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Exposure to occupational agents as a risk factor for adult asthma: A community-based study in Montreal.

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ABSTRACT:

The prevalence of asthma and the role of occupational exposures was investigated in a cross-sectional study of 498 Montreal adults aged 20 to 44 years. Prevalences of asthma standardised for age and gender, using four definitions were: *current wheeze:* 23.8%, *asthma symptoms and or medicine:* 12.9%, *airway hyper-responsiveness:* 15.1%, *airway hyper-responsiveness* and *current wheeze:* 7.0%. Imputation to adjust for non-response to airway challenge gave similar results. 56.9% of subjects reported occupational exposure ever to sensitisers and 10.8% to irritants. *Current wheeze* was associated with exposure to irritants (OR: 2.12 (1.03, 4.34)), and *airway hyper-responsiveness* with exposure to sensitisers (OR: 2.20 (1.10, 4.38)). Childhood asthma and atopy did not affect the associations. Population attributable risk was about 30% for *airway hyper-responsiveness* with exposure to sensitisers, and 5% for *current wheeze* with exposure to irritants. Studies with more precise exposure information may provide better evidence for the causality of the association.

RÉSUMÉ

La prévalence de l'asthme et le rôle de l'exposition professionnelle furent enquêtés dans le cadre d'une étude transversale auprès de 498 adultes Montréalais âgés de 20 à 44 ans. La prévalence de l'asthme, standardisée pour les facteurs d'âge et de sexe, se présente comme suit: *sillements courants*: 23.8%, *symptômes asthmatiques et/ou médicaments*: 12.9%, *hyperréactivité des voies respiratoires et sillements courants*: 7.0%. L'imputation des données visant à compenser pour la non-réponse aux test de réactivité bronchique ont généré des résultats similaires. 56.9% des sujets rapportent avoir déjà été exposé au travail à des produits sensibilisants et 10.8% à des produits irritants. *Les sillements courants* sont associés à l'exposition aux irritants (OR: 2.12 (1.03, 4.34), et l'hyperréactivité bronchique est associée à l'exposition aux produits sensibilisants (OR: 2.20 (1.10, 4.38). L'asthme infantile et l'atopie n'affectent en rien ces associations. Le risque d'hyperréactivité bronchique attribuable à l'exposition aux sensibilisants est estimé à 30%, et le risque de sillements courants dûs à l'exposition aux irritants à 5%. Des études comportant des données plus précises sur l'exposition professionnelle pourraient produire des preuves plus convaincantes de la causalité de ces associations.

ORIGINALITY:

The elements of this thesis, which constitute an original contribution to current knowledge in this field are:

i) Investigation of the association of asthma with occupational exposures categorised as sensitisers and irritants after taking the pertinent risk factors of asthma into account.

ii) Evidence for the different associations of two definitions of asthma (ie *current wheeze*, and *airway hyper-responsiveness*) commonly used in epidemiologic studies with occupational exposures as the independent variable. This raises doubts about the interchangeable usage of these two definitions of asthma in occupational epidemiology.

iii) Evidence for the effect modification by current smoking in the association of asthma defined as *airway hyper-responsiveness* with occupational exposure to sensitisers, and by never smoking, and absence of atopy in the association of asthma defined as *current wheeze* with occupational exposure to irritants.

iv) Evidence suggesting that occupational exposure in the past is more important for the development of current asthma than current exposure. This is consistent with "healthy" worker effect.

GLOSSARY OF TERMS USED:

AHR: Airway hyper-responsiveness

AIC: Akaike information criteria

CI: Confidence interval (mostly 95% Confidence interval, given in paranthesis)

CNSLD: Chronic Non-specific Lung Disease

FEV1: Forced expiratory volume in one seond

FVC: Forced vital capacity

HMW: High molecular weight

HWE: 'Healthy' worker effect

LMW: Low molecular weight

N/A: Not available

OR: Odds ratio

PAR: Population attributable risk

PARP: Population attributable risk percentage

PD10: Provocative dose of the non-specific irritant used in airway challenge testing (eg histamine or methacholine) that would result in a 10% decrease in FEV1 from the baseline level

PD20: Provocative dose of the non-specific irritant used in airway challenge testing (eg histamine or methacholine) that would result in a 20% decrease in FEV1 from the baseline level

SC: Schwarz criterion

SEM: Standard error of the mean

1. INTRODUCTION

1.1 Context:

There is growing public concern about the increasing prevalence, morbidity, and mortality related to asthma, despite recent advances in the understanding of its pathophysiology and its management. Differences in adult prevalence figures between and within countries have been investigated by multicentre population based studies started in European Community and subsequently extended to other countries including Algeria, Canada, United States, and New Zealand (1). These studies have found substantive differences in prevalence between and within countries despite the use of standardised methods for establishing the presence of asthma and the results suggest that environmental exposures play an important role in its genesis. Occupational exposures are an important cause of adult asthma, and may contribute to the recent trends towards an increase in adult asthma, especially in the industrialised countries. This possibility is supported by the findings of voluntary based reporting schemes, which have revealed that occupational asthma is the most common occupational disease in United Kingdom (2), and in Canada (3-4). One of the main difficulties in estimating rates of asthma due to workplace exposures is the 'healthy' worker effect. This is because, in work force based studies the study population is invariably composed of survivors, because affected workers either change or leave their jobs upon developing work related asthmatic complaints (5), and as a result, the observed ill health effects will be an underestimation of the true effect. Community-based studies may therefore provide a better setting to study work related diseases by reaching to those who have left the work force upon developing health problems in addition to current workers (6). In 1991, a multicentre population based project entitled "Lung Health and Canadian Environment" was undertaken to examine the distribution and determinants of adult asthma in 6 centres across Canada, following the European Community Respiratory Health Survey (ECRHS) protocol (1). The Canadian study used a detailed occupational questionnaire in addition to the study instruments used in the ECRHS (7). One of the major objectives of the study was to investigate the role of occupational exposures in the development of asthma in young Canadian adults.

The material for the research described in this thesis was gathered in the context of the study of Lung Health and the Canadian Environment, Montreal being one of the 6 Canadian centres (5 Canadian cities and one Canadian province, the Prince Edward Island) which participated in the study.

1.2. **Outline of the Present Study:**

The outline of the thesis is as follows: "Background" (*Chapter* 2) gives some general information about definitions and determinants of asthma, and mentions the main difficulty in the investigation of asthma as the absence of a specific marker for the disease. *Chapter* 3 summarises some of the recent findings about the distribution of asthma in various countries. *Chapter* 4 includes the definition, criteria for the diagnosis of occupational asthma, and presents various types of evidence ie. surveillance-based, community-based, workforce-based evidence for the prevalence, and the risk of occupational asthma. The 'healthy' worker effect, an important source of bias in the investigation of occupational lung diseases is mentioned in *Chapter* 5. International studies, which is joined by Canada to investigate the prevalence and determinants of asthma using standardised instruments are described in *Chapter* 6. The study objectives, definitions, design, rationale, study population, and methods are given in the *Chapter's 7, 8, and 9.* Results of the study both descriptive and analytic are presented in *Chapter* 10. *Chapter* 11 includes the discussion of the findings, the main weaknesses, and the conclusions of the study.

2. BACKGROUND

2.1.The Natural History of Chronic Airway Diseases:

Two important prospective studies added much to the understanding of the chronic airway diseases and resulted in what came to be known as the British and the Dutch hypotheses of the natural history of chronic airway disease. Both examined the role of endogenous (host) and exogenous (environmental) factors in the pathogenesis of Chronic Non-specific Lung Disease (CNSLD) or Chronic Obstructive Pulmonary Disease (COPD) as it is called in North America, but came to different conclusions (8). The British study was based on 792 (of the original sample of 1137) men, between the ages of 30-59, and employed in mostly skilled manual or clerical jobs, who were followed for 8 years; their main environmental exposure was cigarette smoking. Lung function as measured by FEV1 decreased gradually with age, more rapidly in smokers, and irreversibly in "susceptible" smokers. Contrary to their prior hypothesis, neither chronic mucus hypersecretion nor bronchial infection accelerated the decline of lung function. Susceptibility was described as a continuum rather than an all or nothing phenomenon (9). The British study led to the conclusion that an environmental exposure, cigarette smoking was the major determinant of CNSLD. By contrast, the Dutch study was community-based in 3 areas of different community air pollution, and covered the ages of 15 to 64, and included both genders. Their findings led the authors to the conclusion that asthma, chronic bronchitis, and emphysema should be considered different disease expressions of one disease entity for which they proposed an umbrella title CNSLD and that a host factor, characterised as an "asthmatic tendency" was the major determinant of CNSLD. The Dutch hypothesis was recently revisisted by its proponents and was considered current (10). A similar broad hypothesis indicated that most major chronic diseases probably result from the accumulation of environmental factors over time in genetically susceptible persons (11).

2.2. Asthma:

2.2.1. Definitions and Diagnosis:

Asthma has been defined as a disorder of the airways characterised by paroxysmal or persistent symptoms (dyspnoea, chest tightness, wheeze and cough), with variable airflow limitation and airway hyper-responsiveness to various stimuli (12). A similar definition had been suggested in the Ciba Guest Symposium in 1959, which classified asthma under the subdivision of "intermittent or reversible obstructive lung disease" (13). In an effort to standardise the terminology used for the chronic lung diseases, the Symposium suggested the usage of "chronic non-specific lung disease" (CNSLD) as a collective term for the whole group of chronic bronchitis, asthma and emphysema, which were often interchangeably used by different clinicians without an agreement (13). As described above under 2.1, the proponents of the Dutch hypothesis considered all three conditions to be expression of the same disease entity (10). None of the definitions of asthma in current use include a single underlying cause, an agent or nutritional deficiency, whereas all focus to a greater or less extent distinctive pathophysiological mechanism. Thus, asthma was not considered as a disease by Gross, but as a description of the phenomena without making any aetiologic implications (14). The three main components of the definition accepted by the Canadian consensus, were **symptoms**, functional impairment (**variable airflow limitation**) and susceptibility of the airways to respond to various stimuli (**airway hyper-responsiveness to various stimuli**). None are specific to asthma, and to a greater or less extent all can be seen in other chronic lung diseases, hence the term CNSLD was suggested at the CIBA Symposium (13). Since the diseases listed under the CNSLD have some common features in their clinical presentations and pathogenesis, and pathologies, some of the important facts related to CNSLD will be mentioned below.

2.2.2. Asthma as an Inflammatory Disease:

Recent evidence supports the concept of asthma as an inflammatory disease (15), a concept suggested by Osler, as early as 1892 in his classic textbook, "The Principles and Practice of Medicine, in which he concluded that asthma was "a special form of the inflammation of the smaller bronchioles" (16). Some of the evidence for the inflammatory nature of asthma came from the use of fiberoptic bronchoscopy, which has provided lavage and mucosal biopsy material from asthmatic individuals. An important observation has been the similarity of inflammatory findings in bronchial biopsy specimens from patients with mild, or even asymptomatic asthma with those in autopsy specimens from patients with fatal asthma. This has led to the realisation that inflammation is not restricted to severe disease, but rather is a general characteristic of asthma (17).

Atopy is a manifestation of allergy, an important if not the only established risk factor for the development of asthma (18). It is the characterised by the production of IgE antibodies in response to contact with allergens and can be detected by skin prick testing with aeroallergens or serological testing of IgE (19). The clinical manifestations suggest immediate type hypersensitivity, ie. immediate wheal and flare skin reactions to common environmental antigens, and a family history. Eighty percent of childhood asthmatics are atopic, and the risk of atopy in children is approximately 80% if both parents are atopic and 50% if one parent is atopic. (19).

A good model for the asthmatic response to an allergen can be provided by the inhalation of a suspected allergen in a subject with atopic asthma (17). Following inhalation of an allergen to which he or she has been sensitised, a subject with atopic asthma develops bronchial obstruction within minutes (the peak airflow obstruction in 20-30 minutes) primarily as a result of direct action of mast- cell-derived mediators and their metabolites on the hyper-responsive bronchial smooth muscle. This is termed the early asthmatic reaction and in some cases the reaction soon terminates with the resolution accompanying a decrease in short lived mediator concentrations (17). In many cases (up to 30-50% of atopic asthma patients tested, in some series) a second phase of airflow obstruction occurs

6-10 hours later (17). This reaction is thought to result from specific cytokines released along with or soon after the short lived mediators (17). Those cytokine molecules diffuse into the general circulation, and are able to summon the classical effector cells of the inflammatory response to the site of injury because of their longer half lives and biological potency. These are chiefly eosinophils, T helper lymphocytes, neutrophils, and monocytes. Specific adhesion molecules expressed by venular endothelial cells also play a role as a selectively permeable barrier to effector cell egress (17).

The relationship between magnitude of airway inflammation, as measured by the profusion of inflammatory cells in the asthmatic airway and airway function is not however strong, suggesting that other factors like airway modelling may also affect the airway patency (20). Evidence for the close association between the severity of airway inflammation, assessed at a single time point, and the level of airway responsiveness is less compelling, and better markers of airway inflammation that would indicate the integrated effects of inflammation over time are needed (20).

Airway inflammation also has a role in the pathogenesis of chronic obstructive pulmonary disease (COPD), the collective term used for chronic bronchitis and emphysema, which sometimes leads to confusion in the clinical classification of patients (21). A recent study suggests that, in baseline conditions, the two can be distinguished by their pathology; thus, although biopsies from asthma patients and COPD patients both had an increased number of activated T-lymhocytes, in asthma there were increased numbers of eosinophils and mast cells, and in COPD increased number of macrophages and an increased expression of vascular adhesion molecules (22).

In summary, airway inflammation is an important feature of asthma, and is not restricted to severe or fatal cases of asthma as originally thought, but is also seen in mild, and even asymptomatic asthma patients. Although there are similarities between the inflammatory reaction in COPD and asthma, the two can be distinguished by the abundance of eosinophils, and mast cells in asthma. Atopy, a manifestation of allergic susceptibility, is a

common risk factor for the development of asthma. A complex interplay of inflammatory cells, and mediators play a role in the development of bronchial obstruction when an atopic asthma patient inhales an allergen. However, a direct relationship between the severity of airway inflammation and the impairment of airway function or increase in airway responsiveness in asthma has not yet been clearly established.

2.3. Determinants of Asthma:

2.3.1. Definitions and Categories:

A determinant has been defined as "an individual characteristic (constitutional, environmental, or behavioral) on which the outcome of interest, (asthma in the context of the present study) depends" (23). It may be causal or not, can increase or decrease risk, may be established or putative, and if it is also a risk factor, it may be primary (ie. affects incidence of asthma) or secondary (ie. triggers symptoms, exacerbates disease or increases its severity) (23). *Table* 2.3.1 adapted from Becklake and Ernst (23) summarises most of the known and putative risk factors for asthma. Evidence related to some of these risk factors is discussed below: (occupational exposures will be discussed in a separate chapter later.)

2.4. Host Determinants

2.4.1.Genetic Factors:

Genetic susceptibility is reflected in the atopic status, and family history of allergic conditions. Genes associated with an increased risk of asthma have been identified on chromosomes 5, 11, and 14, and there may well be other genes involved in the development of asthma (24).

2.4.2. Family History of Allergies:

In a questionnaire study of children between 6 months to 16 years, from different rural areas in **Sweden**, the occurrence of allergic asthma was more frequent in children with family history of asthma than those without such a history, both in houses undamaged by dampness (5.9% vs 1.9%) and in houses damaged by dampness (20.4% vs. 2.4%) (25).

Table 2.3.1 Determinants of asthma: (adapted from Becklake and Ernst) (23):

Category	Determinant
Host	Genetic factors
	Family history of allergies
	Atopy
	Race, and ethnic origin
Environmental	Certain occupational exposures
	Community air pollution by allergen
	Exposure to indoor allergens (pre and postnatal)
	Viral infections
	Environmental exposure to tobacco smoke in childhood
	Urban Air pollution
	Changing lifestyles (eg, to Westernised lifestyle, urban vs rural, migration)
	Certain diets, breastfeeding practices, absence of certain infections particularly in the first year of life
	Certain home characteristic (eg, dampness, gas cooking, carpeting, electric home heating)
	Socioeconomic disadvantage (poverty)

2.4.3. Atopy:

There is also evidence for the genetic predisposition to atopy. Individuals with atopic predisposition can develop an IgE immune response only after exposure to an allergen to which they are responsive. Sensitisation may occur after exposure to minute amounts of allergens through epithelial membranes of the respiratory and gastrointestinal tract (26). In a case control study of 122 subjects from 28 families with one member, who had attended the asthma clinic, and 122 subjects from 28 families in the same community with a member, who had asymptomatic airway hyper-responsiveness, first degree relatives of subjects with asthma had a higher prevalence of airway hyperreactivity (51.1% vs. 26.7%, p=0.0002), atopy (69.6% vs. 42.2%, p=0.0002), and elevated serum levels of IgE (108.4, Standard error of the mean (SEM) 1.2 microgram/L vs 58.1, SEM 1.2 microgram/L, p=0.02) than subjects from nonasthmatic families (27).

2.5 Environmental Determinants

2.5.1. Community Air Pollution by Allergen:

Asthma outbreaks in Barcelona during the period 1985-1986, which coincided with the soybean unloading is a well described example for the relationship between asthma and community air pollution by allergen. Epidemiological investigation of the outbreaks found a risk ratio with a lower 95% confidence interval of 7.2 CI and immunological evidence of skin reactivity to an airborne soybean particulate antigen in the serum from epidemic asthma patients vs. endemic asthma patients (28).

2.5.2. Exposure to Indoor Allergens:

Indoor exposure to allergens derived from furred animals (especially cats), moulds, and dust mite exposure is important. Ventilation and humidity condition of the house affect the level of mould and mite antigens which can accumulate in a home, and control of these conditions can avoid this problem (29). Dust mite allergy has been reported as occurring in 45-85% of subjects with asthma compared with 5-30% of control subjects, and there is an increasing risk of asthma with increasing level of mites (dose response relationship) (30).

2.5.3. Viral Infections:

There is epidemiological evidence relating the occurrence of childhood viral bronchiolitis to the subsequent development of asthma. The cumulative incidence of asthma in a 5 year follow-up of children hospitalised with respiratory syncytial virus bronchiolitis in infancy was reported as 92%. Adenovirus infection in childhood has also been linked to the pathology of asthma. (31). Viral infections may also induce airway hyper-responsiveness for up to 8 weeks (12, 19, 32).

