAI, 2009). In Sweden, the prevalence of any positive SPT response was highest, 55%, in subjects aged 20 to 29 years and low, 26%, in subjects aged 50 to 60 years (Warm et al., 2011). In contrast, in developing countries, house dust mite, storage mite and cockroach are often the main sensitizers (Baratawidjaja et al., 1999; Puccio et al., 2004). The most common known sensitizers in Vietnam are mites and cockroach (Sy et al., 2007), results similar to results from other studies in south east Asia (Chew et al., 1999; Prasarnphanich & Sindhurat, 2005). Asthma and AR are known to be associated with atopy documented with measures of serum IgE or by skin prick testing (E. Ronmark et al., 2009a).
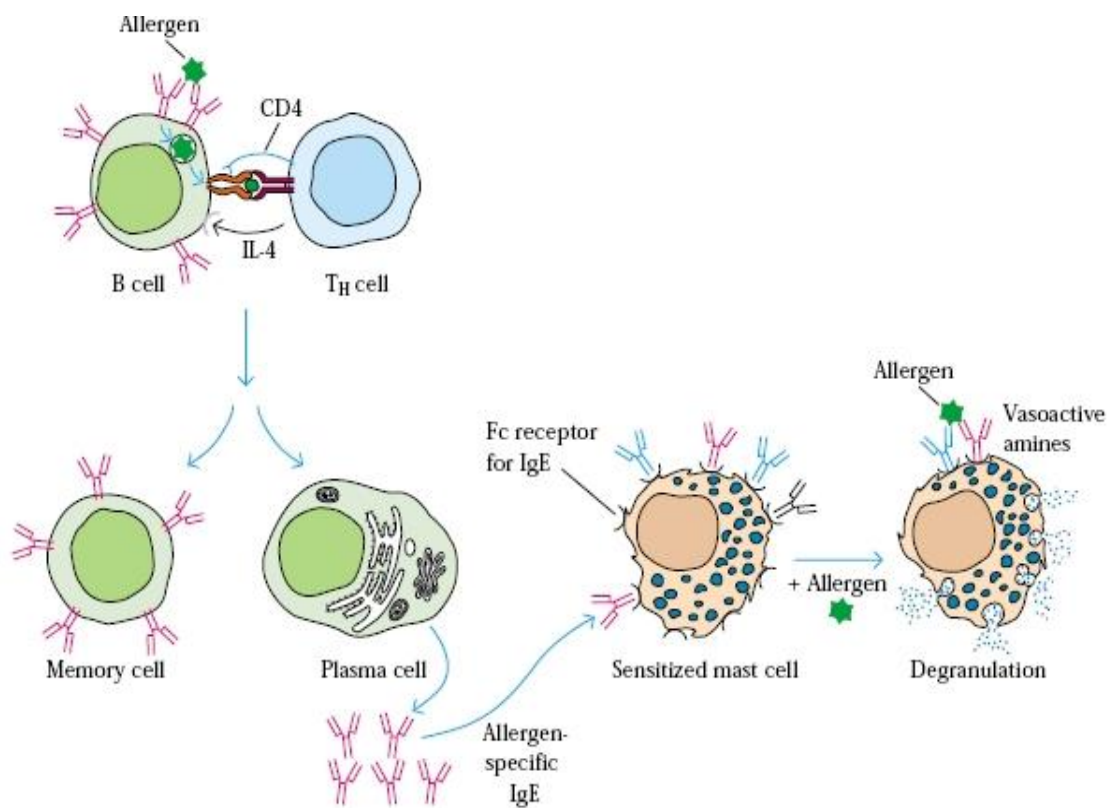
Figure 2. Type I hypersensitivity (W. Zhang, 2007)

For assessing the presence of allergen-specific IgE antibodies, skin prick testing is preferred over blood allergy tests because generally it is more sensitive, simpler to use, less expensive, and was at least previously regarded as more specific (Dreborg et al., 1989). Some patients may believe they have determined their own allergic sensitization by observation, but a skin test has been shown to be better than patient observation to detect allergy.

Skin prick testing may not be an option if the subject has a widespread skin disease or has taken antihistamines less than 72 hours before a planned testing. If

a patient has had a serious life threatening anaphylactic reaction, some allergologists prefer an initial blood test prior to performing a skin prick test.

Airway hyper responsiveness

Airway hyper responsiveness, AHR (or bronchial hyper-reactivity, BHR) refers to a condition in which the airways react with an exaggerated broncho-constriction response to stimuli (Hargreave, et al., 1986).
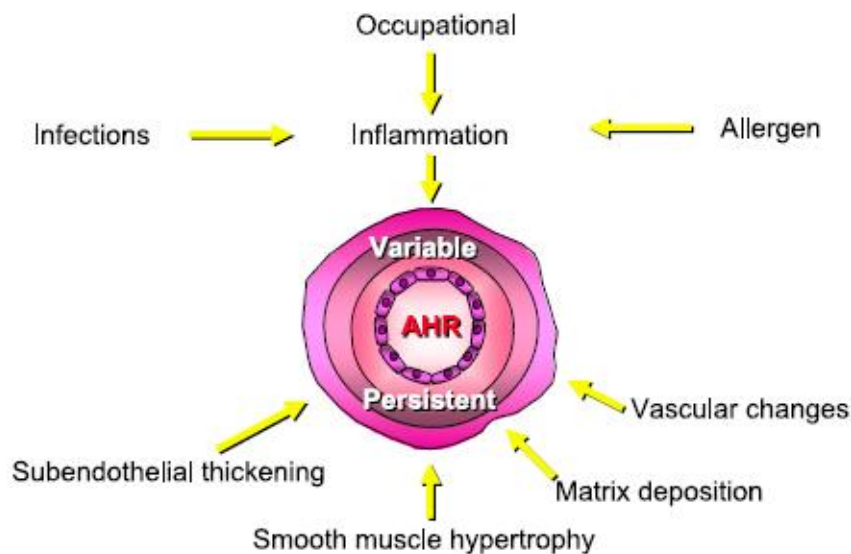

Figure 3. Factors affecting the variable and persistent components of AHR (Busse, 2010)

The airways of asthmatics respond with a greater constriction to a certain stimulus than the airways of healthy subjects. It is a characteristic feature of asthma and can be demonstrated in almost all patients with a clinically relevant asthma (Busse, 2010). Further, AHR occurs often prior to the development of the symptomatic diseases. However, there is a considerable variability in the intensity of AHR in patients with asthma, and the level of AHR varies also within individuals with asthma. In addition, inter-current provokers, such as viral-induced exacerbations, allergen exposure, and occupational exposures, can temporarily enhance the underlying AHR in individual patients (figure 3). Furthermore, treatment of asthma not only can improve airflow limitation and reduce symptoms but can also considerably modify the underlying AHR (Brannan, 2010). Whether AHR is a factor of importance for the development of COPD is under debate.

There are several methods used to measure AHR. Methacholine test is a direct test that has high a sensitivity, is cheap and is easy to perform (Cockcroft, 2010). The prevalence of AHR in different populations may vary considerably and is probably to a great extend a result of different methods of measure and different

definitions of AHR. An epidemiological study in Finland found the prevalence of AHR to be about 20% using both methacholine and histamine (Juusela et al., 2008). In Sweden, when using another method, the prevalence of AHR was 11% in men and 15% in women (Norrman et al., 1998). Following a nationwide cross sectional survey among adults aged 20 to 44 years in Thailand, the prevalence of AHR was only 3% (Dejsomritrutai et al., 2006). The prevalence of AHR in students aged 11-17 years in Guangzhou, China was estimated at 4% (N. S. Zhong et al., 1990).

Major risk factors for asthma, allergic diseases and COPD

In this chapter, mainly genetic factors, air pollution including occupational and other environmental exposures, tobacco smoke, and socio-economic status will be discussed. Other factors that influence the risk of asthma, allergic diseases and COPD, such as infections, diet, life style factors will not be discussed in more detail.

Genetic factors

Asthma and AR are results of the complex interaction between genes and environment. The strongest risk factor for the development of asthma and AR is a family history of asthma or atopy among primary relatives (Bjerg et al., 2007). If one parent is allergic the risk of allergy in the offspring is 50%, and if both parent are allergic this risk increases to 75% (Franzese & Burkhalter, 2010). If one parent has asthma, the risk for the child to develop asthma is three folds higher compared to children without parental asthma, while this risk is ten times higher if both parents have asthma (Bjerg et al., 2007). Family and twin studies strongly indicate that genetics play an importance role in the development of asthma and allergy (van Beijsterveldt & Boomsma, 2007). The risks of developing hay fever, eczema and specific IgE are higher for monozygotic than for dizygotic twins (Strachan et al., 2001), and genetic factors play an important role in the development of these diseases. There are consistently replicated regions on the long arms of chromosomes 2, 5, 6, 12 and 13, and more than 100 gens are associated with allergy or asthma in different populations (Ober & Hoffjan, 2006). Genetic studies of intermediate phenotypes may facilitate the discovery of susceptibility genes for asthma or allergic diseases, or they may only identify genes that influence normal variation in the trait itself (Ober & Yao, 2011).

The best known genetic factor linked to COPD is a deficiency of the serine protease α1-antitrypsin, which varies in 1−3% of patients with COPD (Stoller & Aboussouan, 2005). Alpha-1 antitrypsin is a naturally occurring enzyme that protects the lungs from damage. Having low concentrations of this enzyme, particularly in combination with smoking or other exposures, increases the risk of particularly panlobular emphysema (GOLD, 2010). Smoking has been clearly identified as the primary cause for COPD, and up to 50% of smokers develop COPD sooner or later (Lundback et al., 2003; Vozoris & Stanbrook, 2011). However, not all smokers develop clinically relevant COPD, which suggest that genetic factors may modify each individual's risk (GOLD, 2010).

Air pollution

Importance pollutants that have contributed to the increase in allergic diseases, particularly asthma, include ozone, nitrogen dioxide (NO_2) and diesel exhaust particles (DEPs) (Parnia et al., 2002). Ozone causes increasing permeability of the airways to proteins allowing allergenic particles and proteins to penetrate deeper into the mucosa of the airways, and either increase or alter the immune response to the allergens (Kelly & Fussell, 2011). NO_2 may act by decreasing the threshold of sensitization to allergen exposure as well as by increasing the likelihood of respiratory virus infections in the airway, and may thus cause lower airway symptoms (Kelly & Fussell, 2011). DEPs may act as a carriers for the transport of allergens into the airways by adsorbing allergenic proteins onto their surface (Knox et al., 1997), and thus act as an adjuvants in promoting the switching of B-cells to produce allergen-specific IgE (Takenaka et al., 1995) and affect a number of downstream immunological mechanisms leading to increased prevalence or increased severity of allergic and asthmatic disorders (Terada et al., 1999).

Figure 4. The common way of cooking in rural area in northern Vietnam

Many studies have shown a substantial association between elevated levels of particular pollutants and an increase in allergic conditions (H. Kim & Bernstein, 2009; Lindgren et al., 2009). Exposure from air pollutants inside the homes, particularly in developing countries, is a risk factor for asthma, allergic diseases, and COPD due to exposure from smoke when cooking or from heating when using open fires in poorly ventilated houses. This risk is of importance especially in women (Idolor et al., 2011).

The most important risk factor for development of COPD among non-smokers in developing countries might be exposure to biomass fuels, such as coal, straw, animal dung, crop residues, and wood, which are used for heating and cooking in poorly ventilated homes (figure 4) (GOLD, 2010). In China, the prevalence of COPD in non-smoking women was three times higher in rural areas, where almost all households used biomass fuel for cooking and heating, compared to urban areas where this way of cooking and heating of houses was common (S. Liu et al.,

2007). Globally, WHO estimates that in low and middle level income countries, 35% of subjects with COPD have developed COPD after exposure to indoor smoke from biomass fuels. Furthermore, WHO suggests that 36% of mortality from lower respiratory disease is also related to indoor smoke exposure (Mannino & Buist, 2007). A report from the Philippines showed the prevalence of COPD was three to four times higher in subjects who had used firewood for cooking for more than 60 years (Idolor et al., 2011).

According to several studies among both adults and children, including two studies in Sweden, living close to high traffic flows increased the asthma incidence in adults (Lindgren et al., 2009). As referred previously, several studies have shown that diesel exhaust particles can induce the development of the allergic immune response and enhance allergic inflammation (Polosa et al., 2002). Certain gaseous components of the atmosphere which contribute to keep the Earth warm are called greenhouse gases. Anthropogenic emissions of greenhouse gases, which include carbon dioxide and methane, contribute to this process. The effects of these changes vary by region with implications for many ecosystems as well as for human health. Many studies have indicated that the pollen season, typically indicated by regionally specific tree pollens, is longer and the annual pollen production is increasing (Sheffield et al., 2011).

Exposure to air pollution at work place is significantly associated with allergic diseases and COPD (Hedlund et al., 2008). Asthma is the most common occupational respiratory disorder in most industrialized countries (Hedlund et al., 2008; Kogevinas et al., 2007). These exposures include organic and inorganic dusts, chemical agents, dust and fumes. The most important way of preventing occupational respiratory diseases is elimination or reduction of exposure to occupational exposures including sensitizers.

Tobacco smoke

Cigarette smoking leads to changes in the cells causing swelling and inflammation in the airways and lungs gradually leading to a loss of lung function. These damaging changes cannot be reversed, although quitting smoking reduces inflammation, why quitting smoking in early stages of diseases such as asthma or COPD helps to stay healthier than a continuation of smoking (figure 5) (Fletcher & Peto, 1977).

Exposure to tobacco smoke increases the risk of developing respiratory symptoms such as wheezing, and infants exposed to second hand smoke have up to a four-fold increase in airway hyper-responsiveness to histamine challenge (Nimmagadda & Evans, 1999). In addition, smoking exposure has been shown to increase the number of emergency department visits due to asthma compared to patients not exposed to second hand smoke (Nimmagadda & Evans, 1999). Active smoking during pregnancy will alter the fetal lung development and contribute to the development of asthma in children. In addition, a consequence of passive smoking is lateness in lung development of the fetus (Karmaus et al., 2008).
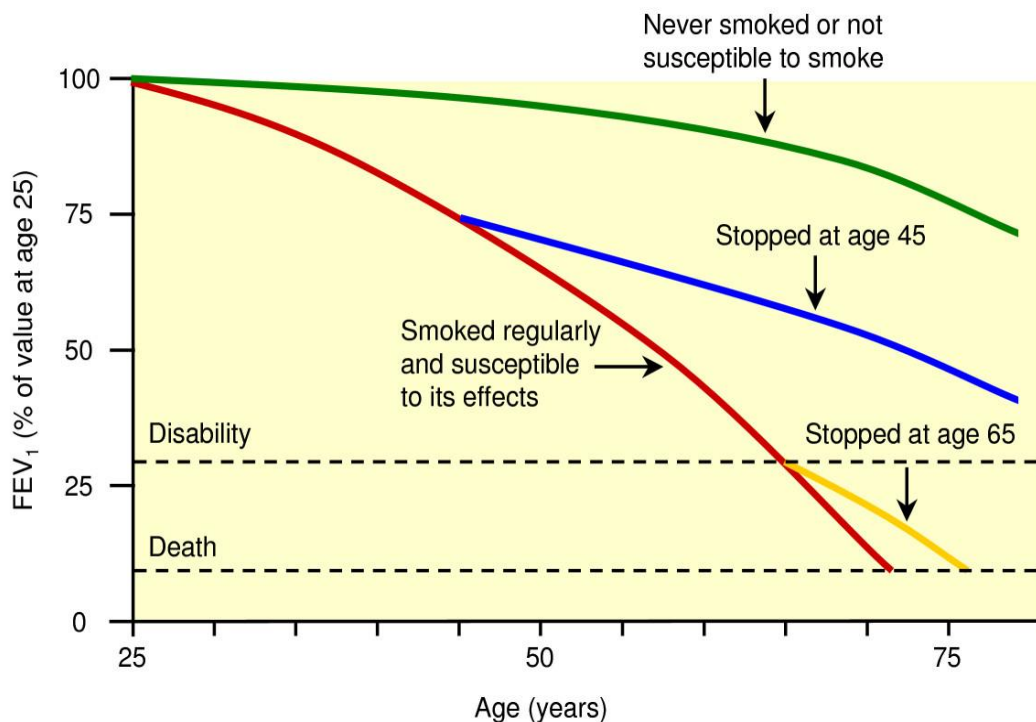
Figure 5. Lung function by age and smoking habits (Fletcher & Peto, 1977)

Whereas in the early 1960s, one out of two adults smoked in the Western world, today fewer than one out of five adults are daily smokers in most industrialised countries (WHO, 2009). Every minute, more than 12 million cigarettes are being smoked throughout the world (WHO, 2009). The tobacco epidemic has moved from the West to the East. In 2010, 28% of adults in China, 53% of men and 2% of women, were estimated to be current smokers (Li et al., 2011). Following a study conducted in the two biggest cities of Vietnam and other cities in several countries, Vietnamese men had the highest smoking prevalence (Jenkins et al., 1997).

Gender and age distribution of asthma, COPD and allergic diseases

Among children, the prevalence of asthma in boys is higher than in girls (Bjerg et al., 2007). In contrast to children, women are more likely to have asthma and other allergic diseases than men (Kynyk et al., 2011), however, there are some results that are conflicting. In addition, women had more asthma control problems and lower asthma related quality of live compared with men (Temprano & Mannino, 2009). Furthermore, asthma triggers have also been more frequently found in women (Kynyk et al., 2011). Peri-menopausal and post-menopausal women have an increased prevalence of asthma, allergic rhinitis, and wheeze (Jensen-Jarolim & Untersmayr, 2008). These gender-related differences might be caused by hypersensitivity to their own sex hormones or by other hormonal processes (Jensen-Jarolim & Untersmayr, 2008).