2.5.4. Environmental Exposure to Tobacco Smoke (ETS) in Childhood:

Passive smoking, or ETS is defined as the exposure of non-smokers to tobacco consumption products in the indoor environment. Passive smoking intensive enough to evoke an inflammatory action in the lung represents an exposure comparable to that, which occurs with active smoking (33). In childhood ETS exposure is a major environmental cause of ongoing inflammation in the airways, in addition to allergen exposure and respiratory infection, all of which may lead to the development of chronic wheezing and airway hyper-responsiveness, hallmarks of the asthma syndrome (19). Among the sources of ETS exposure in childhood, maternal smoking is a well known risk factor for the development of asthma with relative risk estimates (as measured by Odds ratio) between 2.5 and 4.72 (34-36). In a study of 650 US children between 5 and 9 years of age,

exposure to parental smoking, especially maternal smoking was shown to be related to the occurrence of persistent wheeze, 0%, 1.8%, and 7.7% in households with no parent smoking, one parent smoking, and both parents smoking, respectively (37). Evans et al. also showed that passive smoking in asthmatic children between 4 and 17 year-age, accounted for a 63% increase in the average number of emergency room visits per year (3.46 and 2.12 in children exposed to passive smoking and not exposed to passive smoking, respectively) (38). In an Australian study of 500 healthy infants, Stick et al. used the measurements of time to peak tidal expiratory flow (tPTEF) as a proportion of expiratory time (tE) in newborns soon after birth to assess the respiratory function. Maternal smoking during pregnancy (>10 cigarettes daily), and family history of asthma were associated with lower values of tPTEF/tE (39).

2.5.5. Urban Air Pollution:

The potential ill effects of air pollution on asthma range from subclinical effects, through impaired pulmonary function, to emergency room visits and increased mortality (40, 41). In other studies, increased concentrations of ground-level ozone were associated with an increased airway permeability, as determined by bronchoalveolar lavage studies, and radionuclide (DTPA) transport in humans and animal experiments (42-44) and with increased airway hyper-responsiveness when exposed to allergens (45). In a Saint John, New Brunswick study when daily one hour maximum concentration exceeded 75 ppb, frequency of emergency department visits for asthma increased on average by 33% (95%CI: 10-56%) (46). Another Canadian study, conducted in Montreal, investigated the relationship between asthma severity and ozone exposure, or fungal spore exposure in 12 asthmatics, who had asthma exacerbations during several weeks of the warm season on at least 2 days per week, which required the use of oral or inhaled bronchodilator as needed. Asthma severity was measured by symptom score as graded by the subjects at six levels (from 0: no asthma symptom today, to 5: asthma symptom(s) requiring a physician or emergency clinic visit or hospital admission), and the extent of inhaler use. Personal exposure to ozone measured with Harvard personal sampler and exposure to fungal spores

measured with volumetric fungal spore collector were both associated with asthma severity; for a 90th percentile increase in ozone (25ppb), symptom score increased 25% (0,49%) and inhaler use increased 26(3%,48%) over their averages (47).

However, the relationship of asthma and air pollution, or respiratory infection is not always consistent. Lower prevalence of wheezing was found in Moscow, Georgia, Uzbekistan and Romania, than six centres in Sweden, Finland and Norway. Lower prevalence of positive skin prick tests was found in schoolchildren in the heavily polluted city of Konin in Poland than those in Swedish towns (13.7% vs 35.3%) (29). Similarly, children in East Germany exhibited markers of asthma less frequently than children in West Germany. Prevalence of positive skin prick tests (sensitisation to one or more allergens) was 7.4% vs 18.4%, asthma ever diagnosed by a doctor was 7.2% vs. 9.3%, and wheezing was also less frequent (48). These findings could not be linked to the differences in air pollution. The explanations suggested by the authors were lifestyle changes, more infections in early life, or different chemical exposures both in the environment and in foods (48).

2.5.6. Family Characteristics:

In a cross-sectional survey of children aged 9-11 years number of siblings has been shown to be associated with atopy, as detected by skin prick testing, with a decreasing prevalence as the number of siblings increased, (36.1%, 38.0%, 36.5%, 31.7%, 28.6%, 25.0% in West Germany, and 19.4%, 17.7%, 15.5%, 15.4%, 16.7%, 11.1% in East Germany, for 1, 2, 3, 4, 5, and more than 5 siblings respectively) (49). Increased exposure to infections early in life through siblings or socioeconomic factors related to the family size was proposed as an explanation for this finding (49).

2.5.7. Home Characteristics:

Indoor environmental factors were studied in relation to the incidence of asthma among 3 and 4 year-old children, 457 diagnosed with asthma, and 457 matched to these cases on age and census tract, in Montreal, Québec, Canada (50). After controlling for personal factors such as history of allergies and eczema, the independent risk factors for asthma included mother's heavy smoking (>20 cigarettes/day vs 0) (OR=2.77, 95% CI 1.35-5.66), use of humidifier in the child's room (OR=1.89, 95%CI 1.30-2.74), presence of electric heating system in the home (OR=2.27, 95%CI 1.42-3.65), a history of pneumonia (OR=3.12, 95%CI 1.92-5.09), absence of breast feeding (OR=1.47, 95%CI 1.02-2.13), and a family history of asthma (OR=2.39, 95%CI 1.13-5.04 for asthma in father; OR=2.26, 95%CI 1.19-4.29 for asthma in siblings) (50).

Viegi et al. evaluated the effects of indoor air pollution in a general population sample of 3,866 individuals between the ages of 5 and 90 years, living in central **Italy** stratified according to age and socioeconomic characteristics (51). Wheeze and shortness of breath with wheeze in females were associated with the use of a stove or forced air pollution. Prevalences (%) for smokers/non-smokers among groups were: central heating fuelled by natural gas (methane): 6/6; non- natural gas central heating and cooking with bottled gas (mixed propane): 4/9; stove or forced air heating fuelled by natural gas and cooked with natural gas: 11/10; non-natural gas stove or forced air heating and cooked with bottled gas: 8/6. The respective figures for physician diagnosed asthma were: 5/6, 6/4, 8/5, 7/8. The authors offered the explanation that bottled gas ovens were less efficient and might be producing higher amount of CO and NO_2. Indoor pollutant level was not measured objectively, and measurement would be influenced by the tendency of those who resided in homes with high concentrations of NO_2 to spend less time in the kitchen (51).

The relationship of damp housing and adult respiratory symptoms was investigated by a questionnaire, in parents of school-aged children (14,799 adults) from six regions of Canada (52). The presence of home dampness characterised as reports of damp spots, and mould growth was 31.9%, and by reports of visible mould or mildew on indoor surfaces,

and damp, mould or flooding was 37.6%. The odds ratios associated with the reported presence of damp/mould in the home, adjusted for age, sex, region active and passive smoking, natural gas heating, and wood stoves, educational status, household crowding (number of people per room), occupation (employed, unemployed, student, or housewife) for asthma was 1.56, 95%CI: 1.25-1.95 (52).

In another study conducted in Holland among 3344 children aged 6-12 years, using a parent-administered questionnaire, dampness and mould growth on indoor surfaces was reported for 23.6% and 15.0% homes, respectively (53). The odds ratios associated with the reported presence of damp stains and/or mould in the home adjusted for active and passive smoking, indoor nitrogen dioxide sources, and educational status were 1.63 (95%CI: 1.30-2.06) for wheeze, and 1.29 (95%CI: 0.92-1.81) for asthma (53).

2.5.8. Socioeconomic Factors:

A relationship between asthma and socioeconomic status (as by parental occupation) was studied by a questionnaire survey and lung function testing in 1,111 primary school children in Canada (54). Exercise-induced bronchospasm after a 6 minute free-running test was used to assess airways responsiveness, and was more common in children from the least-advantaged homes than in the children from the most advantaged homes (OR: 2.26, 95%CI: 1.12-4.58) adjusted for age, gender, race, and asthma in the parent. Although, there was no significant excess of the report of ever wheeze (OR: 0.80, 95%CI: 0.4-1.70) or diagnosed asthma (OR: 0.80, 95%CI: 0.4-1.62), children from the least-advantaged homes reported higher prevalence of night cough (OR: 2.30, 95%CI: 1.04-5.06), and cough with mucus (OR: 3.15, 95%CI: 1.06-9.33) than the children from the most advantaged homes. The presence of a cat at home (OR: 1.63, 95%CI: 1.02-2.61), and lower respiratory infection before 2 year of age (OR: 1.71, 95%CI: 1.16-2.52) were also associated with an excess of exercise-induced bronchospasm (54).

2.5.9. Synthesis:

The determinants of asthma are grouped under host and environmental factors, consistent with the usual approach of epidemiology (55). Findings from various studies supports the view proposed by the Dutch hypothesis that development of asthma is controlled by the various environmental factors which include community air pollution by allergen, exposure to indoor allergens (pre and postnatal), viral infections, urban air pollution, environmental exposure to tobacco smoke in the childhood, diet, certain home characteristics, and occupational exposures, acting on the susceptible individiual as identified by the host factors which include genetic susceptibility, family history of allergies, and atopy.

3. DISTRIBUTION OF ASTHMA (TIME, PLACE, PERSON)

3.1. Mortality:

Although asthma is defined as a reversible condition, it may lead to irreversible and progressive reduction in airway function and eventually to death (56). In fact, asthma is one of the diseases which are amenable to treatment, and which have exhibited a decrease in mortality over the past two to three decades in many countries (57).

Death rates from asthma per 100,000 population in 5-34 year ages and in all ages (given in brackets) during 1980, from different countries were: USA: 0.2 (1.4), Canada: 0.3 (1.8), West Germany: 0.4 (3.0), England: 0.7 (3.2), Australia 1.0 (4.0), New Zealand: 3.0 (8.0) (9.8 among Polynesians) (58). Comparison of the mortality figures as a function of age in USA and New Zealand showed higher mortality rates in the elderly, and suggested that chronic asthma may cause death in the elderly. There were also wide differences between countries for all ages vs. 5-34 years with a gradient almost three-fold (8.0 vs. 3.0) in New Zealand and seven-fold (1.4 vs. 0.2) in USA. As these figures were obtained from death certificates, differences at least in part might have been due to differences in the coding practices.

Trends of asthma mortality were estimated for the years 1974-1984, in **England** and **Wales** (59). In 1979, introduction of the 9th revision of International Classification of Diseases (ICD) led to the classification of any death with the underlying cause of bronchitis, bronchiolitis, or emphysema, as being due to asthma, if asthma was also mentioned on the death certificate. After considering the ICD revision by regression, women in the 5-34 year age group had about six times the number of excess deaths compared to the 35-64 year age group (352 vs. 56), and men in the 5-34 year age group had about four times the number of excess deaths as did the women in the same age group (279 vs. 73) with 1974 population as the reference. During the period from 1976 to 1983 the prevalence of asthma increased by 4% per year, based on numbers of consultations, but

the lack of age-specific rates made the interpretation difficult. Proportion of the asthma deaths within the first hour of the final attack was 37% in 5-34 age group in 1966-1967, and 23% in 15-64 age group in 1979. (59).

There were reports also from **USA** showing an increased mortality from 1979 to 1980. This coding difference accounted for the 39% increase from 1978 to 1979 (from 0.8 per 100,000 in 1977 and 1978 to 1.3 per 100,000 in 1979), but could not explain the increases after that date (60). The death rates of asthma increased from 1.2 per 100,000 in 1979 to 1.5 per 100,000 in 1984, and to 1.6 per 100,000 in 1985. This increase occurred in both genders, and in every 5 year age groups older than 4 years. Increases were somewhat higher in metropolitan or urbanised areas of at least 50,000 population than non-metropolitan areas; metropolitan rates of death from 1979 to 1984 for black subjects ranged from 1.6 to 2.5, vs. for white subjects 0.9 to 1.4; in non-metropolitan areas, rates of death for black subjects from 1979 to 1984 fell from 2.3 to 2.2, but remained higher than for white subjects, 1.5 to 1.4. The greater increase in deaths from metropolitan area was attributed to air pollution.

Increase in asthma mortality has also been reported in **France** during 1980-1990 by 30%, principally in those aged 5-34 years. The prevalence among French school-age children was between 6 and 10% in the same time period (24).

3.2. Prevalence:

There is also evidence for the increasing prevalence of asthma in both adults and children in many countries. In **Finland**, examination of the military records from 1926 to 1989 revealed an increased percentage of the adult men over age 20 exempted from military service because of incapacitating asthma (61). Since 1947, the asthmatic status was reported after the call up medical examination, and divided into five categories as A: no asthmatic treatment, normal lung function, not asthmatic, fit for service; B: asthmatic treatment, normal lung function, asthmatic but fit for service; C to E: asthmatic treatment,

decreased lung function, exempted from military service by virtue of asthma of varying severity. The prevalence did not change much from 1926 (0.02%) to 1961 (0.08%), but started to rise almost linearly after 1966 (0.29%) to 1989 (1.79%). The proportion of men who were discharged during military service because of asthma also increased. When the years 1966 and 1989 were compared, the proportions of men with the diagnosis of asthma at the call up examination, and of men exempted from military service because of disabling asthma, men discharged during military service because of asthma rose sixfold, fivefold, and 14-fold respectively. The proportions of men exempted for all other somatic causes were 4.6% in 1966, 7.5% in1976, and 5.4% in 1986. The increase was large, and could not conceivably be attributed to improved diagnostic methods, or changing requirements for fitness in the Finnish army. The increase in the proportion of men discharged during military service because of asthma supported this view. Similar trend was also reported in Sweden, with the prevalence of asthma noted in conscripts 1.9% in 1971, and 2.8% in 1981 (61).

Urban rural comparison of the symptom prevalence was examined in a study from UK (62). Adjustment for age and socioeconomic status did not change the results too much (Author's note). Although the prevalences of symptoms, and diagnosis of asthma were similar, more than 12 attacks per year tended to be about twice common in urban areas as in rural areas, and the reasons considered were air pollution from particulates, nitrogen dioxide, and motor vehicle emissions (62).

Airway hyper-responsiveness (Bronchial hyper-reactivity or Bronchial hyper-responsiveness) is an objective measure, which reflects the severity of asthma. Prevalence of increased airway responsiveness were reported as 22% in East Boston USA (1984, among 6-24 years aged), 18% in Australia (1987, among 8-11 years aged), and 22% in New Zealand (1986, among 9 years aged) (19).

Changes in asthma prevalence over 15 years were investigated in another study conducted among 12 year-old children living in **South Wales, UK** (63). The survey was conducted in 1973 (818 children) and 1988 (965 children) using a short questionnaire sent to parents, PEFR measurement and exercise testing for airway responsiveness. The prevalence percentages for total and (boys/girls) were: wheeze in the last 12 months 9.8 (12.3/7.2) in 1973; 15.2 (17.8/12.6) in 1988; reported asthma and wheezing in the last 12 months 4.2 (5.6/2.7), in 1973; 9.1 (10.3/7.9) in 1988; hay fever ever 9.4 (11.2/7.7), and 9.4 in 1973; 14.9 (18.4/11.3), and 14.9 in 1988. The proportion of children whose wheezing was attributed to running increased from 34.1% in 1973 to 47.0% in 1988, and that attributed to animals increased from 10.1% in 1973 to 16.3% in 1988. Bronchial responsiveness measured as fall in PEFR after the exercise as a percentage of the initial PEFR was 2.0% in 1973, and 4.1% in 1988. The percentage of children who had taken bronchodilators or other treatment for asthma 8 hours before the interview increased from 1% in 1973 to 4% in 1988. The increased prevalence of symptoms, and airway hyper-responsiveness, and increased proportion of wheezing attributable to running, or animals all supported the hypothesis that this rise was real (63).

Changes in the prevalence of asthma was investigated in **Busselton, Western Australia** by serial cross sectional studies, 9 years apart in 1981 and 1990 among 553 subjects aged 18-55 years in 1981 and 1028 subjects aged 18-55 years in 1990 (64). In both years, investigators tried to maintain the same sample distribution by age, gender, socioeconomic status similar to that of the total population. The prevalence of wheezing in the last 12 months (17.5% to 28.8%) and of diagnosed asthma (9.0% to 16.3%) increased in the second survey, predominantly in subjects less than 30 years of age. By contrast, airway responsiveness defined as 20% fall in FEV1 with a cumulative dose of 3.9 micromoles of histamine diphosphonate did not increase (10.6% in 1981 and 7.9% in 1990), while current asthma as defined by the combination of airway responsiveness and recent wheeze increased slightly (5.4% in 1981 and 6.3% in 1990). Comparison of the severity of airway responsiveness as measured by mean dose-response ratio between groups according to history of respiratory illness or atopic status did not reveal increased severity except for

the recent wheeze group. However, the prevalence of allergy symptoms almost doubled between 1981 and 1990, but allergy as measured by skin prick testing did not change much (any positive skin test 38.5% in 1981 and 41.2% in 1990, positive skin test for house dust mite: 24.9% in 1981 and 24.5% in 1990). The fact that prevalence of symptoms increased much more than that of airway responsiveness and the prominence of the increase among young adults raised the possibility of diagnostic labelling or environmental changes within this time period. Although the prevalence of symptoms related to allergy also increased, this was not associated with a similar increase in atopy. Thus, the findings were inconclusive for the explanation of the increased prevalence of symptoms.

Changes in asthma prevalence over 10 years, from 1982 to 1992 were investigated in another study conducted among 8-10 year old children living in two towns in **New South Wales, Australia**, **Belmont** which is coastal and humid, and **Wagga Wagga** which is inland and dry (65). Data for respiratory symptoms were collected by self-administered questionnaire given to the parents of children. Skin prick testing with five common aeroallergens was used to define atopy (positive reaction to any of these allergens), and histamine inhalation challenge test was used to define airway hyper-responsiveness (20% fall in FEV1 with a cumulative dose of 3.9 micromoles). Household dust samples were also collected and analysed for house dust mite concentrations. The prevalence of wheeze in the last 12 months increased in Belmont from 10.4% in 1982 to 27.6% in 1992, and in Wagga Wagga from 15.5% in 1982 to 23.1% in 1992. In addition the prevalence of asthma diagnosed in Belmont increased from 9.1% in 1982 to 37.7% in 1992, and in Wagga Wagga from 12.9% in 1982 to 29.7% in 1992. The prevalence of atopy did not change much between the surveys; in Belmont it was 27.7% in 1982, and 29.3% in 1992; and in Wagga Wagga it was 30.3% in 1982 and 34.8% in 1992. The prevalence of airway hyper-responsiveness as measured by histamine challenge test increased in both towns, mostly among atopics. The percentages with airway hyper-responsiveness among all children, and atopic children (in brackets) were in Belmont 9.1 (18.6) in 1982, 19.8 (47.2) in 1992; and in Wagga Wagga 11.7 (25.3) in 1982, 18.1 (36.8) in 1992. Dose response ratio as an indicator of the severity of airway hyper-responsiveness revealed that atopic

children had more severe airway hyper-responsiveness, and the severity had increased in 1992 compared to 1982, in both towns. The prevalence of house dust mites in household dust samples increased in Belmont from 94% in 1982 to 100% in 1992; in Wagga Wagga from 15% in 1982 to 90% in 1992, and geometric mean and (95% CI) of the house dust mites in 1 g of a dust sample also increased in Belmont from 224.9 (121.5, 416.4) in 1982 to 1240.4 (888.1,1735.4) in 1992; in Wagga Wagga from 66.7 (51.1, 85.4) in 1982 to 301.2 (193.2, 472.1) in 1992. The greater increase in prevalence of diagnosed asthma compared with the symptoms, or airway hyper-responsiveness, suggested that there was an increased awareness of asthma in the last years in both of the towns. Although the allergen load as measured by house dust mite increased, prevalence of atopy did not change much between 1982 and 1992, so this made the explanation by increased allergen load less plausible. Atopy was a significant effect modifier in the increase of airway hyper-responsiveness in Belmont, but not in Wagga Wagga, and could be due to the difference between house dust mite levels of the two towns, and role of house dust mite level in the development of airway hyper-responsiveness. Increased severity of airway hyper-responsiveness in the atopics compared with non-atopics was suggestive of the role of higher allergen levels in increasing airway hyper-responsiveness (65).

3.3. Relationship between Childhood and Adult Onset Asthma:

One of the main concerns in the natural history of asthma is the relationship between the asthma in the childhood and asthma in the adults. The classic view was that most of the childhood asthma does not progress to adult period and that of asthmatic children two thirds with milder symptoms grew out of asthma (66); however, there is now some evidence to the contrary.

Jenkins et al. followed 1494 Tasmanian children from age 7 in 1968 to 1991 (mean age: 29-32), for whom the parents had originally completed a questionnaire about a history of wheezing, asthma and other symptoms (67). Children were also tested with spirometry. During 1991, 2000 of the subjects in the birth cohort were randomly selected (1000 from those with reported asthma, 1000 from those for whom asthma was not reported), and a

follow-up questionnaire was sent to the 1723 subjects, who could be located. Information about the original responses was not given to the subjects. current asthma (an attack of asthma in the last 12 months) was reported in 25.6% of the subjects with childhood asthma, and 10.8% of the subjects without childhood asthma. Factors which were present at age of 7 and which independently predicted the current asthma were being female (OR:1.57, 95%CI: 1.19-2.08), a history of eczema (OR:1.45, 95%CI: 1.04-2.03), having a low or mild expiratory flow rate (inter-quartile OR: 1.40, 95%CI: 1.15-1.71), having a mother with a history of asthma (OR: 1.74, 95%CI: 1.23-2.47), or father with a history of asthma (OR: 1.68, 95%CI: 1.18, 2.38), and having had a childhood asthma (OR: 1.59, 95%CI: 1.10, 2.29). Among those who had childhood asthma, having the first attack after the age of 2 (OR:1.66, 95%CI: 1.17, 2.36) and or having had more than 10 attacks up to the age of 7 (OR: 1.70, 95%CI: 1.17, 2.48) further increased the risk (67).

In another study from **Melbourne, Australia,** Oswald et al. prospectively followed 7 year-old children with wheezing and asthma from 1963 for 28 years (68). During 1992, 401 of the 480 subjects were followed (86%), interviewed on the phone (n=101), and physically examined (n=300). The results suggest that the percentage of subjects with asthma in the adulthood increases with the severity of the disease in the childhood. Percentages of peristent asthma at age 35, in groups according to status at age 7 were: 8% in mild wheezy bronchitis, 15% in wheezy bronchitis, 32% in asthma, and 63% in severe asthma groups. The presence of atopy at age 7 did not influence the asthmatic status in the adulthood, and smoking behaviour was reported to be similar in the controls and the four groups (68).

3.4. Synthesis:

In summary, there is worldwide evidence for the increasing prevalence, morbidity, and mortality related to asthma. Strong evidence to this effect is provided by serial cross-sectional studies repeated over time with the same study instruments, and also from objective assessment of airway hyper-responsiveness. Wide variations between the countries do not appear to be solely due to differences in diagnostic labelling and has been

interpreted as indicating that asthma is a preventable disease, and offers the chance to investigate and control what appear to be mainly environmental risk factors. The increase in morbidity and mortality is not limited to particular age groups, and points to the presence of a cohort effect ie. it affects all generations. The rapidity of the increase makes a genetic explanation less likely. On the other hand, there is not enough evidence to implicate only an increase in allergen load over recent years, and the existing evidence cannot explain the trend completely. This has led to the speculation that populations are becoming more susceptible. Thus, there is a need for the investigation of the prevalence and determinants of asthma, coupled with other physiological measurements (to determine atopy, and airway hyperreactivity) using a standardised methodology, which would allow the comparison between different populations, and at different time points.

4. OCCUPATIONAL ASTHMA

4.1. Definitions:

Asthma in the workplace is usually considered under two headings: occupational asthma and work aggravated asthma. Occupational asthma has been defined as "a disease characterised by variable airflow limitation and/or non-specific bronchial hyper-responsiveness due to causes and conditions which are attributable to a particular occupational environment and not to stimuli encountered outside the workplace" (69, 70).

Work aggravated asthma is described as the "concurrent asthma worsened by nontoxic irritants or physical stimuli in the workplace" (70). Thus, a history of childhood asthma does not exclude the possibility that occupational asthma may develop after an appropriate workplace exposure.

Substantive knowledge indicates that about 250 agents can cause asthma. In addition, new agents are continually being identified and added to the list. Aetiologic agents involved in occupational asthma have been classified into immunological and non-immunological. Immunological agents are further divided into those that induce asthma through an immunoglobulin E (IgE) dependent mechanism, and those that induce through a non-IgE-dependent mechanism (71).

4.2. Criteria Used to Classify Occupational Asthma:

Aetiologic agents in occupational asthma have been classified by Chan-Yeung M. and Malo JL as follows (71):

1) Agents causing *asthma through immunological mechanisms*: these may be through:

a) IgE-dependent mechanisms from exposure high molecular weight proteins or polysaccharides, and some low molecular weight compounds. Occupational asthma due to IgE dependent agents mostly affects atopic subjects. Smoking has been shown to be an important determinant of some types of occupational asthma, but not others;

b) *Non-IgE-dependent* mechanisms: the majority of low molecular weight compounds induce asthma by mechanisms as yet unidentified. The clinical picture in these patients is compatible with that of an allergic disease. The majority of the affected subjects are non-atopic and non-smokers.

2) Agents causing *asthma through non-immunological mechanisms*: non-immunological asthma may or may not occur after a latency period of exposure to an agent which does not induce immune sensitisation as determined by currently available technology. The main distinction from immunological asthma is that in the majority of cases re-exposure of the affected subjects to small amounts of the offending agent does not reproduce the symptoms.

Another classification uses the occurrence of asthma after a latency period as the diagnostic criteria. Occupational asthma according to this classification is divided into:

a) *Occupational asthma with a latency period:* this encompasses all instances of immunological asthma for which an immunological mechanism has been identified and includes most high- and some low- molecular weight agents. For some of these agents immunological mechanism is still lacking, and indeed may not exist at all.
b) *Occupational asthma without a latency period*: the typical example is irritant induced asthma, which develops after exposure to high concentrations of irritant gases, fumes or chemicals on one or several occasions. The mechanism is not known. Pathologic changes in the airways of patients with irritant-induced asthma are similar to those of patients with occupational asthma with latency period, striking bronchial fibrosis found in some patients, and fewer T-lymphocytes in some others have suggested the absence of immunological mechanism (72).

Reactive airway dysfunction syndrome (RADS) is an example of irritant induced asthma. This occurs after exposure to high concentrations of irritant gases, fumes, or chemicals on one or several occasions (73). Brooks and Bernstein, two of the three authors responsible for introducing the term RADS, (74), have recently revised their description of irritant asthma to cover asthma of not so sudden onset, to lower exposure levels over a longer period, in whom preexisting allergy which is quiescent may have undergone recrudescence following exposure to irritants (75).

Agents are also classified as *inducers* of asthma, which both provoke airway narrowing and increase non-specific airway responsiveness, and non-specific *inciters* which provoke airway narrowing in individuals whose airways are hyper-responsive, but do not themselves increase airway hyper-responsiveness (76).

Airway hyper-responsiveness induced by methacholine or histamine is a characteristic feature of occupational asthma. The reactions induced by inhalation challenge tests may be

early, isolated late, biphasic, continuous, or atypical. Atypical reactions start two hours after a challenge and last for a few hours. A biphasic reaction includes an early reaction, which after spontaneous recovery is followed by a late reaction. In general, IgE-dependent agents induce isolated early reactions or biphasic reaction, and IgE-independent agents induce isolated late, biphasic, or atypical asthmatic reactions (71).

Occupational asthma on an allergic basis (caused by IgE dependent agents) may develop in an atopic worker with pre-existing non-occupational asthma, and will improve once the occupational exposure is terminated, but symptoms still may not disappear completely due to the underlying disease. On the other hand, symptoms of non-atopic workers who have no underlying disease and develop symptoms at work usually disappear when exposure is terminated. Purely allergic asthma is usually associated with symptom free intervals between the attacks, which are mostly precipitated by exposure to a specific allergen in the workplace. Clinical presentation of asthma in the workplace is not different from that of the other cases of asthma, and ranges from purely allergic (atopic) asthma, to pre-existing asthma aggravated by non-specific irritants at work, or even to status asthmaticus, a severe form of asthma that does not respond to usual treatment and may lead to acute respiratory insufficiency (77).

4.3. Broad Categories of Agents that Induce Asthma:

Occupational agents inducing asthma in the workplace can be conveniently considered in 3 major categories (78) as follows:

A) Agents with high molecular weight:

1) Animals, shellfish, fish, arthropods

2) Woods, plants, vegetables

3) Enzymes, and pharmaceuticals

B) Agents with low molecular weight:

1) Chemicals, including solder fluxes, dyes

2) Metals

C) Irritants:

1) Dusts,

2) Fumes, gases

Evidence for the role of these agents in the development of asthma comes mainly from case reports, and case series, and also from epidemiologic studies (71). The two basic types of epidemiologic study used in the investigation of occupational diseases are workforce-based and community-based studies. Workforce-based studies have the advantage of providing a better characterisation of the exposure, and the availability of a better comparison group sharing the similar selection factors for them to be included in the workforce. By contrast, community-based studies have the advantage of reaching the individuals who would not be available in the workforce for study as they have left or changed jobs after developing a health problem related to the particular occupational exposure in question. Another source of information is the data from health registries, and from occupational disease surveillance systems maintained for legal requirements (compensation cases of occupational diseases), or on voluntary basis as introduced in UK, Canada, Québec. Some of the epidemiological evidence for the role of occupational agents in the development of asthma is presented in the *Table's* included in section 4.4.

4.4. Surveillance Systems for Occupational Asthma:

Surveillance systems for occupational diseases based on voluntary reporting indicate that occupational asthma is currently the most commonly reported occupational lung disease in several jurisdictions including the UK (2), West Midlands (79), British Columbia, (3) and Québec, Canada (4). Asthma was reported as the most common occupational lung disease in all these areas and/or jurisdictions, with the percentage among reported occupational lung diseases ranging from 26.4 in United Kingdom, through 50.4 in British Columbia, and up to 63% in Québec (2-4). Sources of the information were respiratory and occupational disease specialists and pathologists, who were asked to report patients with suspected diagnosis of occupational disease, on a regular basis. Although there were no strict criteria to establish the diagnosis, the information was nevertheless useful in providing estimates of the incidence and causal agents for occupational asthma. Since the participant physicians were specialists with some knowledge of occupational asthma, reliability of the diagnosis was less of a problem. Causality assessment might be less reliable due to the practical limitations of most physicians to investigate the work environment; this may have led to better recognition of certain occupations, which are widely known to be associated with occupational asthma such as laboratory animal workers, bakers, solderers, and spray painters.

Table 4.4 summarises some of these results. Difference in the incidence rates and percentages of asthma cases may at least in part, be related to the differences in the industries operating in these areas. This is also reflected in the distribution of the most commonly reported industries or occupations. For instance, while isocyanate exposure is similar in all three studies, ranging from 16.2% to 22% of the working population, wood dust exposure is not, ranging from 6% in the UK to 41.9% in British Columbia. Another report from SWORD project surveillance scheme in United Kingdom, during 1989 and 1990 gave estimated incidence rate for asthma (per million per year) of 24 in men and 13 in women (80). In other words, in men incidence rates were almost twice those in women, yet asthma was still the most commonly reported occupational lung disease in women. There were also slight increases in rate with increased age: For instance, in Québec

Table 4.4: Estimated incidence rates of occupational asthma (number per million at risk per year) based on surveillance systems dependent on voluntary reporting:

Year, place Reference	Incidence Per million per year	Incidence in most frequently reported occupations Per million per year	Percentage of working populations exposed to the agents implicated
1989, United Kingdom (2)	22	Coach and spray painters: 639 Chemical processors: 424 Bakers: 409 Plastic making/processing: 409	Isocyanates: 22 Flour/grain dusts 8 Solder flux: 6 Wood dusts: 6
1989, West Midlands (80)	30	Painting, and related: 154 Material processing/making/repairing: 111 Farming, fishing: 77 Catering/cleaning/hairdressing/personal service: 50	Not available
1991, British Columbia (3)	92	Not available	Red cedar dust: 41.9 Chemicals: 19.4 Isocyanates: 16.2 Smoke inhalation: 6.5
1992, Québec (4)	63 (based on gender specific rates) 79 (men) 42 (women)	Wood industries: 691.1 Food: 684.0 Furniture and fixture: 487.8 Chemical 376.6	Isocyanates: 17.1 Flour: 11.5 Wood dust: 10.8 Farm/laboratory animal: 6.6

incidence rates (per million per year) in: 15-24 years, 25-44 years, 45 years and over were 55, 57, and 62 respectively (4); in United Kingdom for the ages 16-29 years, 30-44 years, 45 years and over they were 17, 23, and 31 respectively in men, and 11, 12, 15 in women (80). Possible explanations for the trend were higher likelihood of referral of older individuals to a chest physician, when they develop symptoms, and the preference of older individuals to stay in their jobs for security reasons, resulting in late application for medical help (80). The number of cases reported in surveillance scheme from UK was similar to those notified in legal jurisdictions, though almost half of the cases were related to agents not included in the prescribed list of agents (80). In Québec, the number of cases reported in the surveillance scheme was twice that notified under legal jurisdictions, and 15% of the reported occupational lung diseases were not covered by the Workers' Compensation Board, and 67% of these were for asthma (4). Differences between the surveillance schemes and legal notification system could be due to over-reporting in the surveillance scheme, and/or under-reporting in the legal notification system (4). Although, no systemic validation of the reported cases had been undertaken, these estimates still could be an underestimate rather than an overestimate. This has been described as the "tip of an iceberg", because, "the recognition of occupational aetiology both by the patient and the physician is essential to be reported in these surveillance schemes, but is not well established" (80).

4.5. Community-based Studies of Occupational Asthma:

Findings from some of the community-based studies, which provided evidence for the role of occupational exposures in the development of asthma are given in *Table* 4.5. Direct comparison of the study findings is not appropriate since these were conducted at different time points in general population samples from various countries in different age groups by using different study definitions of asthma and occupational exposure. Prevalences range from 6.1% to 13.5% for wheeze, 4.1% to 7.7% for physician diagnosed asthma, and 2.4% for clinical examination. One of the studies was a follow-up study and found cumulative incidence over 25 years of 29.5% and 18.3% in blue collar and white collar workers,

Table 4.5: Community based studies on occupational asthma:

Publication Year, Country	Population M: Men, W: Women	Age range (year)	Study definition of asthma	Prevalence of asthma %	Exposure % D: dust, G: gases, F: fumes	Relative risk estimate	PARP* Reference
1987, US	3646 M, 1952 W	18-64	Physician diagnosed	7.7	Industrial/	1.93 (1.06, 3.50)	37.3 (81)
			Occupational asthma	1.2	Agricultural: (N/A)		
1987, US	3848 M, 4667 W	25-74	Persistent wheeze	6.0	D: 31	1.54 (1.29, 1.84)	33.2
					G/F: 30	1.29 (1.08, 1.55)	26.7 (82)
1988, France	8692 M, 7772 W	25-59	Wheeze any time	11.5	M: 34	1.63 (1.45, 1.85)	16.9
					W: 23	1.70 (1.46, 1.98)	13.2 (83)
1991, Norway	650 M, 625 W	18-73	Asthma	2.4	Moderate: 26	1.2 (0.7, 2.0)	5.9
			COPD	5.3	High: 3	2.5 (1.1, 5.9)	1.5 (84)
1991, Norway	2220 M, 2249 W	15-70	Physician diagnosed	4.1	D/G: 29	1.8 (1.3, 2.6)	18.9(85)
1992, Netherlands	878 M	40-59	CNSLD	Incidence 23.8	D/G/F:51.8	1.68 (1.18, 2.39)	24.8 (86)
1992, China	1762 M, 1844 W	40-69	Wheeze	13.5	D: 32	1.02 (0.77,1.36)	0.06
					G/F: 19	1.62 (1.18, 2.21)	9.6 (87)
1994, Singapore	787asthma 1591control	20-54	Asthma patients	N/A	Service/ Production:78.8	1.72 (1.36, 2.19)	33 (88)

respectively (86). Dust, gas, fume, and occupations in service, production, agriculture, industrial, etc. were considered as the occupational exposures in these studies. Reported prevalence of these exposures was mostly around 15-30%. One of the studies reported about 50% blue-collar workers in the general population, and another reported about 80% service or industrial occupation (86, 88). Relative risk estimates as adjusted for age, gender, smoking, and place of residence ranged from 1.02 to 2.5, mostly excluding unity in 95% confidence interval. The study in Norway suggested dose response relationship with odds ratio for moderate and high exposure to dust, gases, and fumes of 1.2 and 2.5, respectively (84). Population attributable risk percentages were estimated in the range of about 7% to 37%. Although these differences may be at least in part due to differences in the methodology, differences in the distribution of occupational exposures are also likely to be an explanation.

4.6. Workforce-based Studies of Occupational Asthma:

Findings from some of the workforce-based studies, which provided some evidence for the role of occupational exposures in the development of asthma are given in the *Table's* 4.6.1 and 4.6.2 for high molecular weight agents and low molecular weight agents, respectively. Response rates in most studies were above 80%. Different asthma related symptoms, such as wheeze, chest tightness, and shortness of breath were used to establish the presence of asthma, and some studies included objective measurements such as specific inhalation tests and PEFR monitoring after the worker returned to work (92, 96, 105). The presence of symptoms at work, on exposure to specific agents, and/or improvement of these symptoms on weekends or holidays away from work were considered as indicating the work-relatedness of asthma.