In opposite to allergic diseases, COPD is generally more common among men than women (GOLD, 2010). However, over the past decades the prevalence of COPD is increasing especially among women in developed countries. This increase probably reflects changing patterns of smoking habits among men and women (GOLD, 2010). The increase of COPD in women is parallel with the raise in smoking among women. Above that, women are more susceptible to the effect of smoking than men (GOLD, 2010).

Respiratory and allergic diseases vary by age with asthma symptoms peaking in childhood and adolescence (Nathan et al., 2008). Allergic sensitization is also more common among young subjects compared to older (Raukas-Kivioja et al., 2003; Warm et al., 2011). On the other hand, the prevalence of COPD increases with age (Kotaniemi et al., 2005; Lundback et al., 2003). There is a physiological decline in respiratory function by age which begins around the age of 30 to 40 years (Raherison & Girodet, 2009). The life expectancy is increasing all over the world, so this thus can contribute to the increasing prevalence of COPD worldwide.

Socio-economic status

The relation between socio-economic status (SES) and asthma in adults is not well understood. Studies have shown increased asthma hospital admissions among those who are materially deprived and increased asthma severity in low socio-economic classes (Farfel et al., 2010). However, the association between SES and asthma prevalence is less clear. The hygiene hypothesis implies that asthma is more prevalent in higher socio-economic classes (Bloomfield et al., 2006). High socio-economic status was still associated with a relatively high prevalence of asthma according to some studies, for instance a recent study among adolescents in Israel (Farfel et al., 2010). However, in a meta-analysis study, the authors concluded that community influences of living in low-educational areas are associated with asthma, independently of the subjects' own educational level and social class (Basagana et al., 2004). Also recent studies in developed countries, such as Sweden, have found asthma and symptoms of asthma to be more common in low socio-economic classes both in children and adults (Almqvist et al., 2005; Ekerljung et al., 2010b), and also the incidence of asthma was higher in low socio-economic classes in these studies.

Populations living in poor social and economic conditions are at a higher risk of developing COPD even after effects of smoking been taken into account (GOLD, 2010). In USA, low SES is a risk factor for several adverse health outcomes of COPD (Eisner et al., 2011). SES is a risk factor for COPD also in China independently of current or passive smoking (Yin et al., 2011). However, SES probably covers various risk factors, such as diet, infections and occupational exposures and other environmental factors including passive smoking. Since several of these factors exist from childhood, they may have an impact on adult lung function.

AIMS

1. To study the prevalence of respiratory symptoms, asthma and chronic bronchitis, and to explore the association between these respiratory diseases and conditions with demographic data including smoking habits among adults in rural and urban northern Vietnam.

2. To assess the prevalence and risk factors for allergic rhinitis, chronic nasal blocking and chronic runny nose, and to explore the association between the rhinitis conditions and other respiratory symptoms and diseases.

3. To investigate the prevalence of allergic sensitization in rural and urban northern Vietnam, it's determinants and the relation with asthma and rhinitis.

4. To study the prevalence of COPD including the prevalence by disease severity and risk factors for COPD in rural and urban northern Vietnam.

MATERIAL AND METHOD

The studies were based on a cross-sectional survey and were performed in two steps. Part one was a questionnaire survey conducted from September 2007 to January 2008. The results from this part are reported in paper 1 and paper 2. Part two included clinical examinations of a random sample of the questionnaire responders and was carried out from March 2009 to April 2010. Paper 3 and paper 4 are based on data from this part.

Study areas

Vietnam is located in South East Asia (figure 6). The population has been rising rapidly despite governmental family planning and has increased from 54 million people in 1980 to 89 million in 2010 (figure 7).
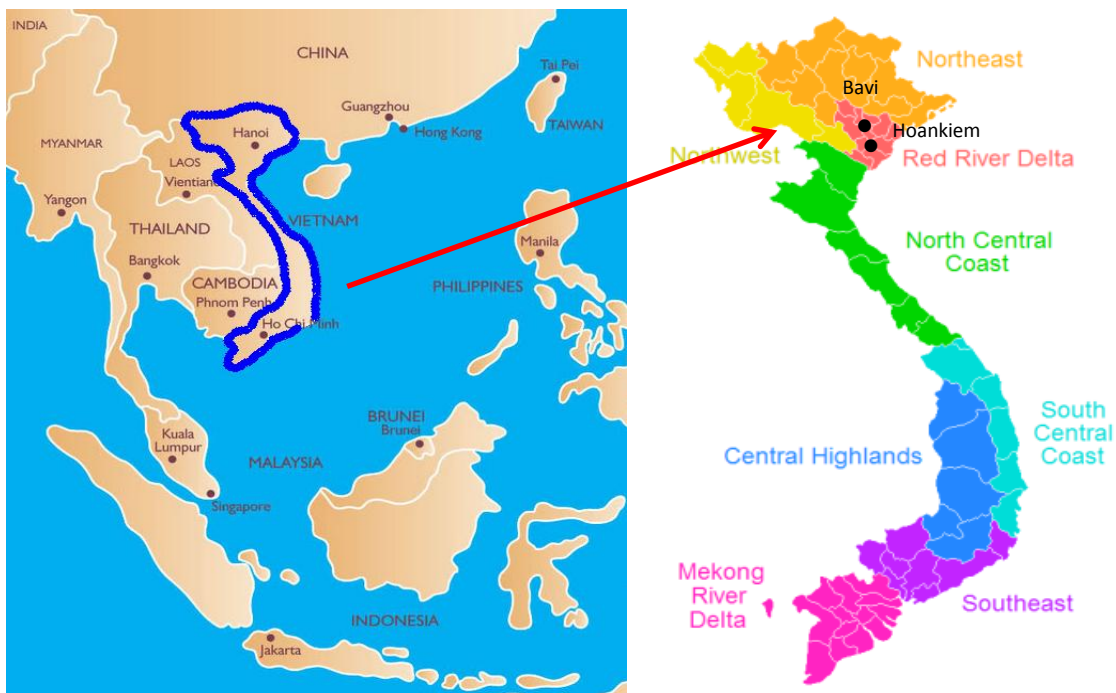
Figure 6. The location of the study areas

The urban part of Hanoi is located in the Red River delta. Due to the low altitude and surrounding highlands, the heavy air pollution stays in the urban Hanoi. Further, urbanization is progressing very fast. The public transportation system doesn't fulfil the requirements of the people why private vehicles are increasingly used, the major part being motorbikes. In urban Hanoi, the infrastructure doesn't

support the amount of transports resulting in traffic jams during the rush hours every day.

The climate in Hanoi is a warm and humid subtropical climate with plenty of rainfalls typical for northern Vietnam. The summer, lasting from May to September, is hot and humid with an average temperature in July from 26^0C-33^0C, and the average humidity is 82%. The temperature can go up to 40^0C. The winter period is short with an average temperature in January from 13^0C - 19^0C, and the average humidity is 78%. The temperature can go down to 6^0C.
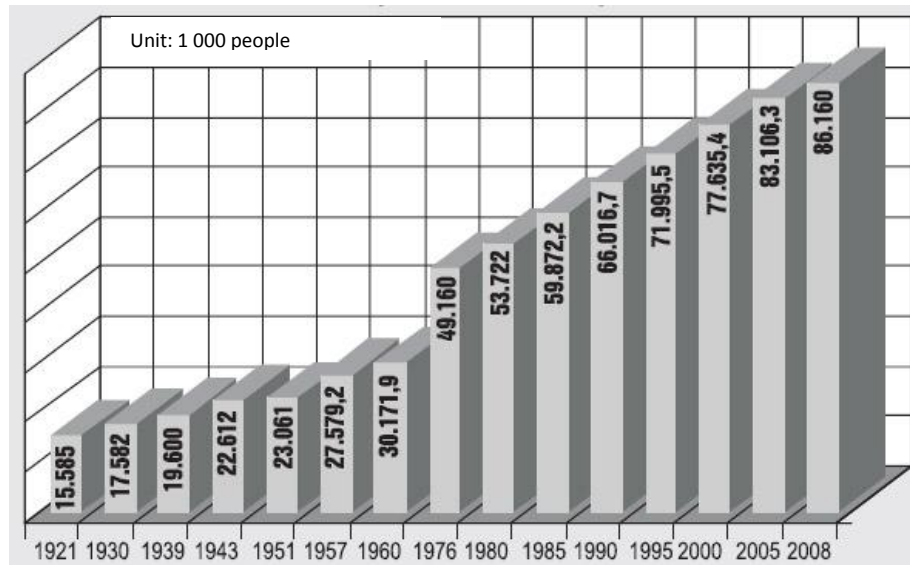

Figure 7: The Vietnam population from 1921 to 2008

The study was performed in two areas of Hanoi, the urban inner city area Hoankiem, and the rural area of Bavi (figure 8). Hanoi is the capital of Vietnam. The choice of these two areas was based on the geographic composition of the areas, one urban and one rural, and differences in air pollution.

Hoankiem is the biggest trading center but also the smallest district of Hanoi. The population in 2006 was 180,000 people and the population density was 32,703 inhabitants/km^2 in the 5.29 km^2 area. Hoankiem is the old town of Hanoi with many small streets always full of vehicles, most of them motorbikes. There are 18 wards in Hoankiem; 16 wards are located inside the Red River dyke system while the two biggest are located outside. Each ward has its own health care station which is under direct supervision of the Hoankiem District Health Care Center. There are 4-6 staffs in each ward health care station, including a medical doctor and nurses. In addition, each ward in Hoankiem has a team of 5-10 freelance citizens, often retired persons, who help as collaborators. Freelance citizens participated in collecting the data of the questionnaire survey.

Bavi is located 60 km west of city center of Hanoi. In the past, Bavi was a district of the Hatay province. Hatay was emerged into Hanoi in 2008 and Bavi became the biggest rural district of Hanoi and includes lowlands, midlands, highlands and mountainous areas. The population in 2006 was 235,000 inhabitants. The major

part of the population is farmers and their income is based on agriculture and livestock breeding. There are 32 village health care stations in the Bavi district, one in each village and they are under the supervision of the Bavi District Health Care Center.

Hoankiem district   Bavi district

Figure 8. The Bavi and the Hoankiem districts

FilaBavi

FilaBavi is a field laboratory for medical research of Hanoi Medical University and is located in the Bavi district. The sampling units are "population units" or "clusters" based on villages. The whole Bavi district has 352 clusters with a mean number of 146 households per cluster. The study population of FilaBavi consists of a sample of 67 clusters (51,000 inhabitants in 11,000 households) randomly selected proportionally to the population size in each of the geographical areas, i.e. lowlands, midlands, and highlands (Chuc & Diwan, 2003).

Study population

The study sample was randomly selected from the official register of the population in both areas. In Hoankiem, 4,000 were selected among 108,000 inhabitants born from 1937 to 1986. However, 992 subjects in two wards located outside of Red River dyke were excluded because their addresses could not be traced (figure 9). In Bavi, also a sample of 4,000 people of same age was randomly chosen from the 51,000 subjects of the FilaBavi population. In total, the sample of both areas was 7,008 subjects. The age distribution of the invited subjects was from 21 to 70 years.

Pilot study

A pilot study was performed in order to know whether a postal survey was suitable in Vietnam. 250 subjects per area were randomly chosen from the original sample of 4,000 subjects. One month after the mailing only 10.2% had responded, and only 1 person had responded in Hoankiem. Among the 51 returned

questionnaires, five were answered by other persons than the invited. The conclusion was that a postal survey was not a suitable method in Vietnam.

Questionnaire survey

Instead of sending postal mails, we decided to personally deliver the questionnaires to the invited subjects. The trained field workers in of FilaBavi (46 professional surveyors and 6 supervisors) and health care staffs and population freelance citizens at each ward of Hoankiem delivered the questionnaires to the invited subjects and asked them to complete the questionnaires.
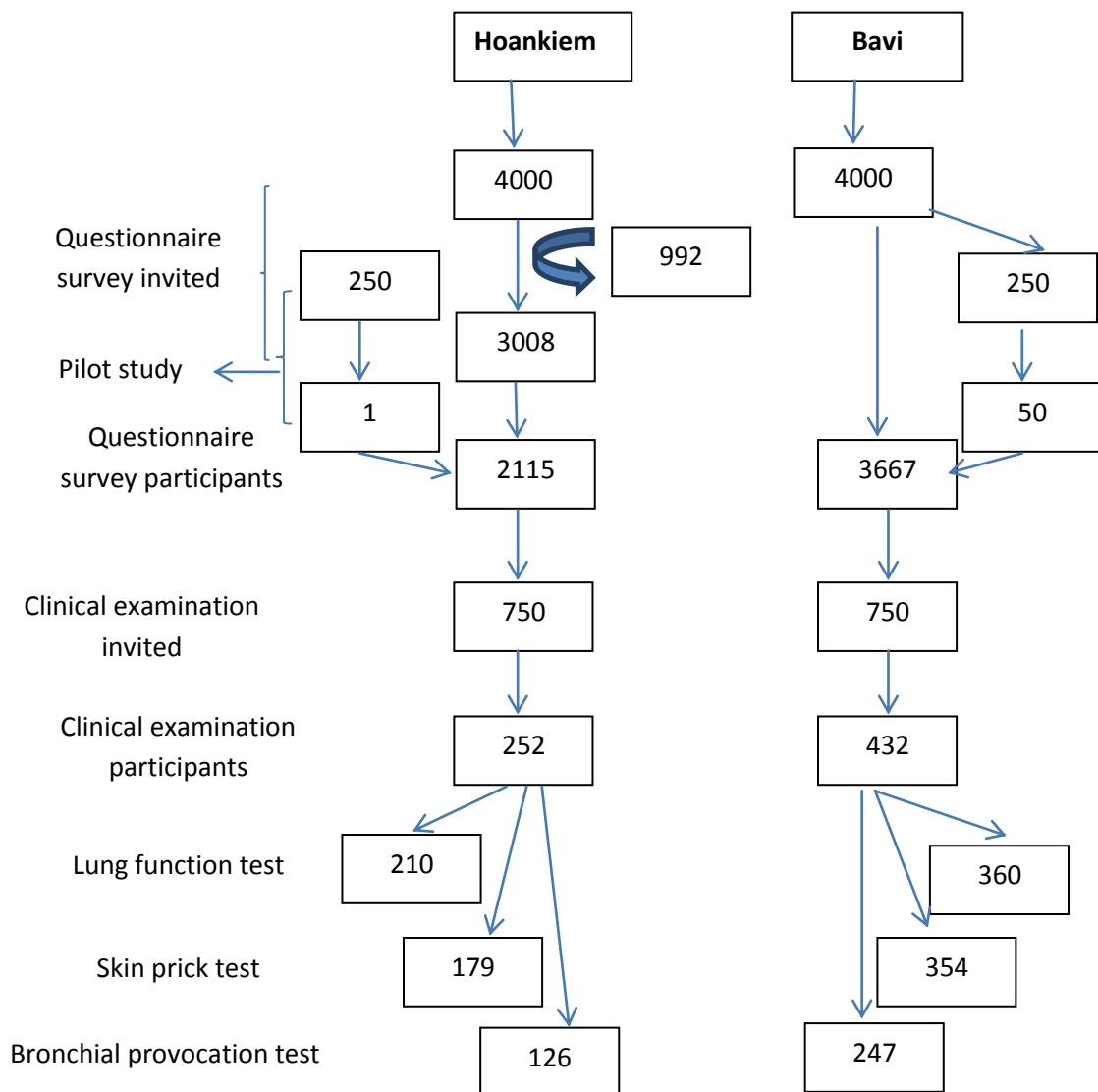

Figure 9. Flow chart of the study design and participation

In case participants could not complete the questionnaires by themselves, the field workers made a structured interview by reading the questions without any other

interfering or explanation to the subjects under study. Almost all questionnaires in Bavi were completed by surveyors, while in Hoankiem the majority of the questionnaires were completed by the participants. The questionnaire survey was conducted at the same time in Hoankiem and Bavi from September 2007 to January 2008.

Clinical examination

The sample invited to the clinical examinations was randomly chosen among the subjects who participated in the questionnaire survey. Totally were 1500 randomly selected subjects invited, 750 from each area. The clinical study was conducted from March 2009 to April 2010 in both areas.

The research team consisted of four medical doctors including myself and four research nurses, who all worked at the Department of Allergology, Hanoi Medical University or the Department of Allergy & Clinical Immunology, Bachmai hospital. The techniques of the skin prick testing, lung function measurements and methacholine testing were provided by the Swedish supervisors, who also trained the research team. Before the start of the study, the research team did several training sessions by themselves and also with the Vietnamese supervisor. The training was performed with volunteers, mostly medical students. All activities of the study were conducted at the local health care stations. The local health care staffs of Hoankiem and the field workers of the FilaBavi invited the study subjects. They also helped the research team in identifying the participants, completing the demographic information, measuring height, weight and blood pressure. All measures in Hoankiem were performed by the research team, however, in FilaBavi some field workers were trained also to do structured interviews. Most examinations were performed during weekends.

Skin prick test

All participants aged ≤60 years and not having contra indications were invited to skin prick testing.

The contraindications were pregnancy, lactation or using anti-histamines within 3 days from the day of examination. Among of the participants, 537 subjects participated at the SPT; however results from four subjects were deleted due to a reaction to the negative control. Of all participants at the clinical examinations, 91 subjects (13.3%) did not fulfil the criteria for SPT including the age criterion and 56 people (8.1%) refused to do the test.