Because of the health selection factors involved, the study populations most likely failed to include workers who had health problems related to work at the time of the survey. Thus the prevalence figures obtained are likely to be an underestimate of the true prevalence. Indeed, some of these studies provided evidence that this had occurred. In the spiramycin

Table 4.6.1: Workforce based studies on occupational asthma: High Molecular Weight Agent:

Workforce, M: Men, W: Women, Country	Mean Age	Study definition of asthma (T: Chest tightness, W: Wheeze, C: Cough, SOB: Shortness of breath)	Asthma %	Smoker %	Atopy %	Reference Publication Year
Detergent industry, 67M, 31W, Australia	34.7	Symptoms. T, SOB, C, W Immediate: within 0.5 hour Delayed: 4-5 hours after exposure	50 13..3 36.7	72.4	63.8	(89), 1971
Laboratory animal, 280M 119W, US	30.9	Bronchospasm after exposure Bronhoprovocation with exposure	7.0 2.5	N/A	21.5	(90) 1980
Locust breeding, 67M 42W, UK	N/A	W or SOB improving away from work	11.5	39.5	43.4	(91) 1980
Papain workers, 33, Germany	38	Asthma symptoms Bronhoprovocation with papain	45.4 24.2	N/A	39.4	(92), 1982
Psyllium processing, 63M, 67W, Quebec, Canada	36.9	Occupational asthma: T/SOB/C improved away from work	30	36.2	61.7	(93), 1987
Spiramycin processing, 25M 26W, Quebec, Canada	37	C, W, T, SOB, and nocturnal symptoms: Symptoms during work:	8 12	51	41	(94), 1988
Bakery (flour), 174M 105W, UK	N/A	Any of: W, T, SOB / Better away from work	33/11	49.1	39.7	(95), 1989
Snow crab processing 303, Quebec, Canada	N/A	Symptoms on working days: Specificinhalation/PEFmonitoring/spirometry	21.1 15.6	66.5	10.7	(96), 1994

Table 4.6.2: Workforce based studies on occupational asthma: Low Molecular Weight Agent, and irritants:

Workforce, M: Men, W: Women, Country	Mean Age	Study definition of asthma (T: Chest tightness, W: Wheeze, C: Cough, SOB: Shortness of breath)	Asthma %	Smoker %	Atopy %	Reference Publication Year
Western cedar 1321M, 476W, Japan	N/A	Asthma symptoms: within 30 minutes after the contact with western cedar	3.4	N/A	8	(97), 1973
Toluene Diisocyanate Manufacture, 103, US	N/A	Lower respiratory symptoms beginning after work	29.2	N/A	27.8	(98), 1977
		Exposed (89):	7.1			
		Unexposed (14):				
Solder manufacture, 29M, 15W, UK	28.7	W or SOB better away from work:	11.1	73.3	17.8	(102), 1981
		Electronic workers (446):	21.7			
Aluminium smelter, 797M, British Columbia, Canada	36.9	W without colds: High exposure (495)	17.1	57.6	19.2	(99), 1983
		Medium exposure (302)	13.6	46.7	21.5	
		Office workers (713)	10.5	42.8	23.7	
Western Red Cedar, 652M, British Columbia, Canada	43.3	Four of the symptom sets:	10.4	33.4	19.2	(100), 1984
		Office workers (440M):	4.3	30.2	32.7	
		Work-related symptoms:	4.1			
		Office workers (440M):	1.6			

/ continued over

Table 4.6.2: Workforce based studies on occupational asthma: Low Molecular Weight Agent, and irritants:

Workforce, M: Men, W: Women, Country	Mean Age	Study definition of asthma (T: Chest tightness, W: Wheeze, C: Cough, SOB: Shortness of breath)	Asthma %	Smoker %	Atopy %	Reference Publication Year
Phtalic anhydride, 128, Sweden	N/A	Recurrent episodes of SOB with W, and C in relation to Phtalic anhydride exposure:	18	74.6	28.5	(102), 1986
		Present workers (48):	12	62.5	24.1	
		Former workers (70):	21	82.8	50.0	
Cigar and cigarette factory, 89M 133W, Italy	38.2	Asthma:	4.5	50.4	24.3	(103), 1986
		W:	19.4			
		SOB with W:	6.8			
Platinum factory, 86M, 5W, UK	N/A	Asthma symptoms (excluding upper respiratory tract infections)	53.8	63	31.8	(104), 1989
Eastern White Cedar, 33M 10W, Quebec, Canada	31	At least 2 of: W, T, SOB, C, T:	65	69.8	N/A	(105), 1994
		Improving away from work:	58			
		Physician diagnosed asthma:	12			
		Specific inhalation challenge:	43			

study, one of the 3 workers who were absent in the second assessment had symptoms suggestive of occupational asthma (94). During the follow-up of platinum refinery workers from 1973 to 1980, 22 workers who developed skin sensitivity to platinum salts and respiratory symptoms had left work at the time of the second study (104). Prevalence of pthalic anhydride induced asthma was higher among the former workers (21.4%) than the present workers (12.5%) (102). In a longitudinal survey by Chan-Yeung et al (not shown in *Table* 4.6.2), aluminium smelter workers involved only in the first survey had slightly higher prevalence of respiratory symptoms (12.5% wheeze, 14.4% dyspnoea), and slightly lower FEV1 (3.907± 852 ml), than those involved in both surveys (12.1% wheeze, 11.4% dyspnoea, FEV1: 3.964± 725 ml) (106). Prevalences for occupational asthma ranged from 7.5% (laboratory animal) (90) to 50% (detergent industry) (89) for HMW agents, and from 3.4% (western red cedar) (97) to 58% (eastern white cedar) (105) for LMW agents. There was some evidence for a dose response relationship: prevalence of wheeze increased from 13.6% with medium exposure to 17.1% with high exposure among aluminium smelter workers (100). In other studies, prevalence was increased in the exposed compared with non-exposed group. For instance, western red cedar workers had a higher prevalence of work-related symptoms of asthma, than office workers (4.1% vs 1.6%) (104); toluene diisocyanate workers had a higher prevalence of lower respiratory tract symptoms (29.2%) than unexposed subjects (7.1%) (98). Different study definitions gave also different prevalence figures: eastern white cedar workers had a 58% prevalence of symptoms, which improved away from work, 12% prevalence of physician diagnosed asthma, and 43% prevalence of response to specific inhalation test (105). Similarly snow crab processing workers had a 21.1% prevalence of symptoms on working days, and 15.6% prevalence of response to specific inhalation test, or PEFR monitoring compatible with occupational asthma (96).

4.7. Synthesis:

Evidence exists for the important role of occupational exposures in the genesis of adult asthma in a number of countries. Voluntary based surveillance schemes showed that asthma was the most common occupational lung disease in UK (26%), British Colombia (50%), and Québec (63%) Canada (2-4). There were, however differences in the agents implicated as the main responsible exposures in different countries/jurisdictions (see *Table* 4.4). Prevalence of asthma and Relative risk estimate of occupational exposures for asthma were in the range of 6%-14%, and 1.02-2.5, with an evidence for increased risk with increased exposure (see *Table* 4.5). Community-based studies found the population attributable risk of reported occupational exposures (dusts, gases, fumes, production industries) ranging from 6 to 37%. However different study definitions of asthma make it almost impossible to compare these findings. Although community-based studies had the advantage of controlling the bias by 'healthy' worker effect due to leaving or transferring job, recall bias is a possible source of error, though this may have been less strong than expected since participation in these studies was not related to the occupational exposures. Workforce-based studies reported prevalence of asthma in different industries ranging from 5% to 65%, again based on different definitions (see *Table*'s 4.6.1-2). Some of the studies used more objective means to establish the presence of occupational asthma (90, 92, 96, 105). Some studies found higher prevalence of asthma symptoms in those leaving the workplace, suggesting the presence of 'healthy' worker effect in workforce-based studies. Community-based epidemiologic studies using standardised protocols and means for the objective assessment of asthma could be expected to contribute to the knowledge for the causative role of occupational exposures in adult onset asthma.

4.8. Work-relatedness of Airway Disease:

The work-relatedness of disease conditions as defined by International Labor Organization, includes the four categories: (i) conditions caused only by specific exposures; (ii) conditions of multi-factorial aetiology in which work exposures may be the main or one of several etiologic factors; (iii) conditions to which an individual is

susceptible and in which the expression of disease is precipitated by a work-related exposure; and (iv) pre-existing conditions aggravated by a work-related exposure. Conditions falling into category 1 are referred to as occupational diseases by WHO, and those in categories 2, 3 and 4 as work-related diseases. According to Becklake, occupational asthma could be regarded as falling in any of the 4 categories depending on its definition, the particular agent involved, and the features of the asthma or asthma-like reaction it evokes (55). Among the occupational lung diseases, occupational asthma is unique in that, the diagnosis can be confirmed by objective means in a truly scientific and experimental way, as opposed to pneumoconiosis, where the exposure history and characteristic changes on chest radiograph are regarded as enough to establish the diagnosis (107, 108). This view restricts the diagnosis of occupational asthma to cases in which an asthmagenic agent can be identified in the workplace, and/or that agent specific laboratory exposures are equivalent to exposures in workplaces contaminated by other pollutants (dusts, gases, fumes), and heat. Once a diagnosis of occupational asthma is made, the affected worker should be withdrawn from the work environment to avoid further deterioration of asthma and to minimise the long term sequelae (107).

Proper diagnosis and causality assessment are necessary both for the protection of the health of affected worker, and for the application of measures to prevent the occurrence of new cases. Determining causality, and the strength of association between occupational exposures and asthma are usually the most difficult steps in the individual case (109). Compensation for occupational asthma is generally based on exposure to a specific sensitising agent rather than exposure to non-specific irritants such as particles, gas, vapours, exercise, or cold air at the work environment (110, 111). This distinction is justified by the scientific evidence, which relates induction of airway hyper-responsiveness, and increased severity of asthma to exposure to sensitising agents. Although exposure to irritant agents may increase the severity of asthma, their role in inducing airway hyper-responsiveness is not considered as convincing. It has been argued that compensating every patient with exacerbated asthma due to irritant factors in the workplace would mean that almost every asthmatic patient would be eligible, since asthmatics could argue that

exposure to irritants related to work was responsible for the exacerbations (76, 110). Thus, in several jurisdictions every case of occupational asthma must be investigated by objective means to be accepted for compensation. The preferred method is specific inhalation challenge test in a laboratory setting or at work, and may also include monitoring peak expiratory flow rate at work alone or combined with non-specific bronchial challenge test (110). In other jurisdictions as in the UK, compensation is limited to certain recognised exposures (112).

Airway hyper-responsiveness assessed by non-specific airway challenge test with pharmacologic agents such as methacholine and histamine may indicate that the diagnosis of asthma due to a specific agent is highly likely (80%), particularly when present with skin reactivity to the same agent. Absence of response to non-specific airway challenge in an individual, who is still working is considered evidence (even strong evidence) against the diagnosis of occupational asthma, but does not exclude the diagnosis, as it may have resolved after a period away from work (113, 114). Challenge tests should be repeated after 2 weeks on the same job to exclude the diagnosis (78, 108). Airway hyper-responsiveness was reported to start reverting to normal soon after exposure ceases but a delay of as long as 2 years after leaving work has been reported in snow crab processing (115).

Table 4.8.1 shows that occupational asthma is the most common respiratory disease claimed for compensation in Québec, in 1988 (110).

Table 4.8.2 shows the distribution of claims for respiratory disease in Québec in 1977 and in 1988 (110). There was a striking increase in the number of claims and accepted claims for asthma in Québec in the 10 year period 1977 to 1987, and a decrease in the number of claims and accepted claims for asbestosis and silicosis. In the case of asbestosis, this is thought to reflect the much more stringent standards for airborne particulates, introduced in 1970's.

Table 4.8.1: Respiratory conditions assessed for workers' compensation in 1988 in Quebec (110):

Diagnosis	New claims	Reassessments	Total
Occupational asthma	81	89	170
Asbestosis	30	111	141
Silicosis	36	103	139
Cancer	46	38	84
Occupational broncitis	15	8	23
Other	20	37	57

Table 4.8.2: Claims for respiratory disease in Quebec in 1977 and in 1988 (110):

	1977		1987	
Diagnosis	Total number of claims	Accepted claims	Total number of claims	Accepted claims
Asbestosis	881	43	112	36
Silicosis	223	36	83	62
Occupational asthma	12	6	213	97

Table 4.8.3: Officially registered cases of occupational asthma, proven by airway challenges with specific agents were reported from Finland (111, 116):

	New cases of occupational asthma in age groups				
Year	0-29 year n (%)	30-49 year n (%)	50- + year n (%)	Total n (%)	Incidence /million/y
1976	18 (22.5)	38 (47.5)	24 (30.0)	80 (100)	36.4
1986				227 Men: 118, Women: 109	
1993				386 Men: 201, Women: 185	192

Table 4.8.3 shows the incidence rate, age distribution and changes in the number of cases in and between 1976 and 1993 in Finland (111, 116). In this period, there was a five-fold increase in the annual incidence of occupational asthma, which was almost parallel to the increase in the number of new cases of occupational asthma (as there was no big change in the population in the working age group).

Information on the incidence of asthma in the general population during 1986 to 1993 (not shown in the Table) showed that total number of new cases of asthma in women increased from 3302 to 4717 (43%), and in men not changed much from 3343 to 3339 (-0.1%). The majority of the increase was seen in the younger age groups: 15-29 year: 87% in men, 91% in women, 30-49 year: 46% in men, 60% in women. In the age group 50-64 year there was a 43% decrease in men, and 7% increase in women (116). This age difference was attributed to the mostly atopic origin of the new cases of asthma. Still, 30% of the new cases of occupational asthma occurred in the age group older than 50 year, which could be due to selective behaviour of the older individuals in seeking for medical care for their work related health problems. Increase in both the incidence of asthma and occupational asthma might be partially related to better awareness and improved diagnosis of the disease. However, this is not a likely explanation, as the change was gradual during this time period.

Occupational asthma has been considered as a good model to elucidate the pathogenesis of asthma, since both exposure and host susceptibility factors can be monitored, and the development of symptoms, antibodies, airway hyper-responsiveness, and lung function abnormalities can be assessed regularly (117).

5. THE HEALTHY WORKER EFFECT

5.1. Definitions and Sources:

An important source of selection bias in studying the epidemiology of occupational diseases is known as 'Healthy' Worker Effect. Ignoring the 'healthy' worker effect can lead to underestimation of ill health consequences of the occupational exposure, and asthma is no exception to that.

The dictionary of epidemiology (Last 1995), describes "Healthy Worker Effect" as a "phenomenon observed initially in studies of occupational diseases. Workers usually exhibit lower overall death rates than the general population, due to the fact that the severely ill and chronically disabled are ordinarily excluded from employment." Then Last adds that "death rates in the general population may be inappropriate for comparison if this effect is not taken into account." (118)

The term was originally introduced to describe a historical cohort mortality study of male rubber workers in Akron, Ohio, followed from 1964 to 1972, and, as is usual in mortality studies rates of the workers were compared with a standard population, in this example US male population (119). Age specific mortality rates of the US male population were used to calculate the expected number of deaths, and divided by the observed number of deaths, to obtain standardised mortality rates, and these were used to compare the mortality in the cohort with that in the general population, taking the differences in age distribution into account. The study yielded a lower mortality rate in the cohort of rubber workers than the general population, as reflected by a standardised mortality rate below unity. The explanation by the authors was: "there is a strong selection process at play, wherein to be employable in an industrial workforce, an individual must be relatively healthy and active. This selection factor acts to produce a 'healthy worker effect', such that in an industry free of significant life-shortening hazards, death rates within the workforce in question will be less than in the general population. Individuals who do not meet the

requirements for the specific industry, do not enter that industry. Those whose health deteriorates below that level do not remain in the industry." (119).

The classical description of the condition is given using mortality studies as the example and it is less well recognised in studies of morbidity where there is an even greater potential for 'healthy' worker effect to operate. This is especially so for the chronic non-malignant disease due to the presence of symptoms that accompany many of these conditions, symptoms which are often clearly work related (as is the case for occupational asthma) and would lead the worker to leave or change his/her job (5). There are two widely recognised sources of 'healthy' worker effect (HWE); those are:

1) Healthy hire: Initial selection of healthier individuals at time of hire;

2) Healthy worker survivor effect : due to less healthy workers leaving the workforce; or transferring to jobs with lower exposure." (5)

An interview study in Sweden with 5346 men and 5486 women, aged 25 to 74 years, provided some evidence for the healthy worker survivor effect (120). Detailed occupational and medical histories of the study subjects revealed an association between long term illnesses including diseases of the musculoskeletal system and circulatory system, and job transfer from physically heavy jobs to physically light jobs. Those who moved from physically heavy jobs to physically light jobs had higher prevalence of long term illnesses than those who had always been in physically light jobs (age adjusted relative risks and 90% confidence intervals were 1.37 (1.23, 1.54) for men, and 1.54 (1.25, 1.67) (120).

In a 12-year follow-up study of Paris area workers from several industries, the lung function levels of 66 workers exposed to silica dust and abrasives were compared with 196 men with slight or no exposure (121). Stratification of the workers according to age at the beginning of the study demonstrated that, those aged 30-39 years who were exposed had higher FEV1, but a higher rate of decline in FEV1 during the follow-up than the comparison group of the same age, but not exposed. By contrast, the older age groups,

40-49 years and 50-54 years with exposure, had both lower levels of FEV1 than the comparison group, as well as a higher rate of decline in FEV1 during the follow-up compared to the age matched non-exposure group. None of these men had changed their jobs during the follow-up (121). A cross sectional study of the workers aged 30-39 years, would have failed to identify the effect of exposure on lung function, and would have underestimated the effect in the older workers.

Zejda et al, analysed annual lung function survey data on 164 new recruits hired for work in grain elevators in **Saskatchewan, Canada** (122). They addressed the question of health selection by comparing workers with different duration of follow-up, and showed that the average decline in lung function per year was associated with duration of follow-up. Thus the annual decline in FEV1 (ml) was 224 in the group who were present for only two surveys, 130 in the group present for three surveys, and 70 group present for all four surveys, suggesting that those, who remained in the industry beyond the fourth annual survey were "survivors", and were least susceptible to lung function decline from exposure

5.2. Bias Due to the 'Healthy' Worker Effect:

An important source of bias in assessing the work-relatedness of a condition is the comparison of workers with general population. Thus, intra-cohort comparisons of workers with different levels of exposure will reduce the bias in all studies. However, survivor bias can still operate, and at times be a bigger threat to the study inferences in such comparisons (especially when the comparison group includes workers who left or changed their jobs). Direct evidence for 'healthy' worker effect can be provided by longitudinal studies, in which less healthy workers are more likely to leave or transfer from high exposure to low exposure, particularly if the follow-up includes retirees. Indirect evidence comes from cross-sectional studies, in which those exposed for longer periods are healthier than shorter exposed group, or the exposed are healthier than external reference group (for those who left their jobs); or the high exposure group is healthier than low exposure reference group (for those who changed their jobs) (5). Recognition of the

'healthy' worker effect requires the prior knowledge about the potential hazard of the occupational exposure.

5.3 Strategies to Minimise Bias:

Suggested strategies to reduce the 'healthy' worker effect are summarised below, according to the study design (5):

In longitudinal studies stratification of the workers by current employment status helps to deal with the HWE due to "job quit", and stratification by time since transfer helps to deal with the HWE due to "job transfer ".

In cross sectional studies, an interesting method introduced to deal with the 'healthy' worker effect of two types is the extraction of the "incidence" from "prevalence" data (5). In this method, time of onset of the ill health condition under question is used to estimate the annual incidence rates conditional on being an active worker at the time of the survey. With the assumption that incidence rates would be constant in the absence of survivor bias, the adjusted rate ratio can be calculated based on the most recent incidence density, which in the presence of 'healthy' worker effect be higher than that of the previous years. Stratification by time since transfer can also help to deal with the 'healthy' worker effect due to "transfer job".

Community-based studies are less compromised of 'healthy' worker effect than longitudinal studies, because, if sampling is random, workers who leave the workplace will be identified for study in proportion to their numbers in the population (123).

A good illustration of the fact and the strategy to deal with it is provided by Eisen et al., in their reanalysis of a cross-sectional study of asthma in a cohort of auto-workers with exposure to metal working fluids (MWF) (124). Metalworking fluids are widely used in

lubricating and cooling metal working operations, and include specific sensitisers, irritants, and toxicants like colophony, formaldehyde, ethanolamine, a variety of metals such as cobalt, chromium, and nickel, as well as microbial contaminants. There is some evidence, mainly clinical, for the asthmagenic potential of MWF, but the epidemiological evidence is less consistent, sometimes suggesting a negative association. To examine the bias through 'healthy' worker effect, in the non-significant results of data on 1,811 auto-workers, the investigators classified physician diagnosed asthma according to its temporal relation to the date of hire as before or after their hire, and defined exposure within 2 years of the onset. Comparison of the incidence rate ratios by the Cox proportional hazards model revealed a rate ratio estimate of 4 (95%CI: 1.6-10.1) for any synthetic MWF exposure in 2 year prior to onset. Further examination of the transfer bias was made by comparison of the exposure trajectories of the workers with controls with the same type of exposure at the time of onset of asthma symptoms. By the time of survey, cases were more likely to be working in jobs without direct exposure (45% vs. 34%), and less likely to be exposed to MWF, either synthetic (10% vs. 20%) or straight fluids (21% vs. 28%) or MWF in grinding operations (7% vs. 17%) (126).

5.4. Synthesis:

The 'healthy' worker effect is a potential source of bias in occupational epidemiology. The main explanation is the fact that workers should have a certain level of health and maintain this level to be employed. Occurrence of a health problem in the workplace can lead to the worker's leaving or transferring his/her job, which makes it difficult to investigate the occurrence of this health problem in workplace studies, and gives an underestimate of the association. Recognition of the problem is the key factor to its documentation and to dealing with it through certain strategies. In this respect, community-based studies have the advantage over workforce-based studies, as they also include those who left or changed their jobs in their study population.

6. INTERNATIONAL STUDIES CONDUCTED TO INVESTIGATE THE STATUS OF ASTHMA

6.1. Background:

Increasing prevalence, morbidity and mortality related to asthma has been and remains a challenge to researchers from many countries. The wide differences between countries, and between different time periods have usually been difficult to interpret, due to the methodological differences. These inconsistencies have led to an appreciation of the role of, and need for epidemiologic studies in aetiologic research into asthma. For instance, Burney has argued that, since asthma was in large part an acquired condition, epidemiological investigations can be expected to provide information on the prevalence, causes, and the effectiveness in the management of asthma, and it is unlikely that the mechanisms of a disease will be discovered before its cause (18).

Against this background, there have been two major international initiatives to develop standardised methods for use in epidemiologic studies of asthma, the European Community Respiratory Health Survey (ECRHS) in which the target population is adults aged 20 to 44 years (1), and the International Study of Asthma and Allergy in Children (ISAAC) in which the target populations are children aged 6 to 7 years, and 14 to 15 years (125).

Pertinent to the present research is the ECRHS, which is described in some detail below, since the study of Lung Health in the Canadian Environment used the ECRHS protocol and most of the same methodology.

6.2. The European Community Respiratory Health Survey (ECRHS) Protocol and Methodology:

Since 1990, the European Community has sponsored investigations to collect information on the determinants of asthma prevalence and information on the management of asthma under the title of ECRHS (1). This study included 33 centres in 11 countries in the European Community, 15 centres in 5 countries in cooperation with the European Community, and 15 centres in 7 other countries, of which one was Canada, where 6 centres took part (1).

Specific objectives of the ECRHS were (1):

1) To estimate the variation in severity and prevalence of asthma, asthma-like symptoms and bronchial lability in Europe;

2) To estimate the variation in exposure to known or suspected risk factors for asthma, to measure their association with asthma, and to further assess the extent to which they explain variations in prevalence across Europe;

3) To estimate the variation in treatment practices for asthma in the European Community.

In each centre, the sampling frame chosen was to cover areas with a total population of around 150, 000, targeting adults aged 20-44 years. To allow analysis of differences between areas, and at least some within country analysis, as well as to reduce the confounding effect of countries and languages, the study aimed to include 30 areas throughout the European Community, and at least 3 areas within each country (1).

Design: The study design was a two stage cross-sectional survey, with some laboratory investigations in the second stage. The first stage included a screening questionnaire to a representative sample of 20-44 year old men and women resident in the area. The second stage targeted a random sample of all individuals who were included in the first stage. Sample size calculation was based on the assumption that prevalence of symptoms would

be approximately 5% and that the prevalence of airway hyper-responsiveness approximately 14%, and that the study should have a 90% chance of detecting a twofold variation in the prevalence between any two areas. The suggested sample sizes in each area were 1,500 each sex for the first stage and 300 each for men and women for the second stage of the study (1).

Questionnaires: These were developed from pre-existing questionnaires, which had already been used in multinational studies. The screening questionnaire used the questions from International Union Against Tuberculosis and Lung Disease (IUATLD) 1984 questionnaire (126, 127). Smoking habit was assessed with questions adapted from American Thoracic Society (ATS) questionnaire (128), home environment questions were derived from those used the Children's Health Study (Harvard School of Public Health and Canadian Health and Welfare) (1). A new questionnaire was devised for use of medication and of health services, as there was no questionnaire available at that time. Occupation and social status questions were taken from the Office of Population Censuses and Surveys (129).

Allergy tests: Two tests were used to assess atopy, skin prick testing and serum IgE measurement. Lancets, precoated with standardised lyophilized allergen extracts were used for skin testing. In all centres a standard list of allergens were used including Dermatophagoides pteronyssinus, cat, Alternaria alternata, Cladosporium herbatum, Timothy, grass, birch, Parietaria judaica, olive and ragweed with a positive control (histamine) and a negative control (uncoated). Each area could add up to two allergens of local importance. Specific and total IgE was measured by Pharmacia CAP system. Specific IgE was measured against Dermatophagoides pteronyssinus, cat, Cladosporium herbatum, grass, and a local allergen, birch for northern Europe, Parietaria for southern Europe, and ragweed for US and Canada (1).

6.3. Validation of the Questionnaires:

Testing the repeatability and the validity of the questionnaires used in the study was considered very important. Repeatability of the IUATLD asthma symptom questionnaire was assessed in a study of four clinical centres in Europe. The centres were Nottingham (England), Berlin (Germany), Helsinki (Finland), and Paris (France). English, German, Finnish, French translations of the questionnaires were applied to 20 diagnosed asthmatics and 20 control subjects in each centre. Repeatability was assessed by a second identical test completed after a minimum of two weeks, and measured both by absolute repeatability and relative repeatability using Cohen's kappa (κ). Information about the repeatability of some of the questionnaire items is given in *Table* 6.3.1 (130). Thus, absolute repeatability of the questions was good for all questions. Relative repeatability was good for most of the questions, especially for questions on asthma and wheeze. There were no major differences between the centres.

Observations on between country differences in the screening questionnaire used in the first stage sampling in ECRHS protocol are also of interest. Prevalences of some symptoms standardised for age and gender are given in *Table* 6.3.2 (131). Thus, the results of the screening questionnaire were distributed in 48 centres to representative samples of men and women between 20-44 years age and revealed substantive between centre differences in asthma symptoms. These centres were mostly in Western Europe, but also included centres from Australia, New Zealand, Algeria, India, and USA. Translation from English (except for the Basque and Catalan questionnaires, which were translated from Spanish) and back-translation to English, and checking of the two translations were carried out. The translators were asked to report difficulties in translation, which was not common according to the authors' note. Finally the questionnaire was sent out in 17 languages, evenly distributed in all seasons, up to three times in most centres if there was no response. For comparison, all prevalence figures were directly standardised by sex and age group, using the 20-24, 25-34 and 35-44 years, the first age group being given half the weight of the other two. Response rates were mostly higher than 70%, with a median of 78% (range 36-99%) and were higher in females then males except for Huelva, Spain. There was

Table 6.3.1: Repeatability of questionnaire information in the ECRHS (130):

	Absolute Repeatability				Relative Repeatability			
Symptom	Finland	G*	France	N†	Finland	G*	France	N†
Wheeze	0.96	0.99	0.96	0.96	0.85	0.95	0.83	0.73
Waking with SOB‡	0.85	0.90	0.85	0.85	0.46	0.40	0.56	0.46
Asthma ever	0.92	1.00	0.93	0.93	0.71	1.00	0.74	0.70
Asthma last 12 Months	0.92	0.99	0.88	0.88	0.73	0.94	0.59	0.85

* : Germany † : Nottingham ‡ : Shortness of breath

Table 6.3.2: Prevalence of certain symptoms standardised for age and gender in the ECRHS study (131):

Symptom	Percent Prevalence					
In the last 12 months	Number of centres	Minimum	25th percentile	Median	75th percentile	Maximum
Wheeze	48	4.1	14.9	20.7	25.2	32.0
Waking with chest tightness	46	6.2	9.7	13.5	17.5	20.5
Waking w SOB*	47	1.5	4.7	7.3	8.9	11.4
Asthma Attack	48	1.3	2.6	3.1	4.5	9.7
Asthma treatment	47	0.6	2.4	3.5	5.0	9.8

* : Waking with shortness of breath

inconsistency between the countries in the associations between age, gender, and symptoms between the centres.

There were some regional differences in the results as follows:

1) In the north of Europe (Netherlands, Estonia, Iceland, Norway, Sweden, Denmark): prevalence of wheeze tended to be high with a lower prevalence of other symptoms;

2) In the western part of central continental Europe (Belgium, France, Germany, Switzerland, and Austria): the prevalence of symptoms was generally low;

3) In the British Isles (UK, Ireland) by contrast, prevalence rates were high.

4) In the Mediterranean countries (Greece, Italy, Spain, Portugal, Algiers) the prevalence of most symptoms was low, particularly in Greece and Algiers. Some of the centres in Spain, Portugal, Italy were the exception.

5) In India, the prevalence of symptoms was low, while in Australia, New Zealand, and USA the prevalence of symptoms was high.

Adjustment for the season, and non-response with different assumptions did not change the results much. Forty two of the 48 centres shared a language with at least one centre, English being used in 13 centres in 5 countries, German in four centres, French in 6 centres, and Dutch in 5 centres in 2 countries. Comparison of the countries by the language they shared, revealed differences between countries having the same language. The English speaking countries generally had higher prevalence of symptoms. As the original language of the questionnaire was English, a possible explanation would be lower sensitivity of the translated versions of the questionnaire. The size of the difference and the general lack of problems reported by the translators made this explanation unlikely. Similar findings in children from England, Australasia, Sweden, Germany associated with the prevalence of exercise induced falls in peak expiratory flow rates was objective evidence for the differences between countries. Objective findings from the second stage of the study may help to explain those differences. Language as a marker of genetic trait or a cultural variable associated with environmental determinants of asthma were the other possible explanations (131).

Validity of the questions was also assessed in the ECRHS study as predictors of "bronchial hyperreactivity" (130). "Bronchial hyperreactivity" was defined as a PD20 (Provocative dose of 20 percent fall in FEV1) of less than or equal to 8 micromoles of histamine. Airway hyper-responsiveness was measured by methacholine challenge test, using the same equipment and standardised procedures in each centre (1). *Table* 6.3.3 shows the sensitivity, specificity, and Youden's index for certain respiratory symptom questions in relation to PD20 in different centres in the ECRHS study (132). Specificity is a criteria which gives the least misclassification, for a condition, with a prevalence less than 50%. Youden's Index measures the magnitude of biased estimate of the differences between two prevalences, regardless of what those prevalences are (Youden's index= Sensitivity of the test + Specificity of the test - 1) (132). In the ECRHS, wheezing as a predictor of airway hyper-responsiveness had the advantage of having the highest Youden Index in all centres. The predictive value of "bronchial hyperreactivity" was further examined by logistic regression, which revealed some differences between the countries. Thus the symptoms

Table 6.3.3: Sensitivity, specificity, and Youden's index for certain respiratory symptom questions in relation to PD20 in the ECRHS study (130):

	Finland			Germany			France			Nottingham		
	Sn* %	Sp† %	Y‡ %	Sn* %	Sp† %	Y‡ %	Sn* %	Sp† %	Y‡ %	Sn* %	Sp† %	Y‡ %
Wheeze	95	74	69	59	80	39	73	65	38	89	62	51
Morning tightness	74	87	61	33	93	26	53	72	25	79	57	36
Waking with SOB§	58	78	36	37	80	17	69	77	46	74	97	71
Asthma ever	74	91	65	33	93	26	80	74	54	53	1.00	53
Asthma last 12 months	68	91	59	26	93	19	50	76	26	47	1.00	47

* : sensitivity †: specificity ‡ : Youden's index)

§ : Shortness of breath

which were found predictive of "bronchial hyperreactivity" in the previous English survey were generally the same symptoms which were associated with "bronchial hyperreactivity" in the ECRHS survey. "Waking with shortness of breath", and "tightness in the chest in association with dust, animals or feathers" were less predictive in the three continental countries as a whole (132).

6.4. Lung Health and the Canadian Environment Study:

Canada was one of the participants in these international studies to investigate the prevalence and determinants of asthma and asthma-like conditions. Six centres from different parts of the country took part in the study: Vancouver, Winnipeg, Hamilton, Montreal, Halifax, and Prince Edward Island. These centres, each of which targeted approximately 20-25% of Canadians between the ages of 20-44 years in their sampling frame, experienced different climates, and different levels of urban air pollution. It was considered that differences (if they existed) between these centres would help to formulate aetiological hypotheses. The study was conducted with basically the same design, sampling strategy, study instruments, as those of the ECRHS as mentioned in the section above and assessed the same objectives. The specific objectives of Canadian study are (7):

1) To determine the prevalence of asthma and asthma-like conditions, bronchial hyper-responsiveness (BHR), and atopy in Canadian males and females aged 20-44 years;

2) To determine if the prevalence of asthma and asthma-like conditions, BHR and atopy vary among four (in the original protocol) or six (in the final protocol) Canadian urban centres;

3) To estimate the variation in exposure to known or suspected risk factors for asthma and asthma like conditions in the different centres in Canada and to assess to what extent these explain the variations, if any, in prevalence among these centres;

4) To measure the association between asthma and asthma-like conditions and BHR, atopy, and risk factors in different urban centres in Canada;

5) To provide Canadian data for an international study of the prevalence of asthma and asthma-like conditions, BHR, and atopy and other risk factors for comparison with data to be gathered in Europe and in North America.

Canadian investigators also decided to include a detailed occupational questionnaire in the second stage of their study. This questionnaire was developed and validated by S. de Grosbois in Montreal (133).

The study on Lung Health and the Canadian Environment was conducted between September 1993, and November, 1994 under the supervision and coordination of the research team.

6.5. Synthesis:

Reports from different parts of the world showing increases in the prevalence, morbidity and mortality related to asthma over the last two decades have attracted a worldwide attention. The time span of the change makes an explanation related to genetic causes unlikely. Differences between the countries and different time points are difficult to analyse, unless special steps have taken to minimise methodological differences. Efforts to standardise the definition of the disease, and the methodology to investigate the distribution and determinants of asthma and asthma-like conditions in the young adult population in international studies started in west Europe, and extended to other countries including Australia, New Zealand, US, and Canada (1). The study protocol for the ECRHS study describes two stages, the first using a screening questionnaire, and the second a more detailed questionnaire on risk factors, and personal characteristics, and laboratory investigations of atopy and bronchial hyper-responsiveness. The screening questionnaire used for the ECRHS study was adapted from IUATLD questionnaire, and

translated into different languages and checked with the original English version revealing no major problems. Repeatability and validity of the questionnaire were found appropriate in international studies. Findings from the first stage of the study in 42 centres in 22 countries revealed wide differences between countries, and some characteristic features in different regions. In general, symptoms were more common in English speaking countries. However, sensitivity difference due to translation is unlikely to explain the big difference observed. Analysis of findings from the second stage of the study, which included more objective assessment of outcome and exposure may throw light on between-centre differences.

The Lung Health and the Canadian Environment Study was part of the international efforts to investigate the prevalence and determinants of asthma. The same protocol, and study instruments were used as in ECRHS. An important addition was the detailed occupational questionnaire, designed to investigate the contribution of occupational exposures to the burden of adult asthma. The material described in the present study and in this thesis was gathered in the second stage of the Montreal component of the Canadian study, which was using, as already indicated, the protocol for the ECRHS.

7. OBJECTIVES, DEFINITIONS, DESIGN AND RATIONALE:

7.1. Overall Objective:

To estimate the contribution of occupational exposures to the burden of adult asthma in an industrialised population.

7.2. Specific Objectives:

I) Primary Objectives:

1) To determine the prevalence of asthma in adults aged 20-44 in the Montreal area.

2) To describe the occupational exposures in the Montreal adult population, by industry, job, and exposure to specific agents.

3) To determine the risk of asthma attributable to occupational exposures.

II) Secondary Objectives:

1) To compare the distribution of occupational exposures in individuals, who received the diagnosis of asthma before they entered the work force, with those who did not.

2) To explore the gender differences in the risk of asthma attributed to occupational exposures.

7.3. Study Definitions:

7.3.1. Study Outcomes:

For the purpose of this study the main study outcomes were defined as follows:

Current Asthma:

1) *Current wheeze*: 'YES' response to the question:

" *Have you had wheezing* or *whistling in your chest at any time in the last 12 months?* "

2) *Airway hyper-responsiveness* (AHR), as defined below:

AHR: 20% fall in FEV1 from the post-diluent level in the methacholine challenge test, before the maximum cumulative dose of 2 mg was reached.

3) *Current wheeze*, and *Airway hyper-responsiveness* (AHR as defined above)

Adult Onset Asthma: asthma starting at/after age 15. This will be considered for each definition by excluding the subjects who reported an age less than 15 to the question:

" How old were you when you had your first attack of asthma?"

To compare the study findings with the other studies, one other definition is used:

Having Current Asthma symptoms and, or using asthma medicine: Woken up with shortness of breath, and/or asthma attack and/or using asthma medicine in the last 12 months, as indicated by 'YES' response(s) to any of the three questions below:

"Have you been woken by an attack of shortness of breath at any time in the last 12 months?";

"Have you had an attack of asthma in the last 12 months?";

"Are you currently taking any medicines including inhalers, aerosols or *tablets for asthma?"*

7.3.2. Exposure measures:

Occupational exposure was considered to have occurred if it lasted for at least three months as reported by the study subjects. The time frame used was as follows:
ever: occurring any time; current: occurring within 12 months of the survey; and past: ended at least 12 months before the survey.

Information on occupational exposures to the agents or occupations or industries recognised as carrying risk for asthma were grouped into sensitisers and irritants, based on the background knowledge. This classification is given in *Table* 9.3.1.

7.3.3. Other Factors Used in the Analysis:

Study definitions of the other factors used in the analysis were based on the questionnaire information, which is listed in *Table* 9.3.2.

7.4. Study Design:

A cross-sectional study was used with two stages, in a random sample of Montreal population between the ages of 20-44.