Figure 10. Allergens and equipments for skin prick test

The test followed the guidelines from the European Academy of Allergy and Clinical Immunology (EAACI) (Dreborg et al., 1989).The panel of SPT included ten well known airborne allergens: Cat, Dog, *D. pteronyssinus, D. farina, Alternaria* and *Clasdosporium* were provided by Soluprick, ALK Hörsholm, Denmark, while Cockroach, *B. tropicalis*, Grass mixture (*cocksfoot, sweet vernal grass, rye grass, meadow grass, timothy)* and Tree mixture *(maple, horse chestnut, plane, false acacia, lime)* were provided by Stallergen Lab., France. Histamine 10 mg/ml and glycerol were used as positive and negative controls (figure 10). The reaction was read after 15 minutes. A wheal size $\geq$ 3 mm was regarded positive.

Lung function, reversibility and methacholine test

A portable spirometer (Multi-functional spirometer HI-801) was used for lung function testing. Calibration of the spirometer was performed daily with a 1 litre syringe. The test procedure followed the ATS recommendations (Laszlo, 2006). Spirometry was performed with the subjects sitting and using a nose-clip. Forced vital capacity (FVC) and forced expired volume in 1 second (FEV_1) manoeuvers were performed at least three times and the difference between the two best FVC and the two best FEV_1 values had to be <5%, or <1dl in case the values were <2 litres. The subjects were instructed carefully how to perform the test before starting the measurements. If the subject couldn´t achieve acceptable tests after 8 manoeuvres, they got a short rest and new attempts were made. The reference values were taken from the equation calculated for the east Asian population. Of all tests, 570 lung function test results (83.3%) were accepted.

The methacholine tests were performed with a nebulizer (Aliolos Systems) following the method developed at the Swedish OLIN studies (Lundback et al., 1993). The recorded FEV_1-value after inhalation of saline (0.9% NaCl) was used as the baseline FEV_1. If the fall in baseline FEV_1 was $\geq$10%, the subjects was labelled 'saline reactive' and the test was stopped and the subject was given 400 µg Salbutamol. The methacholine concentrations used were 0.125, 0.25, 0.5, 1, 2, 4, and 8 mg/ml. Each concentration was inhaled by normal breathing during 1 minute. FEV_1 was measured 2 minutes after each inhalation. The test was stopped when FEV_1 had fallen $\geq$ 20% from baseline or after the last dose of methacholine. After that 400 µg Salbutamol was given and the lung function was re-measured after 20 minutes. The methacholine challenge was not performed if the subject's FEV_1 pre-test was < 1.5 l or < 60% of predicted. Furthermore, the challenge was not conducted if the subjects were > 60 years, had unstable heart disease or hypertension, or was pregnant or lactating, or could not cooperate.

A reversibility test was performed in all subjects with 400 µg salbutamol via an inhaler. Spirometry was re-measured after 20 minutes.

The lung function values used in the analyses were
Forced vital capacity (FVC): The volume of air one can exhale with a forced exhalation after a maximal inhalation.
First second forced expiratory volume (**FEV_1**). The volume of air one can exhale during the first second using maximal force after a maximal inhalation (FEV_1).
The ratio of FEV_1 and FVC was determined for defining airway obstruction.

Questionnaire

The questions used in the questionnaire survey were taken from Swedish OLIN questionnaire (Lundback et al., 1991). The questionnaire has been used in several studies mainly in the Nordic and Baltic countries (Meren et al., 2001; Pallasaho et al., 1999). A recent version of the questionnaire has been published from a study in Helsinki, Finland (Pallasaho et al., 2006) and in Gothenburg, Sweden (E. P. Ronmark et al., 2009b).

The interview questionnaire used was the recently developed GA[2]LEN Study questionnaire (Bousquet et al., 2009), which is mainly based on the ECRHS and the ARIA questionnaires (Biino et al., 2000; Cruz et al., 2007). Additional questions were taken from the Swedish OLIN-questionnaire (Lundback et al., 1991). The questionnaire included questions mainly about respiratory and allergic symptoms, diagnoses, smoking habits, occupation, urban or rural childhood living, and living on a farm the first year of life.

Definitions

In this section the questions regarding the main diseases and symptoms are described. The questions of both the questionnaire survey and the structured interview are given in detail in the appendix. Several questions are identical in the self-administrated questionnaire and the structured interview.

Self-administrated questionnaire (study part I)

Physician-diagnosed asthma: "Have you been diagnosed as having asthma by a doctor?"
Ever asthma: "Have you now or have you ever had asthma?"
Asthma medicine: "Do you currently use asthma medicines (permanently or as needed)?"
Physician-diagnosed chronic bronchitis: "Have you been diagnosed as having chronic bronchitis, COPD or emphysema by a doctor?"
Ever chronic bronchitis: "Have you now or have you ever had chronic bronchitis, COPD or emphysema?"
Allergic rhinitis: "Have you now or have you ever had allergic rhinitis (hay-fever) or allergic eye catarrh?"
Recurrent wheeze: "Do you usually have wheezing, whistling or a noisy sound in your chest when breathing?"
Any wheeze: "Have you at any time during the last 12 months had wheezing or whistling in your chest?"
Wheezing with breathlessness apart from cold: "Yes"-answer to *any wheeze* and to –"Have you been at all breathless when the wheezing or whistling was present" and to –"Have you at any time had this wheezing or whistling when you did not have a cold?"
Dyspnea: "Do you get short of breath when you walk with other people of your own age on level ground at normal pace?"
Longstanding cough: "Have you had longstanding cough during the last year?"

Sputum production: "Do you usually have phlegm when coughing, or do you have phlegm in your chest which is difficult to bring up?"

Chronic productive cough: Was defined as sputum production on most days during at least 3 months at least 2 successive years (please, see appendix).

Family history of asthma and *family of history of chronic bronchitis* (please, see appendix).

Family history of obstructive lung disease (OLD): "Yes"-answer to any of the two questions about *family history of asthma* and *family history of chronic bronchitis*.

Structured interview questionnaire (study part II)

Waken up by shortness of breath (SOB): "Have you been woken by an attack of shortness of breath at any time in the last 12 months?"

AR symptoms last 12 months: "Have you been troubled by nasal allergies in the last 12 months?"

Asthma attacks: "Have you had an attack of asthma in the last 12 months?"

Asthma hospitalisation: "Have you ever been hospitalised for asthma?"

Intermittent AR: If yes to *AR symptoms last 12 months*, "Have you ever been troubled by nasal allergies for more than 4 days in any one week?"

Persistent AR: If yes to *intermittent AR*, "Did this continuously happen for more than 4 weeks?"

Shortness of breath (SOB) when hurrying: "Do you get short of breath when you hurry on level ground or when you walk in your own pace up a stair or a small slope?"

Allergic sensitization: A positive SPT-reaction to any of the allergens.

COPD: Asian reference values of lower limit of normal for the ratio of FEV_1/FVC have not been validated for Vietnam, thus the ATS/ERS standards for defining COPD could not been fully met while COPD was defined using the fixed ratio of $FEV_1/FVC \leq 0.70$ (Celli & MacNee, 2004). The highest FEV_1 and FVC were used including post bronchodilator results. As no subject had exactly the ratio of 0.70, thus the results also were in line with the GOLD guidelines (GOLD, 2010). The severity of COPD was also determined by the spirometric cut off values proposed by GOLD:

GOLD 1 (mild COPD): $FEV_1/FVC < 0.70$ and FEV_1 % predicted ≥ 80
GOLD 2 (moderate COPD): $FEV_1/FVC < 0.70$; and $50 \leq FEV_1$ % predicted < 80
GOLD 3 (severe COPD): $FEV_1/FVC < 0.70$ and $30 \leq FEV_1$ % predicted < 50
GOLD 4 (very severe COPD): $FEV_1/FVC < 0.70$ and FEV_1 % predicted < 30

Due to few cases of severe and very severe COPD, these two groups were combined in the analyses.

Smoking habits

Current smokers were those who were current smokers at the time for the study or those who had stopped smoking within 12 months prior to the study.

Ex-smokers were those who had stopped smoking more than 12 months prior to the study.

Non-smokers were those who never had been smokers or ex-smokers.
1 pack year = 20 cigarettes per day for one year.

Ethical issues

The ethical issue was approved by the Ethics Committee of Hanoi Medical University in July 2006. Consent letters were received from the participants before carrying out the clinical examinations.

Statistical analysis

The data of the clinical examinations were checked one by one by the Swedish supervisors before computerising. The SPSS version 16.0 or PASW 18.0 was used for statistical analyses. Uni-variate analysis was performed using the $\chi 2$ test. One way analysis of variance (ANOVA) and $\chi 2$ were used for test of trends. Data from the initial questionnaire survey was used for paper 1 and paper 2 and also for evaluating the representativeness of the participants of the clinical study. A p-value <0.05 was considered statistically significant. Risk factors for diseases, symptoms and allergic sensitization were calculated by using multiple logistic regression analysis. Demographic and exposure data were used as independent variables. They included sex, age, area, smoking habits, occupational exposure to dust, gases and fumes, and being raised on a farm during the first year of life. The results are expressed as odds ratios (OR) with 95% confidence intervals (CI).

RESULTS

Part 1: Questionnaire survey (Paper 1 and Paper 2)

Participation and smoking habits

The participation rate of the questionnaire survey was 82.5% ranging from 70.3% in the urban Hoankiem to 91.7% in the rural Bavi. The participation rate was similar in men and women, and there was no major difference by age.

Nearly two thirds, 61.0%, of the men but only 2.3 of the women in the study were current smokers. Interestingly, there were differences in smoking habits between the urban and the rural area, more men but fewer women in the rural area were current smokers than in the urban area, $p<0.001$ for both comparisons (figure 6). The prevalence of ex-smokers was low in both areas, 1.7% in Hoankiem and 3.9% in Bavi.
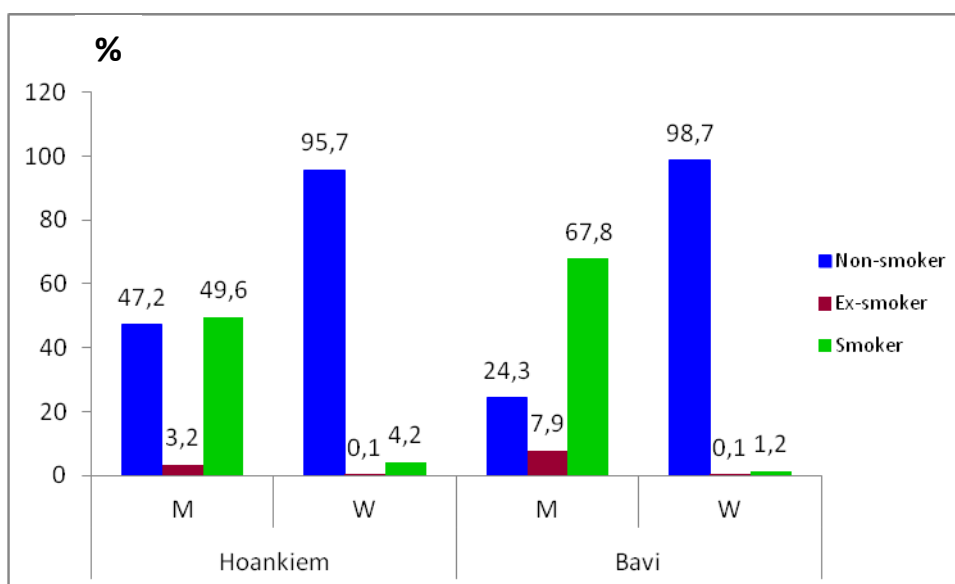

Figure 11. Smoking habits by area in men and women

Prevalence of respiratory symptoms and diseases

The prevalence of asthma ever was higher in Hoankiem, 5.6%, than in Bavi, 3.9% (p=0.003), while the prevalence of physician-diagnosed asthma was similar, 3.9% in Hoankiem and 3.8% in Bavi. Both chronic bronchitis ever (6.2% *vs.* 4.6%; p=0.005) and physican-diagnosed chronic bronchitis (4.1% *vs.* 3.3%; p=0.016) were more common in Hoankiem than in Bavi. Interestingly, the prevalence of

AR ever was three times higher in Hoankiem, 26.9%, than in Bavi, 10.0% (p<0.001).

There was a significant association between smoking habits and asthma as well as physician-diagnosed chronic bronchitis. The highest asthma prevalence was found among ex-smokers (table 1).

Table 1. Prevalence (%) of asthma and chronic bronchitis by smoking habits

	Smoker	Ex-smoker	Non-smoker	p-value, test for trend
Ever asthma	5.4	7.9	3.9	0.004
Ph-diagnosed asthma	4.9	7.9	3.2	<0.001
Ever chronic bronchitis	5.6	7.3	4.8	0.196
Ph-diagnosed chronic bronchitis	3.9	6.7	2.9	0.006

The most common lower airway symptom in both Bavi and Hoankiem was longstanding cough (18.1% *vs.* 12.0%, p<0.001), followed by sputum production (16.0% *vs.* 11.0%, p<0.001). Sputum production was more common among men than women (p=0.017) and in subjects above than subjects below the age of 45 years (p =0.022). All symptoms common in asthma and use of anti-asthma drugs were low, 2.1%, and similar in both areas. No statistically significant difference between the two areas was observed for any wheeze during the last 12 months, 5.1% in Hoankiem *vs.* 4.3% in Bavi. The prevalence of all respiratory symptoms increased with age.

A half of the participants in the study had either chronic nasal blocking or chronic runny nose. Nasal blocking was more prevalent in Hoankiem than in Bavi, 40.2% *vs.* 31.0% (p<0.001). In contrast, no difference in prevalence of runny nose was found between the two areas.

Those who had lived on a farm during the first year of life had lower prevalence of AR ever (p<0.001) and chronic nasal blocking (p=0.002) than those who did not spend their first year on a farm.

The prevalence of all respiratory symptoms and diseases was higher among those who had AR ever, chronic nasal blocking and chronic runny nose compared with those who did not have these nasal conditions (p<0.001 for all comparisons).

Multivariate relationships

Both ex-smoking and current smoking were significant risk factor for physician-diagnosed asthma; OR 3.04 (95% CI 1.51-6.13) and OR 1.61 (95% CI 1.07- 2.42), respectively. In contrast, these smoking variables didn't reach statistical significance physician-diagnosed chronic bronchitis. Current smoking was also a risk factor for long standing cough, OR 1.45 (95% CI 1.16- 1.80) and for chronic productive cough, OR 1.89 (95% CI 1.20-2.99). The prevalence of all respiratory symptoms and of physician-diagnosed chronic bronchitis was higher in subjects

aged >45 years. A family history of obstructive airway diseases was the major risk factor for all asthma and chronic bronchitis conditions.

When including age, sex, area of domicile, exposure to gas, dust, and fumes at work place and smoking habits in the model, exposure to gas, dust and fume at work place appeared as a major risk factor for all nasal conditions. Living in the urban Hoankiem was associated with an increased risk for AR ever, OR, 3.94 (95% CI 3.40-4.56) and chronic nasal blocking, OR, 1.62 (95% CI 1.44-1.81). Being a women versus being a men yielded an OR of 1.47 (95% CI 1.26-1.72) for chronic nasal blocking and an OR of 1.36 (95% CI 1.18-1.58) for chronic runny nose.

Part 2: Clinical examination (Paper 3 and Paper 4)

Participation and representativeness

Of the 1500 invited, 684 subjects (45.6%) attended the clinical examinations, with a higher participation rate in Bavi, 57.5%, than in Hoankiem, 33.6% (p <0.001). Subjects above the age of 50 years were more likely to attend than younger subjects (53.1% *vs.* 41.4%; p <0.001). Similarly, more women, 49.5%, than men participated, 41.7%; p=0.002 (table 2). Among the 684 participants, 683 (99.8%) participated in the structured interviews, 570 (83.3%) in lung function tests and 533 (77.9%) in skin prick testing.

Table 2. Prevalence (%) of participants at the clinical examination by sex, area and age group

| | Participants | | |
	Yes	No	p-value
Men	41.7	58.3	0.002
Women	49.5	50.5	
Hoankiem	33.6	66.4	<0.001
Bavi	57.6	42.4	
≤ 50 y	41.4	58.6	<0.001
>50 y	53.1	46.9	

There were no significant differences in respiratory symptoms or diagnosed asthma or AR ever between those who had participated in the questionnaire survey and those who attended the clinical examinations.

According to the interviews, the prevalence of current smokers was 29.0%, and it was 63.0% among men and 0.5% among women, p<0.001. The men who were current smokers had an average smoking history of 17.9 pack-years. The corresponding figure for women was 12.2 pack-years. The prevalence of ever smokers was similar in the two areas and did not increase with age.

Overweight was more common in Hoankiem than in Bavi, p<0.001 (figure 12). Further, more people in Bavi had a BMI <18.5 than in Hoankiem, p<0.001. Subjects aged > 50 years had a higher BMI than those aged ≤ 50 years, 13.3% *vs.* 8.3%, p=0.033.
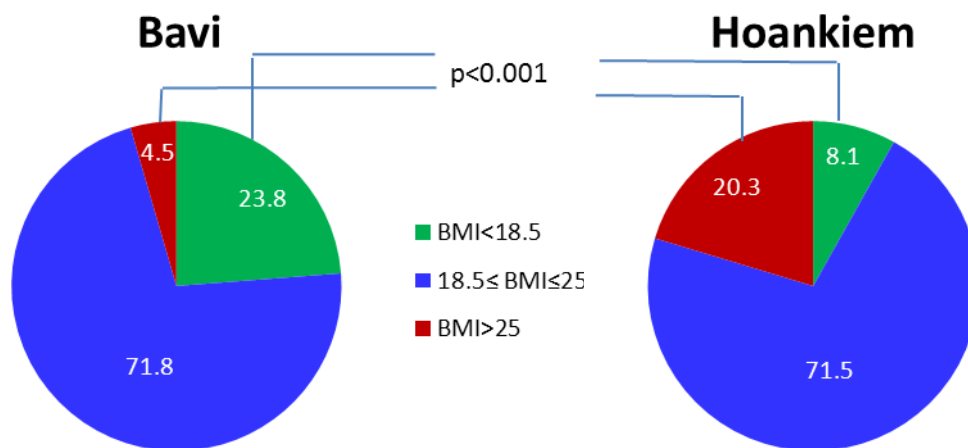

Figure 12. Prevalence (%) of BMI-categories in Hoankiem and Bavi

Prevalence of allergic sensitization and its relation to respiratory conditions

Of the 533 subjects who were skin prick tested, 180 subjects (33.8%) had a positive SPT to at least one allergen and 159 subjects (29.8%) were sensitized to any mite or cockroach. Thus sensitization to any animal, any pollen, or moulds contributed with only 4% units to the total prevalence of allergic sensitisation. The most common sensitizer was the storage mite *B.tropicalis* (22.9%), followed by *D. pteronyssinus* (13.3%), cockroach (13.1%) and *D. farinae* (10.5%) (figure 12). Only 6.8% were sensitized to any animal. Sensitization to any pollen (2.8%) and any of the two moulds (1.5%) was even more uncommon (figure 13).

Among the sensitized, 40.0% reacted to a single allergen while 6.0% were sensitized to ≥5 allergens. Multi-sensitization was significantly more common in the urban area compared to the rural area (p=0.006). Similarly, multi-sensitization was more common among men than among women (p=0.004), while multi-sensitization did not differ between subjects below and above the age of 45 years.

Allergic sensitization was significantly associated for all groups of allergens, i.e. any animal, any pollen, any mite, any mould, and cockroach, with AR ever and symptoms of AR during the last 12 months. Even though, symptoms common in asthma were more common among the sensitized, the only significant associations between sensitization and symptoms were for asthma attacks with any allergen,

26

p=0.036, recurrent wheeze with any mite, p=0.039, and recurrent wheeze with any allergens, p =0.015.
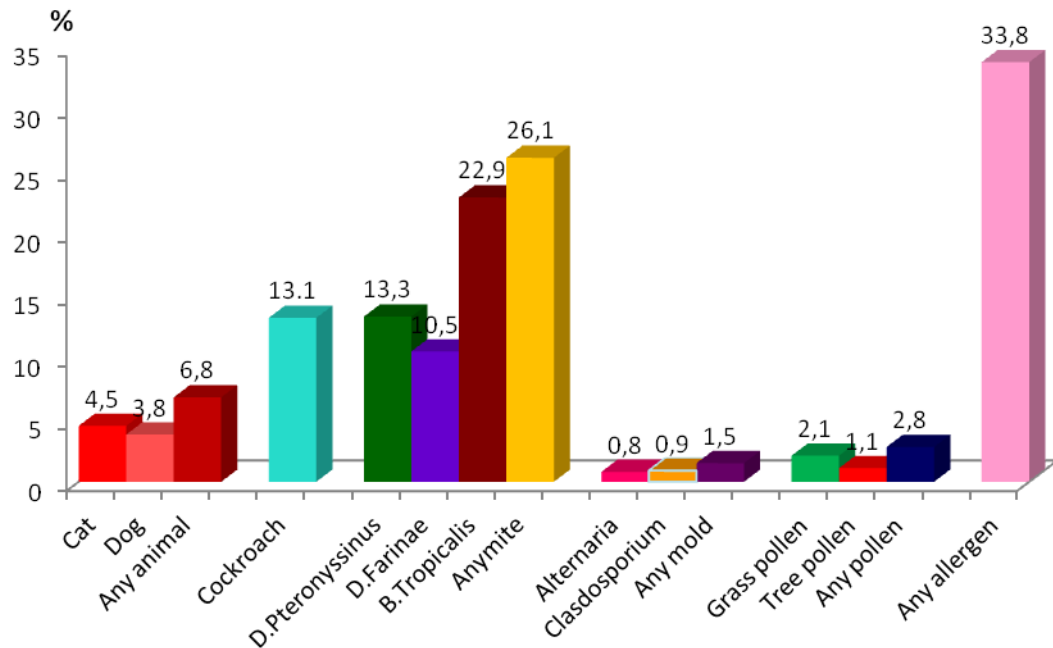

Figure 13. Prevalence (%) of positive SPT to the tested allergens

Age ≤45 years were the strongest risk factor for having a positive SPT to any mite, OR 1.64 (95% CI 1.09-2.45) and to any allergen, OR 1.48 (95% CI 1.02-2.59). Sensitization to any mite was further associated with exposure to gas, dust or fumes at work, OR 1.57 (95% CI 1.02-2.41). Male sex yielded an OR of 2.61 (95% CI 1.16-5.86) for having a positive SPT to cockroach. Sensitization to the different air-born allergens were not dependent on urban living or childhood farm living. Smoking habits were not significantly associated with allergic sensitization.

Prevalence and risk factors of COPD and relation to respiratory conditions

The overall prevalence of COPD was 7.1% by using both the ERS/ATS standards and the GOLD criteria. The prevalence was 10.9% in men and 3.9% in women, (p=0.001). The prevalence of COPD increased with age, and was 2.3% below the age of 50 years, and it was 14.6% among those who were older than 50 years (p<0.001). The prevalence of COPD among subjects aged >50 years old was 23.5% in men and 6.8% in women (p<0.001).

Among men aged ≥60 years, the proportion of subjects having COPD was significantly associated with smoking habits (p=0.04; figure 9). At this age, nearly 50% of current smokers had developed COPD. The prevalence of COPD increased also with the cumulative exposure to tobacco smoke defined as the number of pack years (p<0.001). Among the subjects with COPD, 48.6% had mild COPD, 37.8% moderate and 13.5% had severe or very severe COPD.
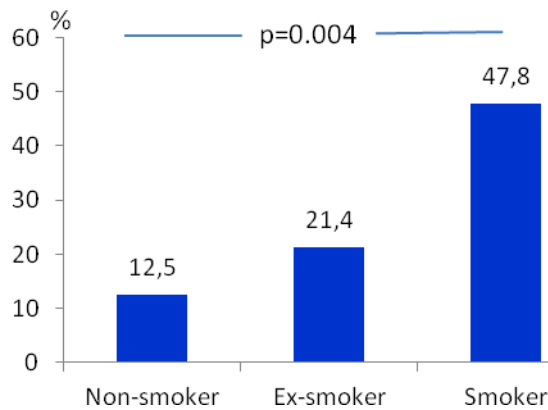
Figure 14. Prevalence (%) of COPD among men aged ≥ 60 years by smoking habits.

Most respiratory symptoms as well as a previously diagnosed asthma and a previously diagnosed COPD were strongly associated with the severity of COPD. Among the subjects with COPD, 35% had a previous diagnosis of COPD and 17.5% had a previous diagnosis of asthma. Further, 60% had longstanding cough, 25% chronic productive cough, 45% shortness of breath associated with physical activity, and 35% used any drug for lung disorders.

Among the subjects with COPD, the proportion having at least one of the symptoms longstanding cough, sputum production, chronic productive cough or wheezing during the last 12 months was high and increased by disease severity (table 3).

Table 3. Prevalence (%) of any respiratory symptom by severity of COPD

	%
COPD stage 1	77.8
COPD stage 2	85.7
COPD stage 3+4	100

When including sex, area of domicile, age and smoking habits combined in a multivariate statistical model, the combination of increasing age and ever smoking appeared as the dominating risk factor for COPD. The age of 50-60 years and ever-smoking yielded an OR of 13.52 (95% CI 2.16-84.5). Age ≥ 60 years combined with ever-smoking yielded a risk of having COPD with an OR of 37.2 (95% CI 6.28-220.6), while the risk for non-smokers aged ≥ 60 years for having COPD was 6.31 (95% CI 1.71- 23.3). Sex and area of domicile were not significantly associated with an increased risk of having COPD.

28

DISCUSSION OF METHODOLOGY

The methods and study designs used in the study will be discussed in this section. Limitations, strengths of the study as well as non-response will be discussed. In addition, different types of bias, which may influence the results, will also be discussed.

Study design and study population

The study was a cross-sectional study performed in two stages aiming at estimate the prevalence and risk factors of the outcomes of interest for the given population. The study areas were chosen in order to adequately reflect the true epidemiology of the diseases under study in urban and rural northern Vietnam. Because the study was a cross-sectional study there was no information of the sequence of events, i.e. whether exposure occurred before or after the onset of disease. Thus the calculations of risks may express cause or consequence or even parallel phenomena, and this is particularly true when discussing risk factors that are not stable over time.

Bias should always be considered as it might affect the study results. It is helpful to classify bias into three broad categories: selection bias, information bias, and confounding. Selection bias is a systematic error in a study that stems from the procedures used to select subjects and from factors that influence study participation.

The study sample was randomly selected from the list of the official registers of the population described in the material and methods section. This method reduces or even avoids selection bias. The sample was determined after power calculations. It was supposed that the prevalence of diseases, i.e. asthma and COPD in the study might vary from about 4% to 6% and with the accuracy in each area of less than ±1% within the limits of the 95% confidence interval. A sample size of 4000 subjects was thus selected for each area and response rate was assumed to be about 75%. The 992 subjects living in the two wards located outside the Red river dyke, who were not possible to trace and were thus excluded from the study, may have some different characteristics compared to the reminding study sample of Hoankiem. An unknown proportion of the 992 subjects may be different for instance regarding socio-economic status, why the exclusion of these 992 subjects may have caused bias of the results. However, we do not believe that a major bias was caused. The invited subjects in the questionnaire survey surpassed the size of the population samples used in the ECRHS, which varied from 3000 up to 6734 subjects (ECRHS, 1996). Furthermore, the response rate in our study was high, 82.5%, thus increasing the validity of the results and reducing bias caused by non-participation.

In the beginning we planned to perform the questionnaire survey as a postal survey following a protocol that has been used in several studies in northern Europe (Lunback et al., 1991; Meren et al., 2001; Pallasaho et al., 1999) . This has been a suitable, cheap and successful method for collecting data from large population samples. However, this method has rarely been used in Vietnam. We thus performed a pilot study using mailed questionnaires to 250 randomly selected subjects out of the 4000 from each of the two areas. The results from the pilot study confirmed our concerns, since only 10% returned the questionnaires, further, among them 10% of the questionnaires were answered by other than the invited subjects. Even though the prevalence of illiterate subjects in Vietnam is very low, specific questions regarding symptoms of medical conditions may be difficult to understand. This may be one reason why the invited subjects did not answer the questions in the questionnaire. Lacking of personal number and often not up-dated addresses contributed to difficulties in recognizing the study subjects. A conclusion is that a postal questionnaire survey was not a suitable method for Vietnam.

Instead of sending the questionnaires by mail, we thus decided to ask field workers to deliver the questionnaires directly to the invited subjects. The strength of this method was a high response rate, and the amount of missing data to specific question was low. However, the limitation of this method is that the field workers might have interfered to the study. The way that field workers explained the study and the questionnaire might have caused information bias.

The response rate in the second part of the study was lower, 45.6%, compared to the questionnaire survey. However, as we invited 1500 subjects, more than 600 subjects participated in the clinical part of the study. Due to the low participation rate in the clinical part, the representativeness was analysed in order to evaluate possible bias caused by non-participation. The participants of the clinical part had reported similar prevalence of symptoms or diseases in the questionnaire survey as all participants of the questionnaire survey. Thus the low response rate in the clinical examinations did not create a significant bias caused by non-participation. There are no definite recommendations of a minimal number of participants in clinical epidemiological studies. However, several studies have aimed at achieve at least 600 participants. Lower numbers result in even wider confidence intervals and risk analyses will be affected by insufficient power. International studies that have aimed at a participation of at least 600 subjects per centre include the ECRHS and the northern European FinEsS-studies (Burney et al., 1994; Pallasaho et al., 2006).

In the clinical part, the older subjects yielded a higher participation rate than the younger (p<0.001), results in line with several other studies (Bjornsson et al., 1994; Milenkovic et al., 2011). This could create bias because the older subjects may be more likely to have diseases, and an altered lung function, and thus might have contributed to higher prevalence of bronchitis symptoms and diseases which are age dependent, in this study bronchitis and COPD. However, by performing the analyses stratified by age, and by using multivariate risk analyses correcting for age, this kind of bias could be controlled.

A limitation of the study was the lack of objective measurements regarding smoking habits, such as measures of cotinine in urine or blood.

30

Questionnaire and structured interview

Most questions used in the questionnaire are well validated in several studies in developed countries all over the world, and the whole questionnaire is well validated in studies in northern Europe (Lundback et al., 2001; Pallasaho et al., 2006). Further, the question about physician-diagnosed asthma and asthma symptoms have been evaluated by some detailed systematic reviews (Samet, 1987; Toren et al., 1993). However, no validation studies have been performed in Vietnam, and as far as the author of this thesis now, not in south-east Asia. Differences in language can cause bias because of both translation and interpretation. The questionnaire was translated from English into Vietnamese and back to English before the printing of the final version. This might reduce misunderstanding and bias caused by translation. The population in Europe is familiar with the symptoms and diseases addressed by the questions in the questionnaire. However, the fully understanding of these questions may not have been easy for the Vietnamese people. The difference between the terms of symptoms and diseases may have created confusion. An example of this is the results of the prevalence of wheeze.

According to several population studies, 'wheezing' is the most common symptom among asthma patients (Lotvall et al., 2009; Lundback et al., 1991; Pallasaho et al., 1999). The prevalence of wheeze in the questionnaire survey was very low and similar to the prevalence of asthma. This result yielded a suspicion of misunderstanding of the term by the participants. The prevalence of 'any wheeze during the last 12 months' obtained from the structured interview at the clinical examination was three times higher compared to the questionnaire survey result. Also the questions about family history of asthma and allergic rhinitis, respectively, caused confusion as several subjects also included themselves when answering the question. This has created the unexpected strong association of asthma and symptoms common in asthma with family history of asthma. Thus data about family history of disease have not been used in other papers than paper 1.

Recall bias, a common type of information bias, might have contributed to our study. The way to frame the time in the questionnaire such as 'last 12 months', 'last year' could prevent this kind of bias. At the clinical examinations, the research team came from a big university and a big hospital. That may have attracted more attention among the participants. Furthermore, the clinical examinations including skin prick and lung function testing together with the structured interview might have contributed to the understanding of several questions, particularly of questions asking about occasional symptoms. This could at least in part explain why the prevalence of symptoms obtained at the clinical examinations was higher than at the initial questionnaire survey.

The structured interview at the clinical examinations was conducted by the well trained research team, however with some exceptions. In Bavi, some of the field workers who conducted the first questionnaire part of the study contributed to the data collection by performing some of the structured interviews after being

carefully trained. Nevertheless, the use of field workers may have caused some inter-observer or information bias. On the other hand, FilaBavi is a field laboratory of Hanoi Medical University, and the staff of Fila Bavi has actively participated in several other similar studies. As the study was conducted all around the year in the two areas, seasonal bias of importance might not be a problem.

Skin prick testing

The results of skin prick testing (SPT) depend on the potency of the allergen extracts, the cut off limits for defining a positive test, and the techniques used. The SPT followed the guidelines of the European Academy of Allergy and Clinical Immunology, EAACI (Dreborg et al., 1989). The hot and high humidity climate in Vietnam causes a lot of sweating on the skin, why drawing of the results could cause difficulties in some subjects. Individual results could thus be biased caused by inexact measuring of the diameter of the weal. Further, the research team who performed the SPT was not exactly the same in Bavi as in Hoankiem. However, all who conducted the SPT were trained and were familiar with the techniques of performing SPT, which thus minimized the possibility of creating bias.

Vietnam has no pollen mapping why it was difficult for the research team to adequately decide which pollen allergens that should be included in the test panel. The choice of German cockroach instead of American cockroach may have resulted in an underestimation of sensitization to cockroach. American cockroach is the predominant species in tropical countries with high temperature and humidity (Arruda et al., 2001). This has been discussed in the discussion of main results.

Lung function and methacholine testing

The lung function measurements were performed following the American ATS recommendations (Laszlo, 2006). The same equipments were used throughout the study, and the two spirometers were calibrated daily. The well trained research team performed all spirometric measurements which minimized a possible inter-observer bias.

Most participants in our study had never done lung function testing before. The research team encouraged the participants to do their very best when performing the test. Despite that, some bias may have occurred regarding mainly forced vital capacity, as some participants may have presented an incomplete blowing out. An eventual bias caused by that may have resulted in an underestimation of the prevalence of COPD. A detailed control of the lung function test results by the supervisors resulted in further training of the research team, and the technique became better. All subjects who failed in performing the lung function test with an acceptable technique were re-invited for a new test, and 50 subjects had to re-do

the test. If they did not attend or could not present a test with an acceptable technique, their test results were deleted.

The methacholine challenge testing was performed following a method develop by the OLIN studies in northern Sweden (Lundback et al., 1993). All methacholine tests were conducted by only four persons from the research team, thus minimizing possibilities of inter-observer bias. As the test was time consuming, some subjects interrupted the test or refused to do the test why the participation rate at the methacholine testing became not optimal.