7.5. Study Rationale:

This study described in this thesis was carried out in Montreal as part of a multi-centre study conducted in Canada, using the ECRHS protocol and addressing the same objectives, namely to investigate the prevalence and determinants of asthma. The rationale for the study has been presented in section 6.5 and follows from the wide differences of asthma prevalence between countries. If not due to methodological differences, these differences imply that environmental factors are important in the genesis of adult asthma and action could be taken to decrease the prevalence of asthma (1). Use of standardised instruments and methods provides the opportunity for a valid comparison of findings from different countries, and would provide a large scale vision of asthma. It would also be helpful for health care planning for asthma care and, hopefully, prevention.

The definitions of *current asthma* used in this study ("yes" response to the question of "wheezing in the last 12 months", and "wheezing in the last 12 months" combined with airway hyper-responsivenes measured by methacholine airway challenge test) have both been evaluated in other studies and considered to have appropriate reproducibility and validity (130, 134).

Definition of the young adult age group for study was the same as that used in the ECRHS protocol (1). Other aspects of the rationale pertinent to the Canadian study protocol were as follows. The mortality related to asthma in this age group has been increasing, symptoms are more readily recognised in this age group as due to asthma compared to children and older age groups, and this age group includes the most economically active and productive age group, and probably the most susceptible to improved management or prevention (Canadian protocol). Finally, the addition of a detailed occupational questionnaire to the Canadian study would provide information on the contribution of occupational exposures to the occurrence of asthma in the adult population of Canada.

8. STUDY POPULATION

8.1. Study Base, Target Population, and Subject Selection:

The study base can be conceptualised as the respiratory health experience of young adult population in the working age group, in an industrialised community, as assessed at the time of the study.

The target population was the adult population of both genders, between the ages of 20 and 44, residing in Montreal during the time of the study.

The study population was a random sample of individuals, of both genders, between the ages of 20 and 44, residing in Montreal, during 1993-1994, who attended to both stages of the study.

Study population was selected by random digit dialling. The objective was to identify 3000 individuals for the first stage of the study, and 600 individuals for the second stage, with an expected response rate of 75% in both stages.

A total of 18,000 telephone numbers in 12 batches each containing 1500 numbers were randomly generated for each telephone exchange of the city, and the selected numbers were called, according to a prescheduled script. The first call was made between 9: 00 am, and 17: 00 PM on a working day. If the number was a business number, or not in service, or the respondent was not cooperative due to a language problem etc. the number was not called any more, and the condition was noted on the random digit dialling form. If there was no response, the call was repeated five times, the last being at least two weeks after the first call. If there was a response, and this was a residential number, the interviewer introduced himself/herself and the study, and asked if there was any individual in the household between the ages of 20 and 44. The study was introduced as: "an important project on lung health and the Canadian environment", and it was also added that similar studies were conducted in other centres (Winnipeg, Hamilton, Vancouver...), and

"Doctor's XXX and YYY" were investigators in the study. If there was an individual or individuals in the household in the eligible age range, one individual was identified according to a preselected format to receive the mail questionnaire, and their address and name obtained. One thousand eight hundred individuals were also invited to the laboratory, one having been preselected at random among the 6 numbers on each page of each 12 batches of 1500 numbers randomly generated for each telephone exchange in the city.

8.2. Ethical Considerations:

Information about the study was given to each subject included in the first stage of the study. A letter of invitation was sent to the subjects invited to the second stage of study, giving brief explanations about the study, procedures, and access to the study results. Written consent for the procedures in the second stage was obtained from each subject, after verbal and written explanation of the procedures. Subjects were told that participation was voluntary, and each subject could decline one or more procedures required by the protocol. They were assured that the results were kept completely confidential, and would be sent to the family physician of the subject given his/her written approval.

9. METHODS

9.1. Measurement Instruments:

9.1.1. Stage 1: Mail Questionnaire:

The self administered mail questionnaire used in the first stage of the study was the same as the ECRHS stage 1 questionnaire, modified with questions added on occupational exposure, some respiratory symptoms, and residential history, and questions about demographics (age and gender), and smoking status (see *section 6.2*: The European Community Respiratory Health Survey (ECRHS) protocol and methodology). Translation into French, and back translation into English were done and accuracy testing was found appropriate. Questionnaires in both languages were sent to all subjects selected, leaving them free to answer in either language.

9.1.2. Stage 2: Laboratory Examination and Procedures:

The second stage was conducted in the laboratory and included administration of the main questionnaire, and a detailed occupational questionnaire by trained interviewers, lung function testing by spirometry, and methacholine airway challenge testing, skin prick testing, and sampling serum for specific IgE testing. These procedures are described below.

Main questionnaire: the main questionnaire included questions from the mail questionnaire, and detailed questions on smoking habits, respiratory symptoms, allergic conditions, history of parental smoking, family history of asthma and allergy, childhood exposures, home characteristics, education, diet, and medicine use. The additional questions were taken from questionnaires, which have been used and validated before, like that of ATS. A French translation of the questionnaire, previously developed and tested in Québec, was used (135).

Occupational questionnaire: the occupational questionnaire included questions on current and past jobs held, occupational exposures, and complaints, accidental exposures, history of changing or leaving job related to the occupational exposures. As indicated in section 6.5 above, this questionnaire was developed, translated into French and validated in a Montreal study (133).

Skin prick testing: skin testing was performed with positive control (histamine) and a negative control (diluent), and 14 allergen extracts: cat, cladosporium herbarum, d. farinae, olive, birch, common ragweed, penicillium, dermatophagoides pteronnysinus, alternaria alternata, timothy grass, cockroach, kentucky blue grass, east/west tree mixture, aspergillus. Testing was carried out with the Prick Lacetter on the left forearm, and reading was done 15 minutes after the application (136). The perimeter of each wheal was marked with a ballpoint pen, or fine felt-tip pen, and copied to a transparent tape, and the diameters at the widest point, and the one perpendicular to this diameter at the mid point were measured, and recorded. All liquid allergen extracts, the negative control, and the prick lacetter were provided by Hollister Stier Laboratories, and the positive control was provided by Bencard Laboratories.

Baseline spirometry: subjects were required to produce two technically satisfactory FEV1 and FVC tests. A satisfactory test was defined as a hard and fast expiration after a deep inhalation, without coughing, with a PEFR (Peak expiratory flow rate) within 10% of the best PEFR, to a maximum of nine attempts. The spirometer used was a dry rolling seal spirometer (Anderson, Spirotech, Inc; Atlanta), with the calibration and testing procedures as suggested by ATS (137).

Excluded from the baseline spirometry was any subject who:

a) smoked a cigarette within the last one hour;

b) received beta-2 agonists or an anthicholinergic inhaler test within the last 4 hours, or oral beat-2 agonists, or oral theophylline within the last 8 hours;

c) had abdominal or chest surgery within the last 3 months.

Methacholine challenge: after the completion of a lung function questionnaire, height and weight recording, and baseline spirometry, eligible subjects were tested by methacholine airway challenge testing, according to the ECRHS protocol. Mefar compressed air dosimeters (Mefar MB3, Bowezzo, Italy) were used to administer methacholine, or saline.

Excluded from the methacholine challenge testing was any subject who:

a) had had a heart attack in the past 3 months, or had any heart disease for which s/he was taking medication;

b) had epilepsy for which s/he was taking medication;

c) was pregnant or was breast feeding;

d) was taking a beta-blocker for any reason (including eye drops);

e) had an FEV1 less than 70% of the predicted value, or 1.5 liters for the baseline spirometry;

f) had refused to do methacholine challenge testing.

All subjects started with 4 inhalations of saline, and the best control FEV1 was obtained after this inhalation was used as the control. If the best control FEV1 was less than 90% of the best baseline FEV1, testing was stopped, and bronchodilator inhalation was administered. There were long and short protocols, with different dosing schedules and FEV1 was measured two minutes following each dose. The long protocol was administered to subjects who had reported any of the following in the last 12 months: wheezing, attacks of shortness of breath, trouble with breathing, being woken up by chest tightness, or an attack of shortness of breath, or ever having asthma in the lung function questionnaire. In addition the long protocol was used for those who started with the short

protocol, but whose FEV1 dropped more than 10% after saline or after any dose of methacholine. The short protocol was administered to the other subjects. The maximal concentration and cumulative dose of methacholine in each protocol were 12.5 mg/ml and 2mg respectively.

Testing was stopped when there was more than a 20% fall in FEV1 from best control FEV1 following inhalation of any concentration of methacholine, or the subject did not wish to go on, or could not provide two technically satisfactory manoeuvres following any dose level. Bronchodilator was administered to subjects after the methacholine challenge, and FEV1 and FVC were measured 10 minutes after the administration of bronchodilator, and had to return within 10% of the best baseline FEV1 before the subject left the laboratory. Preparation of the methacholine solutions, calibration and the quality control of Mefar dosimeters were described in a protocol, and monitored each month by one of the investigators .

9.2. Approach to Analysis

9.2.1. Data Entry and Management:

Data obtained from the study was keypunched, and entered to the computer. Information related to occupational exposure was stored in two files. Dr Johnson, who was working on the complete datasets from the 6 centres in the Canadian study, had identified coding errors in the occupational questionnaires. A computer program was therefore prepared and executed to check for the two common coding errors in the 7th and 8th questions from the occupational questionnaire. To assess the quality of the data further, random selection of 50 occupational questionnaires was checked for all coding. All the questionnaires were then checked for these common coding errors, anf for other questions important for the analysis like those related to changing job, and accidental exposure. Results of the checking and recoding procedures were as follows:

1. A check of all the occupational questionnaires for the common miscodings revealed a total of 15, and 14 miscodings in the questions 6, and 7, respectively (representing a 3% of all the questionnaires);

2. Information about additional occupational exposures (data related to the occupational exposures if there are more than three, and industries or occupations ever held, if there are more than 10) had not been coded at all. This information was then entered to the file;

3. The occupational questionnaire was blank for one subject (the explanation given was a language problem), and missing for another subject. These two subjects were removed from the file. For another subject, information from the occupational questionnaire was entered, but main questionnaire was not. The main questionnaire information of this subject was then added to the file. After these procedures there were 498 observations with complete information for the two questionnaires was complete and whose data was used in the analysis.

4. Information on the fifth item of miscellaneous exposures (exposure to insects) was missing from the French translation of the occupational questionnaires, and therefore excluded altogether from the present analysis.

9.2.2. Plan for the Attainment of Objectives:

9.2.2.1. The Burden of Adult Asthma in the Population due to Occupational Exposures:

The overall estimate for the burden of adult asthma in the population is formulated as the population attributable risk (PAR). The definition given for population attributable risk is the following: "It is the incidence of a disease in a population that is associated with (attributable to) exposure to the risk factor." (120). Population attributable risk is

important for public health, and health planning purposes, since it gives a measure of the proportion of disease due to exposure in the population, which might be prevented by controlling the exposure. Formula for PAR % is shown below: (138)

PAR % = [(RR-1)/P1] ÷ RR, where RR= Relative risk, P_1= Proportion of cases that is exposed.

Thus, estimates of relative risk and proportion of cases exposed are required to obtain the PAR. Substantive knowledge indicates that the rare disease assumption does not hold for asthma in the study population. However prevalence rate ratio (PRR) can be used to give the relative risk estimate. This is justified by the fact that in a dynamic population in a steady state, there is a relationship between the incidence rate and the mean duration of the disease. (Here the young adult Montreal population can be considered as a dynamic population in a steady state).

Prevalence = ID/(ID + 1) (I: incidence rate, D: mean duration of disease), and prevalence odds ratio equals to incidence rate ratio if the prevalence of disease is low (less than 0.1) (139).

Thus,

PRR = P1/P2 = [I1D1/(I1D1 + 1)] / [I2D2/(I2D2 + 1)]

= I1/I2 x (I2D1D2 + D1)/ (I1D1D2 +D2)

I1: Incidence rate of disease in the exposed,

I2: Incidence rate of disease in the unexposed,

D1: mean duration of disease in the exposed;

D2: mean duration of disease in the unexposed.

Considering the characteristics of the factors in the study, it is reasonable to assume that incidence of disease in the exposed group (I1) is not lower than the incidence of disease in the unexposed group (ie. I1 >= I2); and that the mean duration of disease in the unexposed group (D2) is longer than the duration of disease in the exposed group (D1). This is

because those who develop disease in the exposed group will more likely terminate their exposure, and more importantly those who had disease before they entered the working age group will be more likely to have excluded themselves from the exposure or been excluded by pre-employment examination (Healthy worker effect, see Discusion). When these assumptions are entered into the equation:

As I2DID2 < I1D1D2, and D1 < D2,
the term (I2D1D2 + D1)/ (I1D1D2 +D2) will be < 1;
and prevalence rate ratio will not be an overestimation of the incidence rate ratio. Thus, prevalence rate ratio can be regarded as a suitable estimate for the incidence rate ratio, and also relative risk.

An interesting feature of PAR is the fact that it is relatively robust to the misclassification of exposure, unless this is non-differential. Misclassification will change the standard error of the estimate, and decrease the precision of estimate, as shown by Wacholder et al., who stated the following: "Classification of exposure into two levels - one exclusively of unexposed and the other consisting of exposed and perhaps unexposed ones- yields an unbiased estimate of attributable risk when misclassification is non-differential"; and "standard error of the risk estimate increases as the proportion of exposed cases and controls increase." (140).

Variance estimators of the PARP's were calculated as suggested by Greenland to obtain the 95% confidence intervals (141).

9.2.2.2. Imputation of Missing Values for Airway Hyper-Responsiveness:

In the present study the aim of imputation was to adjust for the low response rate in the second stage of the present study, which might undermine the inferences that would be made for the study base. As, information about those, who did not respond to the second stage of the study was not available, adjustment was made taking account of all the subjects who participated in the first stage of the study, but did not undergo or complete

airway challenge testing, as suggested by Rubin et al (142). To do this, a model was developed from first stage factors to predict the state of airway hyper-responsiveness as measured in the second stage. To build this predictive model, all available factors recorded in the target population at the first stage (n=2460) were examined for their relationship to airway hyper-responsiveness, measured in 368/498 subjects tested in the second stage. These included personal characteristics (age, gender), smoking habits, occupational exposure to dust and/or chemical/gas/fume, changing or leaving job, respiratory symptoms, diagnosis of asthma and use of asthma medicine. A similar problem of low response rate in the second stage of the study was encountered in the European Community Respiratory Health Survey (143). Thus the purpose of imputation was to find a good predictive model, and to adjust for age, gender, and stage 1 symptoms. This predictive model was then used to adjust for the missing information on airway hyper-responsiveness in the first stage data set. For each subject who did not have airway challenge testing, probability of having airway hyper-responsiveness was calculated from the model, and compared with a random number generated between 0 and 1 by the computer. If the probability estimate of having airway hyper-responsiveness was higher than the random number generated for the subject, then the subject was considered to have airway hyper-responsiveness. Imputation procedures were performed three times for each model, under the advice and supervision of Dr L Joseph (Ph D, Division of Clinical Epidemiology, Montreal General Hospital).

9.3. Descriptive and Analytic Studies: Study Variables

9.3.1. Occupational Exposure:

Occupational exposure was categorised into HMW and LMW agents and agents related to asthma with non-immunological mechanism, as shown in *Table* 9.3.1. The first two were combined as sensitisers for the multivariate analysis. This distinction is consistent with substantive knowledge. High molecular weight and low molecular weight agents are known to act through IgE dependent (usually) or non-IgE dependent (less common)

Table 9.3.1 : Categories of occupational exposures by agents and/or industries and/or occupations*:

Category	Agents, Industries or Occupations
High Molecular Weight Agents	**Agents:** Grain or flour dust, cotton dust†, fur dust, coffee dust, biological enzymes, vegetable gum, glues‡, **Industries or occupations:** Printing industry, bakery, detergent production, farming, fishing, flour milling, food processing, grain handling, hairdressing, handling lab or farm animals, laboratory work, sea food processing, weaving§
Low Molecular Weight Agents	**Agents:** Dyes, formaldehyde, hardeners, accelerators¶, paints, pharmaceuticals, resins, Platinum, nickel, chromium, cobalt, zinc, **Industries or occupations:** Chemical industry, foundry, metal fabrication, steel, milling, leather industry‡, pharmaceutical industry, rubber manufacture industry, textile industry, auto body repair manufacture, carpentry, furniture making, electronic equipment manufacture, electroplating, epoxy resin manufacture, machining, painting, photography, plastic manufacture, polyurethane manufacture, roofing, varnishing wood floors, sawmilling, shipbuilding‖, soldering, spraying insulation or foam material, welding
Agents Causing Asthma Through Non Immunological Mechanisms	**Agents:** Solvents¶, acids**, ammonia**, alkali**, insecticides or herbicides**, Aluminum, **Industries or occupations:** Pulp and paper industry††, dry cleaning††, firefighting††, railway maintenance††, smeltering

* : References are from Chan-Yeung M, 1994 unless otherwise specified (71)
†: Eur Respir J, 1992 (144)
‡ : Environmental and Occupational medicine (Rom, 1992) (8)
§: Brooks SM, 1977 (77) ¶ : Propulse: Provencher et al. 1997 (4)
‖: Abstract (145)
** : Disease a Month (146) ††: Newman LS 1995 (78)

immunological mechanisms. After sensitisation occurs, re-exposure to the same agent results in an asthmatic reaction. The sensitiser group includes agents, occupations, and industries recognised as causes of occupational asthma by many jurisdictions (110-112). Agents, occupations, and industries were not analysed separately, because of the small numbers of individuals with most of these exposures, which would make it difficult to draw conclusions for most of the specific exposures.

9.3.2. Other Factors Used in the Analysis:

Other factors used in the analysis were chosen based on the substantive knowledge from the available data (23). Log linear graphs of the various factors were used for the categorisation of these study factors. Dummy variables were created where a meaningful reference group was available for the various categories of factors, such as the never smoked for current smoker and exsmoker groups. Study definitions of other factors used in the analysis are described in *Table* 9.3.2.