DISCUSSION OF MAIN RESULTS

Our study was the first large scale-study about respiratory symptoms and diseases including allergic sensitization performed among adults in rural and urban northern Vietnam. The aim of this epidemiological study was to estimate the prevalence of respiratory symptoms and diseases, such as allergic rhinitis, asthma, chronic bronchitis and COPD, and also of allergic sensitization. Further aims include studies of risk factors for the conditions including smoking. The questionnaires and protocols were based on validated questionnaires and protocols concerning respiratory conditions and smoking habits that have been conducted mainly in Europe. Some modifications of the methods were needed in order to make the study possible to be conducted in Vietnam.

Participation

The number of subjects that were not possible to trace was high in the urban area. The Hanoi city population register is not regularly updated, and information about inhabitants who have moved, changed address, or have deceased, is often not available. Nearly 1000 subjects who lived in two wards or areas located outside the Red River dyke system in Hoankiem were excluded, as a large proportion of them were not possible to trace.

The large variation in participation rates between different countries and study centers may be a result of different cultural and societal attitudes. The response rate in the questionnaire part of the study was 82.5%, which corresponds closely to the 90.5% and 77.6% response rates of the northern Sweden and Estonia studies, respectively (Lundback et al., 1991; Meren et al., 2001). However, the participation rate at the clinical examinations was lower, 46.5%, compared to studies performed in northern Europe (Lundback et al., 1993; Pallasaho et al., 2006; Kotaniemi et al., 2005). Our low participation rate may partly be a consequence of the fact that most clinical examinations were performed during weekends. At weekends, the study subjects, most of them healthy, might prefer to relax or to do private activities rather than go to health care centers for participation in a study. The distance from their homes to the health care centers was another obstacle, especially in some villages in the mountain area, since the transport system has limitations. Furthermore, not all subjects had access to a telephone, so it was not possible to remind them about the date of the clinical examination. This might have contributed to the low participation rate. In addition, the tests were time consuming and perceived complicated, why some subjects refused to attend.

In the first part of the study, the questionnaire survey, no difference in the participation rate was observed regarding sex and age, a result in line with studies in northern Sweden in 1980s (Lundback et al., 1991). In the clinical examinations,

34

women and older subjects participated generally more frequently, as was the case in health surveys in northern Europe (Bjornsson et al., 1994; Meren et al., 2001; Warm et al., 2011).

Smoking

Among Vietnamese men, 61% were current smokers. The prevalence of smoking among men in Vietnam was the highest in the Asia Pacific region, since the prevalence of current smoking among men in China, Thailand and Cambodia was 53%, 42%, and 48%, respectively (Li et al., 2011; Mekrungrongwong et al., 2011; Singh et al., 2009). Luckily, women's tobacco use is currently still much lower than it is for men. This reflects the social, cultural, and traditional beliefs that discourage them from smoking. Still being influenced by the traditional values, the Vietnamese do not easily accept the image of a smoking woman. The validity of the reported smoking prevalence in women might, however, be far from true. Following a study in Korea using urinary cotinine concentrations to define smokers, the number of self-reported female smokers was less than a half of cotinine verified smokers (Jung-Choi et al., 2011). However, the prevalence of smoking among women in Asia is following the western trend, with more women take up smoking while men quit. Smoking among the youth in Malaysia increased from 5% in 1996 to 8% in 1999 and to 17% in 2009 (Abdulah, 1999; Al-Naggar et al., 2011).

Tobacco smoking is by far the most important risk factor for most respiratory conditions. Active smoking has been identified as the major causal risk factor for the development of COPD (GOLD, 2010). As expected, the prevalence of COPD in or study was associated with smoking. Fifty percent of smoking men over the age of 60 years fulfilled the spirometric criteria of COPD, results in line with studies conducted in USA and Europe (Kotaniemi et al., 2005; Lundback et al., 2003; Stang et al., 2000). Further, the prevalence of COPD increased with the number of cigarettes consumed, also this result was similar to other studies (Schirnhofer et al., 2007). Respiratory symptoms were also significantly associated with smoking. Also this result was in line with other studies (Lindstrom et al., 2001; Lundback et al., 1991). The relatively high prevalence of longstanding cough and sputum production might reflect the burden of smoking habits in the Vietnamese population.

Asthma and chronic bronchitis were also associated with smoking. The prevalence of these diseases was relatively high among ex-smokers, even though the number of ex-smokers was low. Regarding asthma, this result is in accordance with results from several cross-sectional and other studies (E. Ronmark et al., 1997). Probably the smokers quit smoking after having developed respiratory symptoms. After smoking cessation, the decline in FEV_1 levels off but without a return of FEV_1 to the basal levels (Fletcher & Peto, 1977). There is a clear evidence from the US Lung Health Study that smoking cessation modifies the decline in lung function (Au et al., 2009). That study clearly showed smoking to be a modifiable risk factor for morbidity and mortality. The US Lung Health Study showed further that by quitting early, lives can be saved. Smoking cessation is of proven benefit at any age, but the benefits are greatest for those who stop smoking before the age of 35 years.

Asthma

The burden of asthma and AR is recognized as an important public health problem. The Global Initiative for Asthma (GINA) reports adult asthma prevalence ranging from 5-18% all over the world (GINA, 2010). AR is even more common than asthma and affects 10-20% or even more of the population worldwide (Bousquet et al., 2008).

The prevalence of ever having had asthma was reported higher in urban Hoankiem than rural Bavi, 5.6% *vs.* 3.9% (p =0.003). Similarly, the prevalence of AR was reported three times higher in urban Hoankiem than in rural Bavi, 29.6% *vs.* 10.0% (p<0.001). This very large reported difference will be discussed later in this part of the thesis. Furthermore, living on a farm for the first year of life yielded a lower prevalence of AR compared to those who had not. This result might refer to the increase in allergic diseases associated with urban living. The differences in prevalence of allergic disease between urban and rural areas have been observed in many parts of the world. In a developing country, Mongolia, a low prevalence of allergies was found in rural areas and an increase in prevalence was found parallel to increasing urbanization (Viinanen et al., 2005). Other studies have also pointed out that populations living in rural areas experience a low burden of allergic diseases (Cingi et al., 2005). Such studies offer an excellent framework to investigate the potential risks on one hand and protective factors on the other.

There are several factors related to urban living that may increase the prevalence of allergic diseases. These factors include exposure to outdoor and indoor air pollution and sensitization to several allergens such as cockroach, dust mite, mouse, and rat allergens (Gunnbjornsdottir et al., 2009; Nicolaou et al., 2005). Air pollution is a consequence of industrialization and urbanization, largely caused by emissions from transportation, manufacturing, and power production. Air pollution adversely affects the entire population living in urban settings. Above that there are subgroups that have increased susceptibility to the adverse effects of poor air quality. Among others, the findings of a study suggested that even at low concentrations, indoor pollutants could be of importance in asthma. The authors also showed that urban dwellings were found to be more polluted than rural ones (Hulin et al., 2010). The hygiene hypothesis theory is used for trying to explain the difference in prevalence of allergic diseases between urban and rural areas (Bloomfield et al., 2006).

In studies of prevalence of asthma during the 1980s and early 1990s among adults in Europe, the estimates of prevalence were of similar magnitude as in our study that was performed 15-20 years later than these studies. In northern Sweden the prevalence in mid 1980s was 5% (Lundback et al., 1991) and in southern Sweden in 1992 the corresponding prevalence was around 6% (Montnemery et al., 1998). In Italy in mid 1980s the corresponding prevalence was on a similar level (Paoletti et al., 1989), and also in Australia 5-6% of adults had asthma during that time period (Woolcock et al., 2001). In early 1990s the European Community Respiratory Health Survey (ECHRS) found the asthma prevalence varying from 1% in East-Germany up to 11-13% in Australia and New Zealand (Janson et al.,

1997). Later on, a higher prevalence, 8-10%, of adult asthma has been reported from several developed countries including Sweden (Ekerljung et al., 2010b; Lotvall et al., 2009).

After the millennium shift, high prevalence of asthma has been reported also from some countries in south-east Asia. In one study from Thailand, 11.6% were identified as having physician's diagnosed asthma (Uthaisangsook, 2010). Compared to other studies in Pacific Asia performed in 1990s, such as in China and Singapore, the prevalence of asthma in our study was higher (Chan-Yeung et al., 2002; Ng, 1999). A study in Dalat, a highland city in southern Vietnam, found the prevalence of asthma and asthma like symptoms to be rather low, 2.4% (Sy et al., 2007). The above results confirmed that the prevalence of asthma varies between countries and also between areas within countries, and further, that the prevalence in south-east Asian countries (Quah et al., 2005) nowadays reach the same level as in Europe and Australia 15-20 years ago. However, different methods and definitions make comparisons difficult.

Allergic rhinitis

The prevalence of AR in urban Hoankiem was close to 30%. This result was as high as in several developed countries. A cross sectional survey based on an adult French general population sample showed that the overall prevalence of AR was 31% (Klossek et al., 2009). A recently estimated prevalence of AR both in Gothenburg and Stockholm, Sweden was 28% (Eriksson et al., 2011). Also in Bangkok, Thailand, using the ISAAC questionnaire among university students, the prevalence of AR was high, 26% (Vichyanond et al., 2002). According to a study in Japan, the prevalence of AR among men was 36% (Sakurai et al., 1998). All the above studies showed the prevalence of AR to be similar to the prevalence of AR in urban Hoankiem in our study. In other areas of east Asia a considerably lower prevalence of AR has been found. For instance a study in South Korea reported the prevalence of AR to vary from 6% to 10% (Park et al., 2009), which is similar to or even lower than the prevalence of 10% in rural Bavi in our study. In a cross-sectional study in 11 major cities in China, the prevalence of self-reported AR was lowest in Beijing, 8.7%, and highest in Urumqi, 24.1%, indicating an inverse result regarding the commonly found urban-rural difference (L. Zhang et al., 2009).

The awareness of AR may be poor in developing countries, and probably even poorer in rural areas such as in Bavi in our study. Vietnam is a tropical country with a high temperature and a high humidity. Common colds caused by viruses happen all around the year. Sneezing, scratchy throat, runny nose are symptoms of common cold that exist normally less than one week. The high prevalence of AR in Hoankiem might partly consist of a number of mild common colds that often are ignored in rural areas. This concern is supported by the rather similar prevalence of rhinitis symptoms, such as runny nose and nasal blocking in both Bavi and Hoankiem.

Allergic sensitization

With the current study, we could present the pattern of allergic sensitization among adults in northern Vietnam. Mite and cockroach were the most important sources of allergic sensitization in northern Vietnam. We found that 29.8% of the subjects were sensitized to any mite or cockroach, and 33.8% had a positive SPT to at least one of the tested allergens. Our study contributed to the findings that mites and cockroach are the most common sensitizers in the world (Ghaffari et al., 2010).

The most common sensitizer in our study was the storage mite, *B. tropicalis* (22.9%), followed by *D. pteronyssinus* (13.3%) and *D. farinae* (10.5%). A previously performed study among schoolchildren in a rural area of the middle part of Vietnam found a similar prevalence of sensitization to house dust mites, 14.4% (Flohr et al., 2006). Our study underlines the importance of allergens from the storage mite families. These allergens have 70% amino acid sequence disparity compared with the Dermatophagoides family, why there is only a minimal IgE cross-reactivity. *B. tropicalis*, found mainly in South America, the Caribbean and in Asia, is the most important mite among the storage mites and usually occurs in conjunction with *D. pteronyssinus.* In a study in Singapore, *B. tropicalis* was the dominating sensitizer determined by SPT in patients with asthma or allergic rhinitis, and 96% of them were sensitized to *B. tropicalis* (Chew et al., 1999). Similarly, sensitization to *B. tropicalis* among allergic patients in Indonesia was high, 72% (Baratawidjaja et al., 1999).

The predominant sensitizers in most countries, *D. pteronyssinus* and *D. farinae* coexist in most geographical regions. *D. pteronyssinus* prefers temperate and tropical coastal regions, whereas *D. farinae* is more abundant in continental climates. The allergens of *D. pteronyssinus* and D.*farinae* typically have 15–20% amino acid sequence disparity but they also have unique epitopes, although they are immunologically cross-reactive. House dust mites are the most common source of allergy all over the world (Akdemir & Yilmaz, 2009). Further, mites are important sources of sensitization to indoor allergens associated with asthma as well as with other allergic conditions including allergic rhino-conjunctivitis and atopic eczema (Y. K. Kim et al., 2002) . In Vietnam, Sy DQ found that 50% of atopic subjects had at least one positive skin prick tests to *D. pteronyssinus, D. farinae, or B. tropicalis* (Sy et al., 2007). In our study, allergic sensitization was significantly associated with AR but less so with asthma even though asthma symptoms were more common among the sensitized subjects.

In regions with poor sanitary or socio-economic conditions, also cockroach is one of the most common indoor allergens. In the United States, the prevalence of allergic sensitization to cockroach range from 21% to 35% among children with asthma depending on rural or urban living (Matsui et al., 2003). In Estonia, the prevalence of sensitization to cockroach was 16% (Raukas-Kivioja et al., 2003). In Thailand, 13% of female high school students had a positive SPT to cockroach (Prasarnphanich & Sindhurat, 2005), moreover, 43% of middle schoolchildren with asthma in Taiwan were sensitized to cockroach (Lin et al., 2002). In our study 13% had a positive SPT to cockroach (*B. germanica*). The same prevalence of sensitization among adults to *B. germanica* species was found in the highland

city of Dalat in Vietnam (Sy et al., 2007). When using another cockroach species, *P. Americana*, the prevalence of sensitization among Vietnamese schoolchildren was 27.6% (Flohr et al., 2006).

There are two common domiciliary cockroach species: *Blattella germanica* (German cockroach) and *Periplaneta americana* (American cockroach). *B. germanica* is a small cockroach that commonly infests houses in United State. *P. Americana* is a bigger cockroach that requires higher temperatures and higher humidity for optimal population growth. In Vietnam, we have not performed any study to explore which domiciliary cockroach is the most common. Based on the climate, the most common species of cockroach is probably the American cockroach. Choosing German cockroach might be the reason to the relatively moderate prevalence of sensitization to cockroach in our study.

In cold and dry areas, such as Finland, northern Sweden and parts of Norway, mites are uncommon, and the most common sensitizers are cat, dog and pollen (Bakken et al., 2007; Pallasaho et al., 2006; E. Ronmark et al., 2009a). In our study, the prevalence of positive SPT to pollen was particularly low, 2.8%. In Malaysia, different pollen allergies were observed in urban areas, but none of 200 subjects with asthma was found to be allergic to pollen alone (Sam et al., 1998). Furthermore, the prevalence of sensitization to pollen in China varied from 0.5 to 5% (Z. G. Liu et al., 2010). However, of asthmatic children in Thailand, 30% were sensitized to different pollens from grasses or trees (Kongpanichkul et al., 1997) Although pollens do not belong to the major sensitizers in the tropical zone where climatic variations are attenuated, sensitization to pollen is thus of clinical importance also in south-east Asia.

Bronchitis and COPD

We found in this population based survey among adults in Hoankiem and Bavi a high prevalence of bronchitis symptoms. The prevalence of bronchitis symptoms, such as longstanding cough and sputum production, was similar to what has been reported in several westernised countries (Lundback et al., 1991; Meren et al., 2001; Pallasaho et al., 1999). This may be related to the smoking prevalence in the society.

Worldwide, COPD is one of the leading causes of chronic morbidity and mortality (GOLD, 2010). In developing countries, chronic respiratory diseases represent a challenge to public health because of their frequency, severity, projected trends and economic impact. Still relatively few population studies on COPD have been conducted in Asia, where the burdens of smoking and the use of biomass fuel for cooking and heating houses are high. Even though there are some well documented studies of COPD in Asia, it is not easy to make comparisons due to the use of different study methods including different age compositions of the study samples, different recruitment strategies and different diagnostic criteria. We found the overall prevalence of COPD in our study to be 7%.

In Austria, a population based survey among adults aged ≥40 years using the BOLD study design and protocol yielded a very high prevalence of COPD, 26%

(Schirnhofer et al., 2007). Following a study in the Philippines also using the BOLD protocol, the prevalence of COPD in rural areas was 21% (Idolor et al., 2011). It is hard to find reasons to the very high prevalence of COPD in Austria. The high prevalence of COPD in Philippines may be a consequence of a high prevalence of previous TBC, high prevalence of smoking, and the common use of wood for cooking. Lower estimates of prevalence of COPD have been reported from Japan, China and South Korea. A study in Japan presented a prevalence of 11% using the GOLD criteria (Fukuchi et al., 2004). A Chinese study found the prevalence of COPD to be 8% (N. Zhong et al., 2007), and in South Korea only 4% were found to have COPD in a population survey (S. J. Kim et al., 2006).
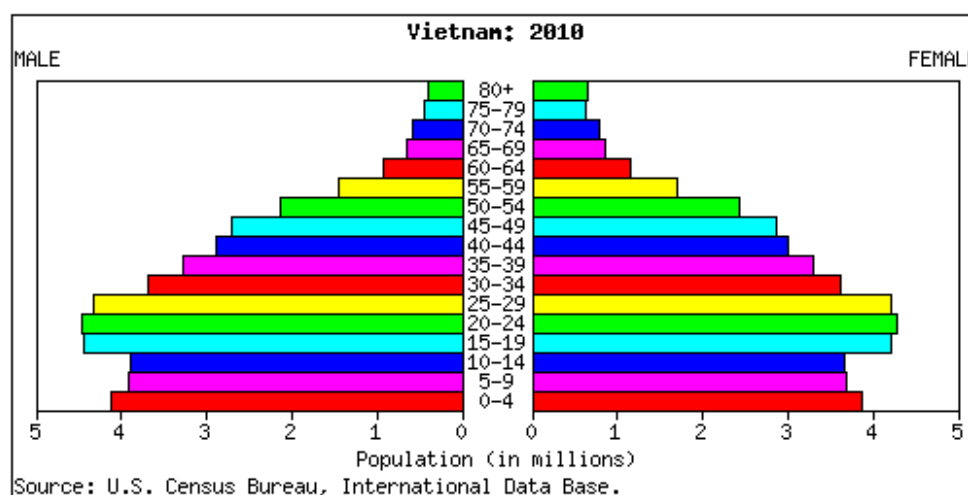
Figure 15. The Vietnamese population pyramid for 2010; distribution by age and sex

Using the GOLD criteria, the prevalence of COPD in Sweden was 14% (Lindberg et al., 2005). The apparently low overall prevalence of COPD in our study, 7%, is due to the very young population of Vietnam (figure 15). When stratified by age, the prevalence of COPD increased considerably by age with 14.6% fulfilling the spirometric GOLD criteria of COPD among those aged >50 years, a result close to identical to what has been found in another study in northern Sweden (Lundback et al., 2003). This finding illustrates the magnitude of the burden that COPD will pose in Vietnam in near future, as the proportion of elderly people in the population is increasing continuously.

The risk for COPD increases considerably with increasing age and cumulative exposure to smoking. Among men older than 60 years in our study, nearly 50% of smokers had developed COPD. This result is in line with other studies in Europe and USA (Lundback et al., 2003; Mannino et al., 2000). Consistent with the present understanding of the role of smoking, as found by others (Schirnhofer et al., 2007), also we found a strong dose-response relationship with pack-years of smoking.

Nevertheless, we also found that 30% of the COPD cases were women, and all of them were non-smokers. These findings suggest that mechanisms or risk factors

40

other than own smoking may play a role in the development of COPD. Using of biomass including wood, dung and crop residues for heating and cooking is widespread in developing countries. There are several studies that have found the use of biomass fuel or solid fuel to be a risk factor for COPD (Hu et al., 2010). This association was mostly attributed to women since they had, and still have, the responsibility for cooking in developing countries. In our study we could not verify this relationship probably due to the small number of COPD cases among women, and further, all women in the rural area were exposed to fume from biomass, and this was the case also for a large proportion of women in the urban area. Furthermore, environmental tobacco smoke may contribute to COPD among Vietnamese women. The smokers in Vietnam are free to smoke inside their homes, and they also smoke inside public places despite the fact that a smoking ban was introduced in 2010.

In our study, the prevalence of respiratory symptoms increased by severity of COPD. Among those with severe and very severe COPD, all had at least one chronic respiratory symptom, a result similar to what was found in the studies in northern Sweden (Lindberg et al., 2006). Similar to European studies (Lindberg et al., 2006; Schirnhofer et al., 2007), also in our study only 35% of subjects with COPD had a previous diagnosis of COPD. It means that the underdiagnosis of COPD is high in Vietnam, however, the underdiagnosis is high worldwide. The results of our study suggest that the prevalence of COPD among smokers in Vietnam is even higher than previously believed. It would be beneficial for all smokers to undergo spirometry testing on an annual basis, and doctors should urge their patients who are smokers to be submitted to such a test. Such screening could make a tremendous difference in the outcome of the disease. Earlier diagnosis through targeted case-finding would allow early, aggressive smoking cessation efforts and might lead to a reduction in the burden of COPD morbidity, and to a reduced impact of the disease on health related quality of life in these patients (Gilljam, 2007). However, spirometry in Vietnam is not performed routinely in medical practice due to lack of specialized technicians, doctors and equipments. It is why most COPD patients cannot be diagnosed early in the disease process.

CONCLUSSIONS

The most common respiratory symptoms in northern Vietnam were long standing cough and sputum production. The prevalence of ever having had asthma was higher in the urban area compared to the rural, 5.6% vs. 3.9%, p=0.003. Also chronic bronchitis ever, 6.2% vs. 4.6%, p=0.005, was more common in the urban area. Among men, 61% were current smokers vs. 2.3% among women. Asthma, chronic bronchitis and bronchitis symptoms were all associated with smoking. All respiratory symptoms increased by age.

Self-reported AR was considerably more common in the urban area compared to the rural, 30% vs. 10%, p<0.001. About 50% had either chronic nasal blocking or chronic runny nose. Being women was associated with chronic nasal blocking and chronic runny nose, and living in the urban area was associated with chronic nasal blocking. All respiratory symptoms and diseases were more common among those with allergic rhinitis, chronic nasal blocking and chronic runny nose compared with those not having the nasal conditions.

Among the skin prick tested subjects (age ≤60 years), 34% were sensitized to at least one airborne allergen, and 30% were sensitized to either mites or cockroach. The storage mite, *Blomia tropicalis,* was the main sensitizer followed by house dust mites and cockroach. Pollen and moulds were no major sources of allergic sensitization, and only 2.8% and 1.5%, respectively, were sensitized to these allergens. Allergic sensitization was significantly associated with allergic rhinitis, but less so with asthma. Young age was a risk factor for having a positive SPT to at least one allergen and to sensitization to mites. Exposure to gas, dust or fumes at work yielded an increased risk for sensitization to any mite.

The overall prevalence of COPD was 7.1%, (men 11% vs. women 3.9%, p=0.001) by using the fixed ratio definition of both ERS/ATS standards and the GOLD criteria, and 1.2% had a severe or very severe COPD. COPD was significantly associated with increasing age and among men with smoking, while no women with COPD had ever been a smoker. Among men, COPD was strongly associated with increasing number of pack-years. Among men ≥60 years old, nearly 50% of current smokers had developed COPD.

PERSPECTIVES

When I came to Sweden, I realised that it was a paradise for scientific studies. I have learned a lot not only about research methodology but also about scientific thinking. The way how to conduct a study in Vietnam is in principle more or less similar to methods in other countries. However, when I conducted the study in Vietnam, I found that we still have some difficulties when performing large scale population studies. There are steps that have to be changed. A publication of 'how to perform an epidemiological study of respiratory diseases in Vietnam' would enhance our knowledge about methods that are suitable for use in Vietnam. It would help us to identify weaknesses as well as to clarify strengths of those kinds of the studies.

Detailed information about exposure from indoor use of biomass fuels is important for analysing effects on airway diseases. The burden of smoking among men in Vietnam is enormous resulting in a high environmental tobacco smoke exposure not only on women and children but in the whole society. A publication about passive smoking and respiratory diseases should be written based on the collected data. Furthermore, intervention studies on smoking cessation and smoking prevention programs particularly in school children and teenagers would be important to reduce the risk of developing lung and airway diseases, and also of several other diseases such as cardiovascular diseases and cancer.

There are limited data about the prevalence of airway hyper-reactivity in Vietnam. In this thesis, I have only used parts of the results of hyper-reactivity to methacholine. From the cross-sectional study such results are ready to be analysed and published. An important question that should be answered is whether asthma is underdiagnosed in Vietnam. Thus the association between hyper-reactivity and the diagnosis of asthma in Vietnam deserves to be evaluated.

The results of this thesis were based on cross-sectional data. In future, longitudinal studies of relevant populations are required to know incidence of disease and for calculation of valid risks. Large studies are required to ensure that the associations can be explained by risk, rather than by chance.

ACKNOWLEDGEMENTS

I thank my brothers in law and my dear sisters for taking care of our Daddy when I was not at home. I thank my parents in law for taking care of my family and my children when I have been abroad.

To my Daddy and my Mommy since long gone, I want to say thank you for growing up me in a loving environment. You always done for the best things and guided me on a right path. Thank you for accepting me exactly as I am. More than anything, I want you to know how much I love you.

Last, but not least, many thanks to my family. My husband, Nguyễn Vũ Trung, thank for being such a great husband and father and making it so easy for me to stay in touch with the most loving side of myself. Thank you for taking care of our family when I was abroad for the PhD studies. Thank for your huge knowledge of IT and willingness to help me always when needed. Kiên and Phú, my lovely boys, thank you for showing up in my life and brightening it by funny things, sweet smiles and nice words. It was hard to live without Mom or Dad, I knew that. Many thanks to both of you for your understanding and patience with me. I love you so much. How great it would be to carry our love with us and maintain it powerfully forever.

REFERENCES

AAAAI (2009). Allergy and asthma statistics. *http://www.aaaai.org/media/statistics/*.

Abdulah, S. (1999). National Health Morbidity Survey: Healthrisk behavior among adolescents. *Ministry of Health in Malaysia*.

Akdemir, C., & Yilmaz, S. (2009). Sensitization to house-dust mite and mite fauna in selected children's homes in Kutahya, Turkey. *Turk J Pediatr,* 51, 232-237.

Al-Naggar, R.A., Al-Dubai, S.A., Al-Naggar, T.H., Chen, R., & Al-Jashamy, K. (2011). Prevalence and of smoking and associated factors among Malaysian University students. *Asian Pac J Cancer Prev,* 12, 619-624.

Almqvist, C., Pershagen, G., & Wickman, M. (2005). Low socioeconomic status as a risk factor for asthma, rhinitis and sensitization at 4 years in a birth cohort. *Clin Exp Allergy,* 35, 612-618.

Arruda, L.K., Vailes, L.D., Ferriani, V.P., Santos, A.B., Pomes, A., & Chapman, M.D. (2001). Cockroach allergens and asthma. *J Allergy Clin Immunol,* 107, 419-428.

Asher, M.I., Montefort, S., Bjorksten, B., Lai, C.K., Strachan, D.P., Weiland, S.K., et al. (2006). Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet,* 368, 733-743.

Au, D.H., Bryson, C.L., Chien, J.W., Sun, H., Udris, E.M., Evans, L.E., et al. (2009). The effects of smoking cessation on the risk of chronic obstructive pulmonary disease exacerbations. *J Gen Intern Med,* 24, 457-463.

Bakken, H.N., Nafstad, P., Bolle, R., & Nystad, W. (2007). Skin sensitization in school children in northern and southern Norway. *J Asthma,* 44, 23-27.

Baratawidjaja, I.R., Baratawidjaja, P.P., Darwis, A., Soo-Hwee, L., Fook-Tim, C., Bee-Wah, L., et al. (1999). Prevalence of allergic sensitization to regional inhalants among allergic patients in Jakarta, Indonesia. *Asian Pac J Allergy Immunol,* 17, 9-12.

Basagana, X., Sunyer, J., Kogevinas, M., Zock, J.P., Duran-Tauleria, E., Jarvis, D., et al. (2004). Socioeconomic status and asthma prevalence in young adults: the European Community Respiratory Health Survey. *Am J Epidemiol,* 160, 178-188.

Bauchau, V., & Durham, S.R. (2004). Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J,* 24, 758-764.

Biino, G., Rezzani, C., Grassi, M., & Marinoni, A. (2000). ECRHS screening questionnaire scoring: a methodological suggestion for asthma assessment. European Community Health Survey. *J Outcome Meas,* 4, 740-762.

Bjerg, A., Hedman, L., Perzanowski, M.S., Platts-Mills, T., Lundback, B., & Ronmark, E. (2007). Family history of asthma and atopy: in-depth

analyses of the impact on asthma and wheeze in 7- to 8-year-old children. *Pediatrics,* 120, 741-748.

Bjornsson, E., Plaschke, P., Norrman, E., Janson, C., Lundback, B., Rosenhall, A., et al. (1994). Symptoms related to asthma and chronic bronchitis in three areas of Sweden. *Eur Respir J,* 7, 2146-2153.

Bloomfield, S.F., Stanwell-Smith, R., Crevel, R.W., & Pickup, J. (2006). Too clean, or not too clean: the hygiene hypothesis and home hygiene. *Clin Exp Allergy,* 36, 402-425.

Bouayad, Z., Aichane, A., Afif, A., Benouhoud, N., Trombati, N., Chan-Yeung, M., et al. (2006). Prevalence and trend of self-reported asthma and other allergic disease symptoms in Morocco: ISAAC phase I and III. *Int J Tuberc Lung Dis,* 10, 371-377.

Bousquet, J., Burney, P.G., Zuberbier, T., Cauwenberge, P.V., Akdis, C.A., Bindslev-Jensen, C., et al. (2009). GA2LEN (Global Allergy and Asthma European Network) addresses the allergy and asthma 'epidemic'. *Allergy,* 64, 969-977.

Bousquet, J., Khaltaev, N., Cruz, A.A., Denburg, J., Fokkens, W.J., Togias, A., et al. (2008). Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy,* 63 (Suppl 86), 8-160.

Brannan, J.D. (2010). Bronchial hyperresponsiveness in the assessment of asthma control: Airway hyperresponsiveness in asthma: its measurement and clinical significance. *Chest,* 138, 11S-17S.

Burney, P.G., Luczynska, C., Chinn, S., & Jarvis, D. (1994). The European Community Respiratory Health Survey. *Eur Respir J,* 7, 954-960.

Busse, W.W. (2010). The relationship of airway hyperresponsiveness and airway inflammation: Airway hyperresponsiveness in asthma: its measurement and clinical significance. *Chest,* 138, 4S-10S.

Celli, B.R., & MacNee, W. (2004). Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J,* 23, 932-946.

Chan-Yeung, M., Zhan, L.X., Tu, D.H., Li, B., He, G.X., Kauppinen, R., et al. (2002). The prevalence of asthma and asthma-like symptoms among adults in rural Beijing, China. *Eur Respir J,* 19, 853-858.

Chew, F.T., Lim, S.H., Goh, D.Y., & Lee, B.W. (1999). Sensitization to local dust-mite fauna in Singapore. *Allergy,* 54, 1150-1159.

Chuc, N.T., & Diwan, V. (2003). FilaBavi, a demographic surveillance site, an epidemiological field laboratory in Vietnam. *Scand J Public Health Suppl,* 62, 3-7.

Cingi, C., Cakli, H., Us, T., Akgun, Y., Kezban, M., Ozudogru, E., et al. (2005). The prevalence of allergic rhinitis in urban and rural areas of Eskisehir-Turkey. *Allergol Immunopathol (Madr),* 33, 151-156.

Cockcroft, D.W. (2010). Direct challenge tests: Airway hyperresponsiveness in asthma: its measurement and clinical significance. *Chest,* 138, 18S-24S.

Cruz, A.A., Popov, T., Pawankar, R., Annesi-Maesano, I., Fokkens, W., Kemp, J., et al. (2007). Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA(2)LEN. *Allergy,* 62 Suppl 84, 1-41.

Curotto de Lafaille, M.A., Lafaille, J.J., & Graca, L. (2010). Mechanisms of tolerance and allergic sensitization in the airways and the lungs. *Curr Opin Immunol,* 22, 616-622.

Dejsomritrutai, W., Nana, A., Chierakul, N., Tscheikuna, J., Sompradeekul, S., Ruttanaumpawan, P., et al. (2006). Prevalence of bronchial hyperresponsiveness and asthma in the adult population in Thailand. *Chest,* 129, 602-609.

Dreborg, S., Backman, A., Basomba, A., Bousquet, J., & Malling, D. (1989). Skin tests used in type 1 allergy testing. Position paper of European Academy of Allergology and Clinical Immunology *Allergy,* 44 (Suppl 10), 1-59.

Ebert, C.S., Jr., & Pillsbury, H.C., 3rd (2011). Epidemiology of allergy. *Otolaryngol Clin North Am,* 44, 537-548, vii.

ECRHS (1996). Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J,* 9, 687-695.

Eisner, M.D., Blanc, P.D., Omachi, T.A., Yelin, E.H., Sidney, S., Katz, P.P., et al. (2011). Socioeconomic status, race and COPD health outcomes. *J Epidemiol Community Health,* 65, 26-34.

Ekerljung, L., Andersson, A., Sundblad, B.M., Ronmark, E., Larsson, K., Ahlstedt, S., et al. (2010a). Has the increase in the prevalence of asthma and respiratory symptoms reached a plateau in Stockholm, Sweden? *Int J Tuberc Lung Dis,* 14, 764-771.

Ekerljung, L., Sundblad, B.M., Ronmark, E., Larsson, K., & Lundback, B. (2010b). Incidence and prevalence of adult asthma is associated with low socio-economic status. *Clin Respir J,* 4, 147-156.

Eriksson, J., Ekerljung, L., Pullerits, T., Holmberg, K., Ronmark, E., Lotvall, J., et al. (2011). Prevalence of chronic nasal symptoms in West Sweden: risk factors and relation to self-reported allergic rhinitis and lower respiratory symptoms. *Int Arch Allergy Immunol,* 154, 155-163.

Farfel, A., Tirosh, A., Derazne, E., Garty, B.Z., & Afek, A. (2010). Association between socioeconomic status and the prevalence of asthma. *Ann Allergy Asthma Immunol,* 104, 490-495.

Fletcher, C., & Peto, R. (1977). The natural history of chronic airflow obstruction. *Br Med J,* 1, 1645-1648.

Flohr, C., Tuyen, L.N., Lewis, S., Quinnell, R., Minh, T.T., Liem, H.T., et al. (2006). Poor sanitation and helminth infection protect against skin sensitization in Vietnamese children: A cross-sectional study. *J Allergy Clin Immunol,* 118, 1305-1311.

Franzese, C.B., & Burkhalter, N.W. (2010). The patient with allergies. *Med Clin North Am,* 94, 891-902.

Fukuchi, Y., Nishimura, M., Ichinose, M., Adachi, M., Nagai, A., Kuriyama, T., et al. (2004). COPD in Japan: the Nippon COPD Epidemiology study. *Respirology,* 9, 458-465.

Fuller, T. (2007). Air pollution fast becoming an issue in booming Vietnam. *The New York Times*, July 6.