Table 9.3.2: Study definitions of personal characteristics and other factors included in the analysis:

Factor	**Study Definition**	**Ref***
Exposures and Respiratory Diseases in the Childhood		
Childhood Respiratory Illness	Childhood asthma: YES response to the question: "Have you ever had asthma?", and an age less than 15 to the question: "How old were you when you had your first attack of asthma?"	No > 14
	Respiratory infection in the childhood: YESto the question: "Did you have a serious respiratory infection before the age of 5 years?"	No
Parental Smoking	Mother smoked: YES response to question: "Did your mother ever smoke regularly during your childhood or before you were born?" Father smoked: YES response to question: "Did your father ever smoke regularly during your childhood?"	No and No
Childhood Exposure	Having an elder sib: responses to questions: "How many brothers do or did you have?", and "How many older brothers?"; and : "How many sisters do or did you have?", and "How many older sisters?";	No No
	Sharing the same bedroom with an older child: YES response to question: "Did you regularly share your bedroom with any older children before the age of 5 years?"	No
	Going to school, playschool, nursery: YES response to question: "Did you go to school, playschool, or nursery with other children before the age of 5 years?"	No
Exposure to Pet	Exposure to pets in the childhood: response to question: "When you were a child did anyone in your household keep any of the following pets?" "cats, dogs; horses, birds, guinea pigs, hamsters, mice, rats, rabbits, gerbils, ferrets, others"	No to All
Personal Factors		
Gender	Response to question: "Are you male or female?"	Male
Age	Survey date minus birth date, in years.	20-24

* : Reference category

Table 9.3.2: Study definitions of personal characteristics and other factors included in the analysis (*continued*):

Factor	Study Definition	Ref*
Exposures in the Adulthood and Related Factors		
Exposure to Tobacco Smoke	Never smoked NO to question: "Have you ever smoked for as long as a year?"	No
	Smoked in the past: YES response to question: "Have you ever smoked for as long as a year?" and NO response to question: "Do you now smoke?"	
	Current smoker: YES response to question: "Have you ever smoked for as long as a year?" and YES response to question: Do you now smoke?"	
Exposure to Pet	Having a cat: YES response to question: "Do you have a cat?";	No
	Having a dog: YES response to question: "Do you have a dog?";	No
	Having bird(s): YES response to question: Do you have any bird(s)?	No
Home Characteristics	Mould or mildew inside the home:	
	Ever: YES response to question "Has there ever been mould or mildew on any surface other than food, inside the home?"	No
	current: YES response to question "Has there been mould or mildew on any surface inside the home in the last 12 months?";	No
	Room with wall to wall carpeting: YES response to question: "Does the room which you use most at home during the day have wall to wall carpeting?";	No
	Bedroom with wall to wall carpeting: YES response to question: "Does your bedroom have wall to wall carpeting?";	No
	Electrical heating: response to question: "Which of the following fuels do you use for heating or for hot water?"	
	"1) Fireplace/woodstove (coal, coke, or wood),	
	2) Gas fireplace,	Any,
	3) Electric heater,	but 3
	5) Gas-fired boiler or gas furnace,	
	6) Oil-fired boiler or oil furnace;"	
	Electric cooking: response to question: "What kind of stove do you mostly use for cooking?"	B or None
	"B) Gas, **C) Electric**"	

Table 9.3.2: Study definitions of personal characteristics and other factors included in the analysis (*continued*):

Factor	Study Definition	Ref*
Education Level	Completion of secondary education or less than secondary education: according to the response to question: "At what age did you complete full time education?"	< 17
Dietary Habits	Eating pre-packaged food: responses to questions: "How often do you eat pre-packaged food such as canned food or prepared frozen meals?" ; "How often do you drink soft drinks or sodas?" A) every day or most days, B) at least once a week, C) less than once a week	C or None
	Eating fruit or vegetables between meals: YES response to question:"Do you eat snacks between meals?", and response to question: "Which of the following would you have as a snack at least once a week?" "1) cheeses, crackers; 2) candy, chocolates or cookies. 3) fruit or vegetables"	No to 3 or None
Atopy and Family History of Allergic Diseases		
Atopy	Skin prick reaction (+) to any of the allergens tested (reaction +: the mean of reaction diameters measured minus the mean of diameters of negative control is greater than 3 mm)	No +
Family History Of Asthma	Asthma in the parents or sibs: YES response to any of the questions: "Did your mother ever have asthma?" (similar question for "father"), response to questions: "How many of your brothers ever had asthma?" (similar question for "sisters")	No And 0
Family History Of Allergy	Allergy in the parents or sibs: YES response to any of the questions: "Did your mother ever have eczema, skin or nasal allergy or 'hay fever'?" (similar question for "father"), response to questions: "How many of your brothers (who did not have asthma) ever had have eczema, skin or nasal allergy or 'hay fever'?" (similar question for "sisters")	No and 0

* : Reference category

9.3.3. Association between Study Outcomes, and Exposure and Other Factors:

Association of asthma symptoms and, airway hyper-responsiveness with occupational exposures were expressed using odds ratios in univariate and multivariate analysis. To determine the risk of asthma in the adult population attributable to occupational exposures, two types of models were used, one taking into account age, gender, smoking; and the other taking into account pertinent risk factors.

9.3.4. Model Selection:

Adjustment for age, gender, and smoking was done through including all these factors into the model. Pertinent host factors were selected from among the questionnaire items based on substantive knowledge. Model selection was performed for *current wheeze* and the same factors were used in the model selection for outcome measures, namely asthma symptom and/ or medicine, and airway hyper-responsiveness. Potential confounders were identified through examining the association of each factor with the outcome and with the occupational exposures. Correlation matrices of the factors were used to indicate the strength of the association between the factors, and to help in early detection of the collinearity. Stepwise selection procedure taking 0.20 level as the entry and exclusion level was used for the model selection. The selected model was then modified by entry, or removal of a factor at each step. Models were compared according to Schwarz criterion (SC), and Akaike information criteria (AIC), but not according to the significance of each factor. The Schwarz criterion is a rough approximation to the logarithm of Bayes factor, which provides a tool to compare hypotheses (147). It is available and easy to use with SAS program, and helpful for the model selection. Akaike information criteria (AIC) is also helpful in model selection, as a measure incorporating the logarithm of maximised likelihood, but has been criticised for its weakness in the usual "situation, where the prior information is small relative to the information provided by the data" (147). Model selection based on statistical significance of a factor by bivariate analysis may wrongly reject a potentially important factor, when the relationship between this factor and the outcome is confounded, and the confounder is not properly controlled (148).

Examination of effect modification was based on the principle that biologically plausible interaction is additive (139). Interaction terms, consistent with the substantive knowledge and scientifically plausable, were put into the model in a stepwise procedure. Those with p values less than 0.20 were reconsidered together with the terms they included, alone or in different combinations, as suggested by Kleinbaum (149). The final decision about a potential interaction was based on its interpretation, and the contribution to the predictive power of the model, as measured by SC and AIC. Introduction of interaction terms to the model is not of main interest, except for the possible interactions with occupational exposures such as smoking, and atopy. This is because the main objective of this thesis is the assessment of the population burden of asthma related to occupational exposure, and as the design was cross-sectional study the study has limitations for the causal interpretation of associations. Effect modification was also explored by repeating the analysis in different groups of the potential effect modifier, as in the separate analysis in men and women to explore the effect modification by gender.

All statistical analysis was performed with SAS program (6.12 release).

10. RESULTS

10.1. Descriptive Information on Study Subjects and Study Outcomes:

10.1.1. Comparison of Stage 1 and 2 Samples: "How Representative is the Second Stage Sample?"

Of 3454 men and women invited into the study, who accepted by phone to take part in the study, 2959 responded to the first stage mail survey (response rate: 85.7%). Among 1369 individuals invited to take part in the second stage of the study, 499 participated (response rate: 36.4%). *Table* 10.1.1 shows the main demographic characteristics, the symptom prevalence and exposure characteristics of the subjects, who participated in the first and second stage survey (n=499) with those who only took part in the first stage (n=2460). Age and gender distribution of the two groups was similar. However the second stage study participants had a higher prevalence of non-smoking individuals, and of all the asthma symptoms and related conditions. Thus, asthma diagnosed by a physician was reported by 85/499 (16.8%) of the subjects involved in the second stage, and 294/2460 (11.9%) of the subjects involved in the first stage only. Having received asthma medication in the last 12 months was reported by 43/499 (8.6%), and 138/2460 (5.6%) of the subjects in two groups respectively (not shown in *Table* 10.1.1). Chest tightness in the last 12 months was reported by 117/499 (23.4%) subjects involved in the second stage, and 453/2460 (18.4%) subjects involved in the first stage only. On the other hand symptoms reported with similar frequency in the two groups were usual cough, by 88/499 (17.6%), and by 451/2460 (18.3%) respectively, and usual phlegm, by 94/499 (18.8%), and by 429/2460 (17.4%) in the two groups respectively. Exposure ever to dust (37.3% and 35.6%), and to chemicals, or gases, or fumes in the work place were reported in a similar proportion of the two groups (24.9% and 22.4%, respectively). A slightly higher proportion of those with exposure ever to any dust, and/or chemicals or gases or fumes in the work place reported changing or leaving job due to a respiratory complaint in the

Table 10.1.1 : Comparison of the study population with the source population:

	Subjects studied in the laboratory* n (%)	Subjects involved in the mail survey only* n (%)
Age (years) mean (SD)	32.3 (6.9)	32.0 (6.9)
Number of subjects	499 (100)	2460 (100)
Women	261 (52.3)	1372 (55.8)
Smoking status:		
Never smoked	218 (43.7)	978 (39.8)
Smoked in the past	103 (20.6)	560 (22.8)
Current smoker	178 (35.7)	922 (37.5)
Current† symptoms:		
Wheeze	146 (29.3)	556 (22.6)
Woken by SOB‡	51 (10.2)	169 (6.9)
Chest tightness	117 (23.4)	453 (18.4)
Usual cough	88 (17.6)	451 (18.3)
Usual phlegm	94 (18.8)	429 (17.4)
Asthma:		
Physician diagnosed	85 (16.8)	294 (11.9)
Onset before age 15	50 (10.0)	149 (6.0)
Changed or left job	20 (4.0)	80 (3.2)
Occupational exposure:		
None	282 (56.7)	1405 (57.1)
Dust	186 (37.3)	875 (35.6)
Chemicals/Gas/Fume	124 (24.9)	552 (22.4)
Any	217 (43.5)	1055 (42.8)
Changed or left job among those ever exposed §	19 (8.8)	67 (6.4)

*:Response rate: mail survey: *2959 3454 (85.7%)*; laboratory study: *499 1369 (36.4 %)*

† : In the last 12 months ‡ : Shortness of breath

§ : Changed or left job among those ever exposed to any dust, and/or chemicals/gas/fume at work

group that involved in both stages of the study (19/217, 8.8%) than that involved in the first stage only (67/1055, 6.4 %).

Distribution of the current jobs as coded according to Standard Occupation Classification 1980 (Statistics Canada) were also similar in both groups (not shown in *Table* 10.1.1). The most common major grouping of jobs was clerical and related jobs (485/2460: 19.7%, and 93/499: 18.6%), followed by service related jobs (261/2460: 10.6%, and 44/499: 8.8%).

10.1.2. Stage 2 Sample Used in the Analysis (Study Population): Data Checking and Editing Procedures in the Study Population:

The second stage response rate was considerably lower than that of the first stage and comparison of the two groups suggested that subjects who participated in the second stage of the study were systematically different from the subjects who were involved only in the first stage of the study. Higher prevalence of symptoms, and never smoking in the second stage subjects suggested a higher level of health concern in those individuals who agreed to participate. Similarity of the occupational exposures and current jobs indicates that this self selection was not related to occupational exposures, and hence does not threaten the interpretation of the study findings related to occupational exposures.

Data from the second stage of the study was used in the analysis to explore evidence regarding the objectives of this thesis, and subjects who participated in both stages of the study will be called as study population. After completion of all data checking procedures, as outlined in data entry and management section (section 9.2.1), the study population i.e. subjects with the complete questionnaire (respiratory, occupational) data was established as 498 subjects, 238 men, and 260 women.

10.1.3. Study Population: Demographic and Other Personal Characteristics:

Demographic and other characteristics of the study population are shown in *Table* 10.1.3. Mean age, age distribution and prevalence of smoking were similar in both men and

Table 10.1.3 : Demographic and other characteristics of the study population:

	Men n (%)	**Women n (%)**	**Total n (%)**
Age (years) mean (SD)	31.7 (6.86)	31.6 (6.92)	31.6 (6.89)
Number of subjects	238 (100)	260 (100)	498 (100)
Smoking status:			
Never smoked	115 (48.3)	111 (42.7)	226 (45.4)
Smoked in the past	40 (16.8)	53 (20.4)	93 (18.7)
Currently smoking	83 (34.9)	96 (36.9)	179 (35.9)
Parents smoking:			
Either	187 (78.6)	195 (75.0)	382 (76.7)
Mother	101 (42.4)	92 (35.4)	193 (38.8)
Skin prick test reactions†:			
Number tested	228 (95.7)	245 (94.2)	473 (95.0)
Any (+)	155 (68.0)	153 (62.4)	308 (65.1)
D. pteronyssinus	96 (42.1)	112 (45.7)	208 (44.0)
D. farinae	94 (41.2)	106 (43.2)	200 (42.3)
Ragweed	76 (33.3)	83 (33.9)	159 (33.6)
Cat	47 (20.6)	58 (23.7)	105 (22.2)
Pets in home:			
In childhood	181 (76.0)	200 (76.9)	381 (76.5)
Current	175 (73.5)	199 (76.5)	374 (75.1)
Changed or left job	18 (7.6)	12 (4.6)	30 (6.0)
Occupational exposure:			
None	119 (50.0)	183 (66.5)	292 (58.6)
Dust or Chemicals/ Gas/ Fume	119 (50.0)	87 (33.5)	206 (41.4)
Changed or left job among exposed *	15/119 (12.6)	7/87 (8.0)	22/206 (10.7)

* : Changed or left job among those ever exposed to any of the dust, and/or chemicals/gas/fume at work

† : Percentages are calculated among those who were tested by skin prick tests

women. History of any parent smoking in childhood was reported commonly by both men and women. The prevalence of any skin test reaction positivity was slightly higher among men than women tested (68.0% and 62.4%, respectively), with the most common allergens evoking a reaction being D. pteronyssinus and D. farinae. Having a cat, dog, or birds as a pet currently and having a pet in the household in childhood was reported with similar frequencies by both men (76.0%, and 73.5%), and women (76.9%, and 76.5%), respectively.

Among individuals who had ever smoked for more than a year, median age of onset smoking was higher among men, than women (men:16 years, and women:15 years), and median number of cigarettes smoked daily (men: 20, and women:15) (data not shown in *Table* 10.1.3).

Ever occupational exposure to dust, and/or chemicals and/or gas and/or fume, and changing or leaving job due to a respiratory complaint were reported by almost 50%, and 8% of the men, and 30%, and 5% of the women, respectively. The proportion of those who reported exposure ever to dust, and/or chemicals and/or gas and/or fume, and who reported changing or leaving a job due to a respiratory complaint was higher in men (13%) than that in women (8%).

10.1.4. Prevalence of Respiratory Symptoms and Other Conditions:

Table 10.1.4 shows the prevalence of respiratory symptoms, asthma medication use, and other respiratory conditions, and a family history of asthma and allergy. Symptoms present in the last 12 months before the survey were considered as current symptoms. All the symptoms related to asthma were less common in men than in women. Thus, current wheeze was reported by 51/238 men (21.4%) and 79/260 women (30.4%); wheeze with breathlessness by 24/238 men (10.1%) and 58/260 women (22.3%); and wheeze without cold by 37/238 men (15.5%), and 58/260 women (22.3%) (data not shown in *Table* 10.1.4).

Table 10.1.4 : Prevalence of reported symptoms and conditions in the study population:

	Men n (%)	**Women n (%)**	**Total n (%)**
	238 (100)	260 (100)	498 (100)
Current* symptoms:			
Wheeze	51 (21.4)	79 (30.4)	130 (26.1)
Asthma attack	14 (5.9)	28 (10.8)	42 (8.4)
Woken by SOB†	22 (9.2)	27 (10.4)	49 (9.8)
Asthma:			
Physician diagnosed	28 (11.8)	48 (18.5)	74 (14.8)
Onset before age 15	18 (7.6)	22 (8.5)	40 (8.0)
Current use of medicine for asthma	13 (5.5)	23 (8.8)	36 (7.2)
Bronchitis:			
Phlegm for at least 3 months in the year	22 (9.2)	15 (5.8)	37 (7.4)
SOB when walking‡‡	8 (3.4)	28 (10.8)	36 (7.2)
Respiratory illness before age 5	17 (7.1)	24 (9.2)	41 (8.2)
Family history of asthma:			
Either parent or any sib	47 (19.7)	68 (26.2)	115 (23.1)
Mother	15 (6.3)	12 (4.6)	27 (5.4)
Family history of allergy: (including eczema)			
Any parent or sib	124 (52.1)	152 58.5)	276 (55.4)
Mother	44 (18.5)	75 (28.9)	119 (23.9)

* : In the last 12 months
† : Shortness of breath
‡‡ : Shortness of breath when walking with other people of the similar age on level ground

Almost all the subjects who reported past history of asthma had a physician diagnosis, and about third of these, 13 men (5.5%), and 23 women (8.8%) were currently using medicine for asthma. The most common medicine used to help breathing in the last 12 months was oral medicines in 36 men (15.1%), and 59 women (22.7%), followed by inhaled medicines in 17 men (7.1%), and 40 women (15.4%) (data not shown in *Table* 10.1.4). Asthma attack in the last 12 months was reported by 14 (5.9%) of the men, and 28 (10.8%) of the women. Childhood onset asthma (first asthma attack before age 15) was reported by 18 (7.6%) men and 22 (8.5%) women. Symptoms characteristic of chronic bronchitis, such as phlegm for at least 3 months of the year was more common in men than women 9.2% and 5.85, respectively). A family history of allergy was reported by almost half of the study population. A family history of asthma was more common in women (68/260, 26.2%) than men (47/238, 19.7%), asthma in the mother was reported with similar frequency in both men and women (6.3% and 4.6%, respectively). Seventeen men (7.1%), and 24 (9.2%) women reported respiratory illness before age 5.

10.1.5. Airway Hyper-Responsiveness as Measured by Methacholine Challenge:

Airway hyper-responsiveness was assessed by methacholine challenge test in 372 of the subjects, 368 of whom completed the tests. *Table* 10.1.5 compares the subjects who completed methacholine challenge test results with the others, who did not. Subjects who did not have methacholine challenge included a higher percentage of women (58.4, vs. 50%), age group 30-39 year (47.7%, vs. 38.3%), and currently smoking (39.2%, vs. 34.8%) than those who completed it. Current Asthma symptoms (current wheeze: 43.1%, vs. 20.1%), and physician diagnosed asthma (23.8%, vs. 11.7%), asthma attack before age 15 (childhood onset asthma: 12.3% vs. 6.5%,) were more common in those who did not have methacholine challenge test than those who completed it. The group who did not have methacholine challenge test had a higher prevalence of positive reaction to any aeroallergen tested in skin prick testing (68.3%) than those who completed it (64.0%). Both groups had similar prevalence of occupational exposure to HMW agents, or LMW agents, and in the past, or currently, and of changing or leaving job due to respiratory

Table 10.1.5 : Comparison of the subjects, who had methacholine airway challenge tests with those who did not:

	Subjects with MC* (n %)	Subjects without MC n (%)	Total n (%)
Number of subjects	368 (100)	130 (100)	498 (100)
Women	184 (50.0)	76 (58.4)	260 (52.2)
Age group:			
20-29 year	164 (44.6)	42 (32.3)	206 (41.4)
30-39 year	141 (38.3)	62 (47.7)	203 (40.8)
40-44 year	63 (17.1)	26 (20.0)	89 (17.9)
Smoking status:			
Never smoked	174 (47.3)	52 (40.0)	226 (45.4)
Smoked in the past	66 (17.9)	27 (20.8)	93 (18.7)
Smoking currently	128 (34.8)	51 (39.2)	179 (35.9)
Asthma:			
Physician diagnosed	43 (11.7)	31 (23.8)	74 (14.8)
Onset before age15	24 (6.5)	16 (12.3)	40 (8.0)
Current† symptoms:			
Wheeze	74 (20.1)	56 (43.1)	130 (26.1)
Woken by SOB‡	23 (6.2)	26 (20.0)	49 (9.8)
Skin prick test: any (+)	226 (64.0)	82 (68.3)	308 (65.1)
Changed or left job	23 (6.2)	7 (5.4)	30 (6.0)
Occupational exposure:			
Ever to sensitisers	209 (56.8)	74 (56.9)	253 (56.8)
Ever to irritants	36 (9.8)	18 (13.8)	54 (10.8)
Past§: HMW¶agents	131 (35.6)	49 (37.7)	180 (36.1)
LMW‖ agents	115 (31.2)	43 (33.1)	158 (31.7)
Irritants	26 (7.1)	15 (11.5)	41 (8.2)
Current: HMW agents**	59 (16.0)	23 (17.7)	82 (16.5)
LMW agents	57 (15.4)	17 (13.1)	74 (14.9)
Irritants	11 (3.0)	5 (3.8)	16 (3.2)

*:Methacholine airway challenge test † : In the last 12 months ‡ : Shortness of breath
§ : Past :exposure occurred more than 1 year prior to the survey
¶ : High molecular weight ‖ : Low molecular weight
** : Current: exposure present during the year before the survey.

complaint, but the group who did not have methacholine challenge test had a higher prevalence of exposure to irritants (ever: 13.8%, past: 11.5%, current: 3.8%) than those who completed it (ever: 9.8%, past: 7.1%, current: 3.0%), in the past and as ever.