Ghaffari, J., Khademloo, M., Saffar, M.J., Rafiei, A., & Masiha, F. (2010). Hypersensitivity to house dust mite and cockroach is the most common allergy in north of Iran. *Iran J Immunol,* 7, 234-239.

Gilljam, H. (2007). Smoking cessation the most important causal treatment in COPD. *Lakartidningen*, 104 (13), 1047-1049.

GINA (2010). Global initiative for asthma (GINA). *Available from* *http://www.ginasthma.org* 3.

GOLD (2010). Global Initiative for chronic obstructive lung disease. *Available from http://www.goldcopd.org*, 7-12.

Gunnbjornsdottir, M.I., Norback, D., Bjornsson, E., Soon, A., Jarvis, D., Jogi, R., et al. (2009). Indoor environment in three North European cities in relationship to atopy and respiratory symptoms. *Clin Respir J,* 3, 85-94.

Hargreave, F.E., Dolovich, J., O'Byrne, P.M., Ramsdale, E.H., Daniel, E.E. (1986). The origin of airway hyperresponsiveness. *J Allergy Clin Immunol*, 78(5), 825-832.

Hedlund, U., Ronmark, E., Eriksson, K., Lundback, B., & Jarvholm, B. (2008). Occupational exposure to dust, gases and fumes, a family history of asthma and impaired respiratory health. *Scand J Work Environ Health,* 34, 381-386.

Hu, G., Zhou, Y., Tian, J., Yao, W., Li, J., Li, B., et al. (2010). Risk of COPD from exposure to biomass smoke: a metaanalysis. *Chest,* 138, 20-31.

Hulin, M., Caillaud, D., & Annesi-Maesano, I. (2010). Indoor air pollution and childhood asthma: variations between urban and rural areas. *Indoor Air,* 20, 502-514.

Idolor, L.F., TS, D.E.G., Francisco, N.A., Roa, C.C., Ayuyao, F.G., Tady, C.Z., et al. (2011). Burden of obstructive lung disease in a rural setting in the Philippines. *Respirology,* 16, 1111-1118.

Janson, C., Chinn, S., Jarvis, D., & Burney, P. (1997). Physician-diagnosed asthma and drug utilization in the European Community Respiratory Health Survey. *Eur Respir J,* 10, 1795-1802.

Jenkins, C.N., Dai, P.X., Ngoc, D.H., Kinh, H.V., Hoang, T.T., Bales, S., et al. (1997). Tobacco use in Vietnam. Prevalence, predictors, and the role of the transnational tobacco corporations. *JAMA,* 277, 1726-1731.

Jensen-Jarolim, E., & Untersmayr, E. (2008). Gender-medicine aspects in allergology. *Allergy,* 63, 610-615.

Jung-Choi, K.H., Khang, Y.H., & Cho, H.J. (2011). Hidden female smokers in Asia: a comparison of self-reported with cotinine-verified smoking prevalence rates in representative national data from an Asian population. *Tob Control*.

Juusela, M., Poussa, T., Kotaniemi, J., Lundback, B., & Sovijarvi, A. (2008). Bronchial hyperresponsiveness in a population of north Finland with no previous diagnosis of asthma or chronic bronchitis assessed with histamine and methacholine tests. *Int J Circumpolar Health,* 67, 308-317.

Karmaus, W., Dobai, A.L., Ogbuanu, I., Arshard, S.H., Matthews, S., & Ewart, S. (2008). Long-term effects of breastfeeding, maternal smoking during pregnancy, and recurrent lower respiratory tract infections on asthma in children. *J Asthma,* 45, 688-695.

Kelly, F.J., & Fussell, J.C. (2011). Air pollution and airway disease. *Clin Exp Allergy,* 41, 1059-1071.

Kim, H., & Bernstein, J.A. (2009). Air pollution and allergic disease. *Curr Allergy Asthma Rep,* 9, 128-133.

Kim, S.J., Suk, M.H., Choi, H.M., Kimm, K.C., Jung, K.H., Lee, S.Y., et al. (2006). The local prevalence of COPD by post-bronchodilator GOLD criteria in Korea. *Int J Tuberc Lung Dis,* 10, 1393-1398.

Kim, Y.K., Chang, Y.S., Lee, M.H., Hong, S.C., Bae, J.M., Jee, Y.K., et al. (2002). Role of environmental exposure to spider mites in the sensitization and the clinical manifestation of asthma and rhinitis in children and

adolescents living in rural and urban areas. *Clin Exp Allergy,* 32, 1305-1309.

Klossek, J.M., Annesi-Maesano, I., Pribil, C., & Didier, A. (2009). [INSTANT: national survey of allergic rhinitis in a French adult population based-sample]. *Presse Med,* 38, 1220-1229.

Knox, R.B., Suphioglu, C., Taylor, P., Desai, R., Watson, H.C., Peng, J.L., et al. (1997). Major grass pollen allergen Lol p 1 binds to diesel exhaust particles: implications for asthma and air pollution. *Clin Exp Allergy,* 27, 246-251.

Kogevinas, M., Zock, J.P., Jarvis, D., Kromhout, H., Lillienberg, L., Plana, E., et al. (2007). Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). *Lancet,* 370, 336-341.

Kongpanichkul, A., Vichyanond, P., & Tuchinda, M. (1997). Allergen skin test reactivities among asthmatic Thai children. *J Med Assoc Thai,* 80, 69-75.

Kotaniemi, J., Sovijarvi, A., & Lundback, B. (2005). Chronic obstructive pulmonary disease in Finland: prevalence and risk factors. *COPD,* 2, 331-339.

Kynyk, J.A., Mastronarde, J.G., & McCallister, J.W. (2011). Asthma, the sex difference. *Curr Opin Pulm Med,* 17, 6-11.

Laszlo, G. (2006). Standardisation of lung function testing: helpful guidance from the ATS/ERS Task Force. *Thorax,* 61, 744-746.

Lee, Y.L., Hwang, B.F., Lin, Y.C., & Guo, Y.L. (2007). Time trend of asthma prevalence among school children in Taiwan: ISAAC phase I and III surveys. *Pediatr Allergy Immunol,* 18, 188-195.

Li, Q., Hsia, J., & Yang, G. (2011). Prevalence of smoking in China in 2010. *N Engl J Med,* 364, 2469-2470.

Lin, Y.C., Su, H.J., Hsiue, T.R., Lee, C.H., Chen, C.W., & Guo, Y.L. (2002). Levels of house dust mite-specific IgE and cockroach-specific IgE and their association with lower pulmonary function in Taiwanese children. *Chest,* 121, 347-353.

Lindberg, A., Bjerg, A., Ronmark, E., Larsson, L.G., & Lundback, B. (2006). Prevalence and underdiagnosis of COPD by disease severity and the attributable fraction of smoking Report from the Obstructive Lung Disease in Northern Sweden Studies. *Respir Med,* 100, 264-272.

Lindberg, A., Jonsson, A.C., Ronmark, E., Lundgren, R., Larsson, L.G., & Lundback, B. (2005). Prevalence of chronic obstructive pulmonary disease according to BTS, ERS, GOLD and ATS criteria in relation to doctor's diagnosis, symptoms, age, gender, and smoking habits. *Respiration,* 72, 471-479.

Lindgren, A., Stroh, E., Nihlen, U., Montnemery, P., Axmon, A., & Jakobsson, K. (2009). Traffic exposure associated with allergic asthma and allergic rhinitis in adults. A cross-sectional study in southern Sweden. *Int J Health Geogr,* 8, 25.

Lindstrom, M., Kotaniemi, J., Jonsson, E., & Lundback, B. (2001). Smoking, respiratory symptoms, and diseases : a comparative study between northern Sweden and northern Finland: report from the FinEsS study. *Chest,* 119, 852-861.

Liu, S., Zhou, Y., Wang, X., Wang, D., Lu, J., Zheng, J., et al. (2007). Biomass fuels are the probable risk factor for chronic obstructive pulmonary disease in rural South China. *Thorax,* 62, 889-897.

Liu, Z.G., Song, J.J., & Kong, X.L. (2010). A study on pollen allergens in China. *Biomed Environ Sci,* 23, 319-322.

Lotvall, J., Ekerljung, L., Ronmark, E.P., Wennergren, G., Linden, A., Ronmark, E., et al. (2009). West Sweden Asthma Study: prevalence trends over the last 18 years argues no recent increase in asthma. *Respir Res,* 10, 94. (E-pub: October 12)

Lundback, B., Lindberg, A., Lindstrom, M., Ronmark, E., Jonsson, A.C., Jonsson, E., et al. (2003). Not 15 but 50% of smokers develop COPD?--Report from the Obstructive Lung Disease in Northern Sweden Studies. *Respir Med,* 97, 115-122.

Lundback, B., Ronmark, E., Jonsson, E., Larsson, K., Sandstrom, T. (2001). Incidence of physician-diagnosed asthma in adults--a real incidence or a result of increased awareness? Report from The Obstructive Lung Disease in Northern Sweden Studies. *Respir Med*, 95 (8), 685-692.

Lundback, B., Nystrom, L., Rosenhall, L., & Stjernberg, N. (1991). Obstructive lung disease in northern Sweden: respiratory symptoms assessed in a postal survey. *Eur Respir J,* 4, 257-266.

Lundback, B., Stjernberg, N., Rosenhall, L., Lindstrom, M., Jonsson, E., & Andersson, S. (1993). Methacholine reactivity and asthma. Report from the Northern Sweden Obstructive Lung Disease Project. *Allergy,* 48, 117-124.

Mannino, D.M., & Buist, A.S. (2007). Global burden of COPD: risk factors, prevalence, and future trends. *Lancet,* 370, 765-773.

Mannino, D.M., Gagnon, R.C., Petty, T.L., & Lydick, E. (2000). Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988-1994. *Arch Intern Med,* 160, 1683-1689.

Matsui, E.C., Wood, R.A., Rand, C., Kanchanaraksa, S., Swartz, L., Curtin-Brosnan, J., et al. (2003). Cockroach allergen exposure and sensitization in suburban middle-class children with asthma. *J Allergy Clin Immunol,* 112, 87-92.

Mekrungrongwong, S., Nakamura, K., Kizuki, M., Morita, A., Somkotra, T., Seino, K., et al. (2011). Great inclination to smoke among younger adults coming from low-socioeconomic class in Thailand. *Int Arch Med,* 4, 29.

Meren, M., Jannus-Pruljan, L., Loit, H.M., Polluste, J., Jonsson, E., Kiviloog, J., et al. (2001). Asthma, chronic bronchitis and respiratory symptoms among adults in Estonia according to a postal questionnaire. *Respir Med,* 95, 954-964.

Milenkovic, B., Mitic-Milikic, M., Rebic, P., Vukcevic, M., Dudvarski-Ilic, A., Nagorni-Obradovic, L., et al. (2011). Asthma and chronic bronchitis symptoms among adult population of Belgrade. *Srp Arh Celok Lek,* 139, 149-154.

Montnemery, P., Adelroth, E., Heuman, K., Johannisson, A., Johansson, S.A., Lindholm, L.H., et al. (1998). Prevalence of obstructive lung diseases and respiratory symptoms in southern Sweden. *Respir Med,* 92, 1337-1345.

Nathan, R.A., Meltzer, E.O., Derebery, J., Campbell, U.B., Stang, P.E., Corrao, M.A., et al. (2008). The prevalence of nasal symptoms attributed to allergies in the United States: findings from the burden of rhinitis in an America survey. *Allergy Asthma Proc,* 29, 600-608.

Ng, T.P. (1999). Adult asthma prevalence, morbidity and mortality and their relationships with environmental and medical care factors in Singapore. *Asian Pac J Allergy Immunol,* 17, 127-135.

Nga, N.N., Chai, S.K., Bihn, T.T., Redding, G., Takaro, T., Checkoway, H., et al. (2003). ISAAC-based asthma and atopic symptoms among Ha Noi school children. *Pediatr Allergy Immunol,* 14, 272-279.

Nicolaou, N., Siddique, N., & Custovic, A. (2005). Allergic disease in urban and rural populations: increasing prevalence with increasing urbanization. *Allergy,* 60, 1357-1360.

Nimmagadda, S.R., & Evans, R., 3rd (1999). Allergy: etiology and epidemiology. *Pediatr Rev,* 20, 111-115; quiz 116.

Norrman, E., Plaschke, P., Bjornsson, E., Rosenhall, L., Lundback, B., Jansson, C., et al. (1998). Prevalence of bronchial hyper-responsiveness in the southern, central and northern parts of Sweden. *Respir Med,* 92, 480-487.

Ober, C., & Hoffjan, S. (2006). Asthma genetics 2006: the long and winding road to gene discovery. *Genes Immun,* 7, 95-100.

Ober, C., & Yao, T.C. (2011). The genetics of asthma and allergic disease: a 21st century perspective. *Immunol Rev,* 242, 10-30.

Pallasaho, P., Ronmark, E., Haahtela, T., Sovijarvi, A.R., & Lundback, B. (2006). Degree and clinical relevance of sensitization to common allergens among adults: a population study in Helsinki, Finland. *Clin Exp Allergy,* 36, 503-509.

Pallasaho, P., Lundback, B., Laspa, S.L., Jonsson, E., Kotaniemi, J., Jovijarvi, A.R., et al. (1999). Increasing prevalence of asthma but not of chronic bronchitis in Finland? Report from the FinEsS-Helsinki Study. *Respir Med*, 93 (11), 798-809.

Paoletti, P., Carmignani, G., Viegi, G., Carrozzi, L., Bertieri, C., Di Pede, F., et al. (1989). Prevalence of asthma and asthma symptoms in a general population sample of north Italy. *Eur Respir J Suppl,* 6, 527s-531s.

Park, H.S., Choi, G.S., Cho, J.S., & Kim, Y.Y. (2009). Epidemiology and current status of allergic rhinitis, asthma, and associated allergic diseases in Korea: ARIA Asia-Pacific workshop report. *Asian Pac J Allergy Immunol,* 27, 167-171.

Parnia, S., Brown, J.L., & Frew, A.J. (2002). The role of pollutants in allergic sensitization and the development of asthma. *Allergy,* 57, 1111-1117.

Phan, T.P., Ngo, Q.C., & Duong, D.T. (2010). The study of the epidemiology of chronic obstructive pulmonary disease in suburban population of Hanoi city and Bacgiang province, Vietnam. *ERS annual congress abstract,* Barcelona, 2010.

Platts-Mills, T.A., Erwin, E., Heymann, P., & Woodfolk, J. (2005). Is the hygiene hypothesis still a viable explanation for the increased prevalence of asthma? *Allergy,* 60 Suppl 79, 25-31.

Polosa, R., Salvi, S., & Di Maria, G.U. (2002). Allergic susceptibility associated with diesel exhaust particle exposure: clear as mud. *Arch Environ Health,* 57, 188-193.

Prasarnphanich, T., & Sindhurat, S. (2005). Sensitization to common indoor allergens and its association with allergic diseases in Thai female high-school students. *Pediatr Allergy Immunol,* 16, 402-407.

Puccio, F.A., Lynch, N.R., Noya, O., Noda, A., Hagel, I., Lopez, E., et al. (2004). Importance of including Blomia tropicalis in the routine diagnosis of

Venezuelan patients with persistent allergic symptoms. *Allergy,* 59, 753-757.

Quah, B.S., Wan-Pauzi, I., Ariffin, N., & Mazidah, A.R. (2005). Prevalence of asthma, eczema and allergic rhinitis: two surveys, 6 years apart, in Kota Bharu, Malaysia. *Respirology,* 10, 244-249.

Raherison, C., & Girodet, P.O. (2009). Epidemiology of COPD. *Eur Respir Rev,* 18, 213-221.

Raukas-Kivioja, A., Raukas, E., Loit, H.M., Kiviloog, J., Ronmark, E., Larsson, K., et al. (2003). Allergic sensitization among adults in Tallinn, Estonia. *Clin Exp Allergy,* 33, 1342-1348.

Ronmark, E., Bjerg, A., Perzanowski, M., Platts-Mills, T., & Lundback, B. (2009a). Major increase in allergic sensitization in schoolchildren from 1996 to 2006 in northern Sweden. *J Allergy Clin Immunol,* 124, 357-363, 363 e351-315.

Ronmark, E., Lundback, B., Jonsson, E., Jonsson, A.C., Lindstrom, M., & Sandstrom, T. (1997). Incidence of asthma in adults--report from the Obstructive Lung Disease in Northern Sweden Study. *Allergy,* 52, 1071-1078.

Ronmark, E.P., Ekerljung, L., Lotvall, J., Toren, K., Ronmark, E., & Lundback, B. (2009b). Large scale questionnaire survey on respiratory health in Sweden: effects of late- and non-response. *Respir Med,* 103, 1807-1815.

Saenghirunvattana, S., Kongngeon, V., Aeimrrerksiri, B., Jerathamopart, P., Thamakumpee, K., Reechaipichitkul, W., et al. (2001). Chronic obstructive pulmonary diseases in Thailand: incidence, prevalence, present status and future trends. *J Med Assoc Thai,* 84, 1407-1411.

Sakurai, Y., Nakamura, K., Teruya, K., Shimada, N., Umeda, T., Tanaka, H., et al. (1998). Prevalence and risk factors of allergic rhinitis and cedar pollinosis among Japanese men. *Prev Med,* 27, 617-622.

Sam, C.K., Soon, S.C., Liam, C.K., Padmaja, K., & Cheng, H.M. (1998). An investigation of aeroallergens affecting urban Malaysian asthmatics. *Asian Pac J Allergy Immunol,* 16, 17-20.

Samet, J.M. (1987). Epidemiologic approaches for the identification of asthma. *Chest,* 91, 74S-78S.

Schirnhofer, L., Lamprecht, B., Vollmer, W.M., Allison, M.J., Studnicka, M., Jensen, R.L., et al. (2007). COPD prevalence in Salzburg, Austria: results from the Burden of Obstructive Lung Disease (BOLD) Study. *Chest,* 131, 29-36.

Seth, D., Secord, E., & Kamat, D. (2007). Allergic rhinitis. *Clin Pediatr (Phila),* 46, 401-407.

Sheffield, P.E., Weinberger, K.R., & Kinney, P.L. (2011). Climate change, aeroallergens, and pediatric allergic disease. *Mt Sinai J Med,* 78, 78-84.

Simpson, C.R., & Sheikh, A. (2010). Trends in the epidemiology of asthma in England: a national study of 333,294 patients. *J R Soc Med,* 103, 98-106.

Singh, P.N., Yel, D., Sin, S., Khieng, S., Lopez, J., Job, J., et al. (2009). Tobacco use among adults in Cambodia: evidence for a tobacco epidemic among women. *Bull World Health Organ,* 87, 905-912.

Stang, P., Lydick, E., Silberman, C., Kempel, A., & Keating, E.T. (2000). The prevalence of COPD: using smoking rates to estimate disease frequency in the general population. *Chest,* 117, 354S-359S.

Stempel, D.A., & Woolf, R. (2002). The cost of treating allergic rhinitis. *Curr Allergy Asthma Rep,* 2, 223-230.

Stoller, J.K., & Aboussouan, L.S. (2005). Alpha1-antitrypsin deficiency. *Lancet,* 365, 2225-2236.

Strachan, D.P., Wong, H.J., & Spector, T.D. (2001). Concordance and interrelationship of atopic diseases and markers of allergic sensitization among adult female twins. *J Allergy Clin Immunol,* 108, 901-907.

Sullivan, P.W., Ghushchyan, V.H., Slejko, J.F., Belozeroff, V., Globe, D.R., & Lin, S.L. (2011). The burden of adult asthma in the United States: evidence from the Medical Expenditure Panel Survey. *J Allergy Clin Immunol,* 127, 363-369.

Sy, D.Q., Thanh Binh, M.H., Quoc, N.T., Hung, N.V., Quynh Nhu, D.T., Bao, N.Q., et al. (2007). Prevalence of asthma and asthma-like symptoms in Dalat Highlands, Vietnam. *Singapore Med J,* 48, 294-303.

Takenaka, H., Zhang, K., Diaz-Sanchez, D., Tsien, A., & Saxon, A. (1995). Enhanced human IgE production results from exposure to the aromatic hydrocarbons from diesel exhaust: direct effects on B-cell IgE production. *J Allergy Clin Immunol,* 95, 103-115.

Tan, W.C., Seale, J.P., Charaoenratanakul, S., Guia, T.D., Ip, M., Mahayiddin, A., et al. (2003). COPD prevalence in 12 Asia-Pacific countries and regions: projections based on the COPD prevalence estimation model. *Respirology,* 8, 192-198.

Temprano, J., & Mannino, D.M. (2009). The effect of sex on asthma control from the National Asthma Survey. *J Allergy Clin Immunol,* 123, 854-860.

Terada, N., Hamano, N., Maesako, K.I., Hiruma, K., Hohki, G., Suzuki, K., et al. (1999). Diesel exhaust particulates upregulate histamine receptor mRNA and increase histamine-induced IL-8 and GM-CSF production in nasal epithelial cells and endothelial cells. *Clin Exp Allergy,* 29, 52-59.

Toren, K., Brisman, J., & Jarvholm, B. (1993). Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. *Chest,* 104, 600-608.

Uthaisangsook, S. (2010). Risk factors for development of asthma in Thai adults in Phitsanulok: a university-based study. *Asian Pac J Allergy Immunol,* 28, 23-28.

van Beijsterveldt, C.E., & Boomsma, D.I. (2007). Genetics of parentally reported asthma, eczema and rhinitis in 5-yr-old twins. *Eur Respir J,* 29, 516-521.

Vichyanond, P., Sunthornchart, S., Singhirannusorn, V., Ruangrat, S., Kaewsomboon, S., & Visitsunthorn, N. (2002). Prevalence of asthma, allergic rhinitis and eczema among university students in Bangkok. *Respir Med,* 96, 34-38.

Viinanen, A., Munhbayarlah, S., Zevgee, T., Narantsetseg, L., Naidansuren, T., Koskenvuo, M., et al. (2005). Prevalence of asthma, allergic rhinoconjunctivitis and allergic sensitization in Mongolia. *Allergy,* 60, 1370-1377.

Vozoris, N.T., & Stanbrook, M.B. (2011). Smoking prevalence, behaviours, and cessation among individuals with COPD or asthma. *Respir Med,* 105, 477-484.

Warm, K., Backman, H., Lindberg, A., Lundback, B., & Ronmark, E. (2011). Low incidence and high remission of allergic sensitization among adults. *J Allergy Clin Immunol*. Oct 3, E-pub ahead of print.

WHO (2009). WHO Report on the Global Tobacco Epidemic 2009: Implementing Smoke-Free Environments. *Geneva, World Health Organization*.

Woolcock, A.J., Bastiampillai, S.A., Marks, G.B., & Keena, V.A. (2001). The burden of asthma in Australia. *Med J Aust,* 175, 141-145.

Yin, P., Zhang, M., Li, Y., Jiang, Y., & Zhao, W. (2011). Prevalence of COPD and its association with socioeconomic status in China: findings from China Chronic Disease Risk Factor Surveillance 2007. *BMC Public Health,* 11, 586.

Zhang, L., Han, D., Huang, D., Wu, Y., Dong, Z., Xu, G., et al. (2009). Prevalence of self-reported allergic rhinitis in eleven major cities in china. *Int Arch Allergy Immunol,* 149, 47-57.

Zhang, W. (2007). Hypersensitivity diseases *Available from http://wenliang.myweb.uga.edu/mystudy/immunology/ScienceOfImmunology/Hypersensitivitydiseases.html*.

Zhong, N., Wang, C., Yao, W., Chen, P., Kang, J., Huang, S., et al. (2007). Prevalence of chronic obstructive pulmonary disease in China: a large, population-based survey. *Am J Respir Crit Care Med,* 176, 753-760.

Zhong, N.S., Chen, R.C., O-Yang, M., Wu, J.Y., Fu, W.X., & Shi, L.J. (1990). Bronchial hyperresponsiveness in young students of southern China: relation to respiratory symptoms, diagnosed asthma, and risk factors. *Thorax,* 45, 860-865.

Zilmer, M., Steen, N.P., Zachariassen, G., Duus, T., Kristiansen, B., & Halken, S. (2011). Prevalence of asthma and bronchial hyperreactivity in Danish schoolchildren: no change over 10 years. *Acta Paediatr,* 100, 385-389.

APPENDIX

Self-administrated questionnaire

Answer be ticking a cross (x) in the bracelets or writing on appropriate line.

Name:………………………………… Sex: M ( ) W ( )   Age……………………
Address:………………………………………… Phone number:………………
ID:…………………………….HHID………………….Cluster:………………..

	Yes	No/ don't now
1. Have or have any of your parents, brothers or sisters had:		
a) Asthma	( )	( )
b) Allergic rhinitis (hay-fever) or allergic eye catarrh	( )	( )
c) Chronic bronchitis, COPD or emphysema	( )	( )
2. Have you now or have you ever had any of the following diseases :		
a) Asthma	( )	( )
b) Allergic rhinitis (hay-fever) or allergic eye catarrh	( )	( )
c) Chronic bronchitis, COPD or emphysema	( )	( )
d) Any other lung- or airways disease	( )	( )
If "yes", which?..		
3. Have you been diagnosed as having asthma by a doctor?	( )	( )
If "yes":		
a) How old were you when you got asthma?................years		
4. Have you been diagnosed as having chronic bronchitis, COPD or emphysema by a doctor?	( )	( )
5. Do you currently use asthma medicines (permanently or as needed)?	( )	( )
6. Have you now or have you had asthma symptoms during the last 10 years (intermittent breathlessness or attacks of shortness of breath, the symptoms may exist simultaneously with or without cough or wheezing)?	( )	( )
If "yes":		
a) Have you had these symptoms during the last year (last 12 months)?	( )	( )
7. Have you had longstanding cough during the last year?	( )	( )
8. Do you usually have phlegm when coughing, or do you have phlegm in your chest, which is difficult to bring up?	( )	( )

If "yes":

a) Do you bring up phlegm on most days during periods of at least three months? ( ) ( )

b) Have you had such periods during at least two successive years? ( ) ( )

9. Do you usually have wheezing, whistling or a noisy sound in your chest when breathing? ( ) ( )

10. Have you **at any time** during the last 12 months had wheezing or whistling in your chest? ( ) ( )

If "yes":

a) Have you been **at all breathless** when the wheezing or whistling was present? ( ) ( )

b) Have you at any time had this wheezing or whistling when you **did not** have a cold? ( ) ( )

11. Have you woken up with tightness in your chest at any time during the last 12 months? ( ) ( )

12. Do you get short of breath when you walk with other people of your own age on level ground at normal pace? ( ) ( )

13. Do you usually have breathlessness, wheeze or severe cough:

a) on effort ( ) ( )
b) in cold weather ( ) ( )
c) on effort in cold weather during winter ( ) ( )
d) in dusty places ( ) ( )
e) by cigarette or tobacco smoke ( ) ( )
f) by car exhaust fumes ( ) ( )
g) by strong smelling scents (parfumes, spices, printing ink, cleaner, smelling flowers)? ( ) ( )
h) by pollen from grass and/or trees ( ) ( )
i) at contact with furred animals (cat, dog, horse, pets or other furred animals) ( ) ( )

14. Have you ever reacted with breathing difficulties within 3 hours after taking a pain killer? ( ) ( )

If "yes":

a) Do you remember the name of the tablet?............................

15. Do you have blocking of your nose more or less permanently?

Irrespectively of "yes" or "no": ( ) ( )

a) Do you have rhinitis or a runny nose more or less permanently? ( ) ( )

16. Do you smoke? (Smokers also include those who smoke a few cigarettes or pipe fills a week and those who have stopped smoking during the last 12 months) ( ) ( )

58

If "yes":
a) How many cigarettes do you smoke per day?
Less than 5 ( )   5 – 14 ( )   15 – 24 ( )   25 or more ( )
If "no":
b) Have you been a smoker but have stopped smoking more   ( )   ( )
than one year ago?
   If you are or have been a smoker:
b) How old were you when you started to smoke?
    ……years

17. What is or what has been your **main** work or occupation?
....
   a) How many years have you had this main work or
occupation?   ....years

18. Have you now another work or occupation (other work /
profession, or are you studying, unemployed, house-wife, retired,   ( )   ( )
have sickness pension etc.)?
   If "yes":
a) What work or occupation? ....
b) Since how many years? ………….. years

19. Have you been heavily exposed to dust, gases or fumes at   ( )   ( )
your work?

20. How many times a week (in average) do you eat fish?
....

21. How many times a week do you exercise or do sports so
much that you sweat or get breathless, or go for long-walks,
skiing or similar activities?   ....

22. Did you live at country-side (not town or suburb) during your   ( )   ( )
first years of life?
   a) Did your family live on a farm during your first years of   ( )   ( )
life?

23. Do you have any ventilation fans in your house?   ( )   ( )

24. Is the kitchen separated from the living room and/or sleeping   ( )   ( )
room in your house?

25. What kind of oven/production do you use to heat the food?
Coal ( )   Dung ( )   Wood ( )   Straw ( )
Leaves ( )   Kerosene ( )   Electricity ( )   Gas ( )

Thank you for your participation!

Questionnaire for the structured interview survey

Name: ....Sex: M ( ) W ( )
Date of birth: ……./……./………
Adress:..Phone number: ……………..
ID:……...................... HHID:…………………….Cluster:……………….…
Interviewer: ....

Answer be ticking a cross (x) in the bracelets or writing on appropriate line.

	No	Yes
1. Have you had wheezing or whistling in your chest at any time *in the last 12 months*?	( )	( )
if 'yes'		
1.1. Have you been at all breathless when the wheezing noise was present?	( )	( )
1.2. Have you had this wheezing or whistling when you did *not* have a cold?	( )	( )
2. Do you usually have wheezing, whistling or a noisy sound in your chest when breathing?	( )	( )
3. Have you woken up with a feeling of tightness in your chest at any time *in the last 12 months*?	( )	( )
4. Have you been woken by an attack of shortness of breath at any time *in the last 12 months*?	( )	( )
5. Have you had longstanding cough during the last year?	( )	( )
6. Do you usually cough in the morning?	( )	( )
7. Do you usually cough during other times of the day, or at night?	( )	( )
8. Have you been woken by an attack of coughing at any time *in the last 12 months*?	( )	( )
9. Do you usually have phlegm when coughing, or do you have phlegm in your chest which is difficult to bring up?	( )	( )
10. Do you bring up phlegm from your chest on most days for as much as three months each year?	( )	( )
If yes,		
10.1. For how many years? Year………….		

11. Do you currently take asthma medicines or medicines for any airway or lung disease (permanently or as needed)? ( ) ( )

12. Has a doctor ever told you that you have chronic bronchitis or emphysema or COPD? ( ) ( )

13. Have you *ever* had asthma? ( ) ( )

14. Have you been diagnosed as having asthma by a doctor? ( ) ( )
If 'yes' to any question 13 or 14
    14.1 How old were you when you had your first attack of asthma?
(If unsure, *give your best guess!)* Year:…………………….
    14.2 Have you *ever* been hospitalised for asthma? ( ) ( )
    14.3 Have you had an attack of asthma *in the last 12 months*? ( ) ( )
    14.4. Are you *currently* taking any medicine (including inhalers, aerosols or tables) for *asthma*? ( ) ( )

15. Have you ever had TBC? ( ) ( )

16. Do you currently have or have you ever had any lung or airway disease except asthma, chronic bronchitis, emphysema or COPD, or TBC? ( ) ( )
If 'yes'
    16.1. What disease?...

17. Do you get short of breath when you hurry on level ground or when you walk in you own pace up a stair or a small slope? ( ) ( )
If 'yes'
    17.1. Do you get short of breath when you walk with other people of your own age on level ground at normal pace? ( ) ( )

18. Do you have any nasal allergies including hay fever? ( ) ( )
If 'yes'
    18.1 Have you been troubled by nasal allergies *in the last 12 months*? ( ) ( )
    18.2 Have you ever been troubled by nasal allergies for *more than 4 days in any one week*? ( ) ( )
    18.3 *If yes* did this happen for *more than 4 weeks continuously*? ( ) ( )

19. Has your nose been blocked *for more than 12 weeks during the last 12 months*? ( ) ( )

20. Have you had pain or pressure around the forehead, nose or eyes *for more than 12 weeks during the last 12 months*? ( ) ( )

21. Have you had discoloured nasal discharge (snot) or discoloured mucus in the throat *for more than 12 weeks during the last 12 months*?   ( )   ( )

22. Has your sense of smell been reduced or absent *for more than 12 weeks during the last 12 months*?   ( )   ( )

23. Has a doctor *ever* told you that you have *chronic* sinusitis?   ( )   ( )

24. Have you ever had an itchy rash that was coming and going *for at least 6 months?*   ( )   ( )

If 'yes'
     24.1 Have you had this itchy rash in the last 12 months?   ( )   ( )
     24.2 Does this affect only your hands?   ( )   ( )

25. Have you ever had eczema or any kind of skin allergy?   ( )   ( )

26. Have you ever smoked for as long as a year (means at least one cigarette per day or one cigar per week for one year)?   ( )   ( )
If 'yes'
     26.1 How old were you when you started smoking?   ( )   ( )
     26.2 Have you smoked at all in the last month?   ( )   ( )
     26.3. Have you smoked at all in the last 12 months   ( )   ( )
If 'yes'
         26.3.1 How old were you when you stopped smoking?
            Years…………..
     26.4 *On average* how much do you (or did you) smoke? Cigarettes per day ………

27. Does any member of your family smoke?   ( )   ( )
If 'yes'
     27.1. How many? Number: ………..
     27.2. How many of them smoke inside the house? Number…….

28. Are you currently (Tick one box only)
a.   Employed   ( )
b.   Self-employed   ( )
c.   Unemployed   ( )
d.   Not working because of poor health   ( )
e.   Full-time house person   ( )
f.   Full-time student   ( )
g.   Retired   ( )
h.   Other   ( )

29. What is your current work?..
If 'yes'
     29.1. How many years have you worked at this occupation?
            Years:………………………………

30. Have you been worked in another occupation or in another field more than five years?   ( )   ( )

If 'yes'

    30.1. In what work/occupation?..

    30.2. How many years did you work at this occupation?

                    Years:……………..

31. Do you currently have or have you ever had any heart problems or heart disease?

No ( )   Cardiac ( )

Angina ( )   Heart dysrhythmia ( )

Coronary artery surgery   ( )   Other heart disease ( )

Balloon dilatation(Angioplasty) ( )

32. Do you currently use any heart medication, including low dose ASA for preventing thrombosis?   ( )   ( )

33. Do you currently have or have you ever had hypertension?   ( )   ( )

34. Do you currently use any medication against hypertension?   ( )   ( )

35. Do you currently have or have you ever had diabetes?   ( )   ( )

36. Do you currently have or have you ever had a rheumatic disease?   ( )   ( )

37. Height: ……………cm

    Weight…………….kg

    Blood pressure…………………mm Hg

38. What is today's date………….../……./……..

Signature of interviewer