Table 10.1.6 shows the prevalence of various measurements of airway hyper-responsiveness derived from the methacholine challenge test in the study population. Airway hyper-responsiveness was assessed by the parameters of PD10, PD20, and slope by regressing the logarithm of the cumulative dose on the difference between the maximum FEV1 and the FEV1 (150). Data from the doses 0.0078 to 1 mg cumulative dose was used in the analysis as suggested by S. Chinn et al. for comparison of the results with the other studies (143). Dose response slope was calculated as the percentage decline in FEV1 from the post saline value to that of the total cumulative dose, divided by the total dose (151). The results show that the PD10 and PD20 had highly skewed distributions. Women had higher values, which suggested higher level of airway hyper-responsiveness.

10.2. Prevalence of Asthma in the Adult Population Using the Three Definitions of Asthma in the Present Study:

10.2.1. Prevalence of Asthma in the First and Second Stage Study Populations Using the Four Different Definitions of Asthma:

Table 10.2.1 shows prevalence of asthma in the first stage population according to the four different definitions of asthma used in the study: *current wheeze*, *asthma symptoms and or medicine*, *airway hyper-responsiveness*, and *crrent wheeze* combined with *airway hyper-responsiveness*. The results are obtained from the first stage study population for the first two definitions, and from the second stage study population involved in airway challenge test for the latter two definitions, which include *airway hyper-responsiveness*. Prevalence figures are given for the overall study population with and without the

Table 10.1.6. : Airway hyperresponsiveness as measured by methacholine challenge in the study population:

	Men n (%)	**Women n (%)**	**Total n (%)**
	184 (100)	184 (100)	368 (100)
FEV1 fall >20% from postsaline value*	22 (11.96)	32 (17.39)	54 (14.67)
Provocative dose (PD)			
PD10	8.48	5.10	6.79
Standard deviation	37.24	19.67	29.77
PD20	16.97	10.20	13.58
Standard deviation	74.49	39.34	59.54
Dose response slope			
Mean	17.44	84.69	51.07
Standard deviation	262.72	476.37	385.62
Range	(-1282, 4171.26)	(-188, 4763.54)	(-1282, 4763.54)

* : Cumulative dose of methacholine is 2 mg

Table 10.2.1: Prevalence of asthma in the study population using the four different definitions of asthma:

	Current wheeze	Asthma symptom and/or medicine	AHR*	Current wheeze + AHR
	% (95 % CI)	% (95 % CI)	% (95 % CI)	% (95 % CI)
All study population				
All	23.7 (22.2, 25.3)	12.8 (11.6, 14.0)	14.7 (11.1, 18.3)	6.8 (4.2, 9.4)
Men	21.9 (19.6, 24.1)	11.6 (9.9, 13.3)	11.9 (7.2, 16.6)	3.8 (1.0, 6.6)
Women	25.2 (23.1, 27.3)	13.8 (12.1, 15.4)	17.4 (11.9, 22.9)	9.8 (5.4, 14.1)
Standardised‡				
All	23.8 (23.1, 24.4)	12.9 (12.4, 13.4)	15.1 (13.5, 16.6)	7.0 (5.9, 8.1)
Men	21.7 (20.4, 23.0)	11.6 (10.6, 12.7)	12.4 (9.6, 15.3)	4.0 (2.2, 5.7)
Women	25.8 (24.5, 27.0)	14.0 (13.1, 15.1)	17.7 (14.4, 20.9)	10.0 (7.4, 12.5)
Excluding childhood asthmatics†				
All	21.3 (19.7, 22.8)	10.2 (9.0, 11.3)	12.5 (8.9, 16.0)	4.4 (2.2, 6.6)
Men	19.3 (17.1, 21.5)	9.2 (7.6, 10.8)	10.7 (6.0, 15.4)	2.4 (0.1, 4.7)
Women	22.8 (20.7, 25.0)	11.0 (9.4, 12.6)	14.2 (8.9, 19.4)	6.5 (2.8, 10.2)
Standardised				
All	21.0 (20.4, 21.7)	10.1 (9.6, 10.5)	12.9 (11.4, 14.4)	4.6 (3.7, 5.6)
Men	19.2 (17.9, 20.6)	9.2 (8.2, 10.2)	11.3 (8.5, 14.2)	2.6 (1.1, 4.2)
Women	22.8 (21.5, 24.0)	11.0 (10.1, 11.9)	14.5 (11.3, 17.6)	6.6 (4.4, 8.8)

* : Airway hyper-responsiveness

† : Excluding study subjects who reported asthma attack before age 15 years

‡ :Standardisation was made for gender, and age giving equal weights to men and women, and half the weight of age group 25-34 and 35-44 year to age group 20-24 year.

childhood asthmatics, in men, and women, both as crude rates and standardised rates to allow comparison of the study results with the other studies using the same study protocol. Direct standardisation was applied for the gender and age specific rates, giving equal weights to men and women, and half the weight of the age group 25-34, and 35-44 years to the age group 20-24 years (131). The prevalence was in the range of 19%-26% for *current wheeze*, 9%-14% for *asthma symptoms and/or medicine*, 11-18% for *airway hyper-responsiveness*, and 2-10% for *current wheeze* combined with *airway hyper-responsiveness*. For all the definitions women had a higher prevalence of asthma than that of men. The study population excluding childhood asthmatics had about 2% lower prevalence of asthma than that of the overall study population. Difference between the prevalence of asthma in men and women were significant after standardisation for all three definitions of asthma in all the study population, and for current wheeze in the study population excluding childhood asthmatics.

10.2.2. Imputation of Airway Hyper-Responsiveness in the Study Population:

As mentioned in the comparison of the subjects who only participated in the first stage of the study with those who participated in both stages of the study ie. study population (see *Table* 10.1.1), there was a systemic difference between these two groups, the latter having higher prevalence of symptoms. This made representativeness of the study population vs the target population questionable. Thus, inference to be made for the prevalence of asthma in the target population from findings in the study population would be likely to be biased. For this reason, prevalence estimates were obtained from the first stage sample using the two proposed study definitions of asthma (*current wheeze*, and *asthma symptoms and/or medicine*). Since information on airway hyper-responsiveness was not available in the first stage of the study, a multiple imputation technique was used to assign airway hyper-responsiveness status to first stage study population as described in section 9.2.2. *Table* 10.2.2 shows the parameters and statistics of the model used in the imputation and the prevalence estimates for *airway hyper-responsiveness* and *current wheeze* combined

Table 10.2.2: Parameters and statistics of the model used in the imputation and the prevalence estimates for *airway hyper-responsiveness* (**AHR**) and *current wheeze* combined with *airway hyper-responsiveness* (**W+ AHR**) with and without imputation:

	AHR* N (%)	Imputation model OR 95% CI	AHR* Imputation results			W + AHR†	W +AHR† Imputation results		
			1 N (%)	2 N (%)	3 N (%)		1 N (%)	2 N (%)	3 N (%)
All	54 (14.7)		381 (15.5)	397 (16.1)	357 (14.5)	15 (6.8)	135 (5.5)	131 (5.3)	116 (4.7)
Age (years)									
20-24	14 (18.9)	1.00	95 (24.9)	95 (24.9)	88 (18.6)	6 (8.1)	32 (5.8)	27 (4.9)	36 (6.6)
25-29	9 (10.3)	0.50 (0.19, 1.28)	61 (11.2)	57 (10.4)	48 (8.8)	5 (5.8)	26 (4.8)	19 (3.5)	14 (2.6)
30-34	8 (10.3)	0.51 (0.19, 1.37)	61 (9.7)	71 (11.3)	68 (10.8)	3 (3.8)	31 (4.9)	26 (4.2)	26 (4.2)
35-39	8 (13.3)	0.59 (0.21, 1.65)	57 (11.5)	68 (13.7)	58 (11.7)	2 (3.3)	10 (2.0)	27 (5.4)	20 (4.0)
40-44	15 (21.7)	1.25 (0.51, 1.38)	105 (23.4)	106 (23.7)	95 (21.2)	9 (13.0)	30 (6.7)	32 (7.1)	20 (4.4)
Diagnosis of asthma	18 (38.3)	**4.88 (2.40, 9.44)**	142 (37.6)	142 (37.6)	144 (38.1)	14 (29.8)	91 (24.1)	97 (25.7)	91 (24.1)

*: *Airway hyper-responsiveness* †: *Current wheeze* combined with *airway hyper-responsiveness*

/ continued over

Table 10.2.2: Parameters and statistics of the model used in the imputation and the prevalence estimates for *airway hyper-responsiveness* (**AHR**) and *current wheeze* combined with *airway hyper-responsiveness* (**W+ AHR**) with and without imputation:

	AHR* N (%)	Imputation model OR 95% CI	AHR* Imputation results			W +AHR† N (%)	W +AHR† Imputation results		
			1 N (%)	2 N (%)	3 N (%)		1 N (%)	2 N (%)	3 N (%)
All	54 (14.7)		381 (15.5)	397 (16.1)	357 (14.5)	15 (6.8)	135 (5.5)	131 (5.3)	116 (4.7)
Men	22 (12.0)	1.00	128 (11.2)	151 (13.2)	123 (10.8)	7 (3.8)	56 (4.9)	51 (4.5)	35 (3.1)
Women	32 (17.4)	1.44 (0.78, 2.68)	253 (17.5)	246 (16.9)	234 (16.2)	18 (9.8)	79 (5.4)	80 (5.5)	81 (5.6)
Never‡	19 (11.6)	1.00	103 (10.0)	138 (13.4)	122 (11.8)	8 (4.9)	15 (1.4)	32 (3.1)	28 (2.7)
Past §	9 (12.0)	0.81 (0.32, 2.04)	66 (11.2)	59 (10.0)	57 (9.7)	4 (5.3)	21 (3.6)	17 (2.9)	21 (3.6)
Current ¶	26 (20.2)	1.82 (0.90, 3.68)	212 (21.8)	200 (20.6)	178 (18.3)	16 (10.1)	99 (10.2)	86 (8.9)	67 (6.9)

*: *Airway hyper-responsiveness* †: *Current wheeze* combined with *airway hyper-responsiveness*

‡: Never smoked §: Smoked in the past ¶: Currently smoking

with *airway hyper-responsiveness*. The only significant factor was diagnosis of asthma (by a physician), which had an OR of 4.88 (2.40, 9.94). Currently smoking, female gender, age group 40-44 years age were the other possible risk factors, although they were not statistically significant. Results of imputation were similar to that of the prevalence of *airway hyper-responsiveness*.

10.3. Occupational Exposure Information:

10.3.1. Prevalence of Reported Employment in Industries or Occupations Defined a priori As High Risk for Occupational Asthma:

These are shown in *Table* 10.3.1. As one individual could report more than one such industry or occupation, the sum of these percentages is above 100. Almost 3/5 of the men, and 2/5 of the women reported employment ever in any of these industries or occupations. Food processing in men (11.8% vs. 8.5%) and textile industry in women (10.0% vs. 8.4%) were the most commonly reported industries or occupations. Prevalence differences between men and women for the industries or occupations most commonly reported were small. Among other industries or occupations, handling lab/farm animals, carpentry/furniture making, electronic equipment manufacture, chemical industry, soldering, electroplating were reported more frequently by men than women, whereas hairdressing was reported more frequently by women than men.

10.3.2. Commonly Reported Occupational Exposures Recognised As Asthmagenic:

Table 10.3.2 shows the distribution of commonly reported exposures recognised as asthmagenic through immunologic (sensitisers), or non-immunologic mechanisms (irritants). Almost 3/5 of men and 2/5 women reported any such exposure. Chemicals/fuels/solvents, which mainly included the irritants, comprised the most common categories of exposures reported (51.2 % for men and 21.9% for women). Organic dusts,

Table 10.3.1 : Prevalence of reported employment in industries or occupations defined a priori as high risk for occupational asthma*:

	Men n (%)	**Women n (%)**	**Total n (%)**
	238 (100)	260 (100)	498 (100)
Any†	**141 (59.2)**	**95 (36.5)**	**236 (47.4)**
Food processing	28 (11.8)	22 (8.5)	50 (10.0)
Textile	20 (8.4)	26 (10.0)	46 (9.2)
Bakery	13 (5.5)	17 (6.5)	30 (6.0)
Handling lab/ farm animals	22 (9.2)	6 (2.3)	28 (5.6)
Carpentry/ furniture making	22 (9.2)	4 (1.5)	26 (5.2)
Laboratory work	15 (6.3)	9 (3.5)	24 (4.8)
Electronic equipment manufacture	16 (6.7)	4 (1.5)	20 (4.0)
Chemical industry	15 (6.3)	4 (1.5)	19 (3.8)
Soldering	15 (6.3)	3 (1.2)	18 (3.6)
Hairdressing	3 (1.3)	8 (3.1)	11 (2.2)
Pharmaceutical	4 (1.7)	5 (1.9)	9 (1.8)
Electroplating	6 (2.5)	0 (0)	6 (1.2)
Any of the others‡	94 (39.4)	33 (12.7)	127 (25.5)

* : Listed in decreasing order of prevalence (total). Industries or occupations defined a priori as high risk for occupational asthma for this study are given in *Table 9.3.1*

† : Exposure in one or more industry or occupation at high risk.

‡ : Included under "any of the others" were those with prevalences below 1 %, such as detergent production, sea food processing.

Table 10.3.2 : Prevalence of commonly reported occupational exposures recognized as asthmagenic through immunological or non-immunological (irritant) mechanisms*:

	Men n (%)	**Women n (%)**	**Total n (%)**
	238 (100)	260 (100)	498 (100)
Any	**139 (58.4)**	**86 (33.1)**	**225 (45.2)**
Chemicals/ fuels / solvents:	**122 (51.2)**	**57 (21.9)**	**179 (35.9)**
Solvents	72 (30.2)	30 (11.5)	102 (20.5)
Glues	54 (22.6)	20 (7.7)	74 (14.8)
Paints	54 (22.6)	13 (5.0)	67 (13.4)
Acids	55 (23.1)	14 (5.4)	69 (13.8)
Ammonia	28 (11.8)	22 (8.5)	50 (10.0)
Organic dusts:	**69 (29.0)**	**47 (19.7)**	**116 (23.3)**
Grain or flour dust	22 (9.2)	10 (3.8)	32 (6.4)
Cotton dust	9 (3.8)	21 (8.1)	30 (6.0)
Wood dust	37 (15.5)	6 (2.3)	43 (8.6)
Biological enzymes	21 (8.8)	13 (5.0)	34 (6.8)
Metal fume/ dust:	**33 (13.9)**	**8 (3.1)**	**41 (8.2)**
Aluminum	26 (10.9)	6 (2.3)	32 (6.4)
Chromium	9 (3.8)	1 (0.8)	10 (2.0)
Zinc	8 (3.4)	1 (0.8)	9 (1.8)

* : For the complete list of agents in each of the categories used in this study see *Table* 9.3.1

which included the main group of sensitisers, were reported by almost 1/4 of the study population. Except for cotton dust (3.8% men and 8.1% women reported), all the exposures were reported more commonly by men than by women.

10.3.3. Past and Current Occupational Exposures According to the Categories of Agents, Occupations and Industries:

Table 10.3.3 shows the temporal distribution of the reported occupational exposures as past and current, again by categories of agents, occupations and industries, listed in *Table* 9.3.1. Almost half of the men and one fourth of the women reported past exposure to high molecular weight agents, and to low molecular weight agents. About 20% of the men, and about 10-15% of the women, reported current exposure to each of these agents. Thirteen percent of men and 3.9% of women reported past exposure to irritants, while 5% of men and 1.5% of women reported current exposure to irritants. Among the non-specific occupational exposures, cigarette smoke was the most common, reported by 42% of men and 26% of women in the past, and by almost 30% of men and women currently. Exposure to combustion smoke, and to excess cold were reported by almost 10% of men, and around 3-6% of women, in the past, and currently for each. Exposure to excess heat in the past, and currently, was reported by 13.9%, and 10.5% of men, and 4.2 %, and 11.2% of women, respectively. Exposure to inorganic dusts, which are not considered among the occupational causes of asthma, was reported by 13% of men and 4% of women in the past, and by 9% of men and 4% of women currently.

Table 10.3.3 : Reported past and current occupational exposures by category :

	Men n (%)	Women n (%)	Total n (%)
	238 (100)	260 (100)	498 (100)
HMW† agents			
• **Past**	114 (47.9)	67 (25.8)	181 (36.4)
Current	45 (18.9)	37 (14.2)	82 (16.5)
LMW‡ agents			
• **Past**	108 (45.4)	53 (20.4)	161 (32.3)
Current	52 (21.8)	26 (10.0)	78 (15.7)
Irritants			
• **Past**	31 (13.0)	10 (3.9)	41 (8.2)
Current	12 (5.0)	4 (1.5)	16 (3.2)
Other agents:			
Inorganic dust			
• **Past**	32 (13.4)	10 (3.9)	42 (8.4)
Current	22 (9.2)	11 (4.2)	33 (6.6)
Cigarette smoke			
• **Past**	49 (41.9)	68 (26.2)	117 (33.5)
Current	70 (29.4)	82 (31.5)	152 (30.5)
Combustion smoke			
• **Past**	30 (12.6)	8 (3.1)	38 (7.6)
Current	26 (10.9)	6 (2.3)	32 (6.4)
Excess cold			
• **Past**	27 (11.3)	17 (6.5)	44 (8.8)
Current	25 (10.5)	16 (6.2)	41 (8.2)
Excess heat			
• **Past**	33 (13.9)	11 (4.2)	44 (8.8)
Current	25 (10.5)	29 (11.2)	54 (10.8)

* : For the complete list of agents in each of the categories used in this study see *Table* 9.3.1. Past : exposure occurred more than 1 year prior to the survey, Current : exposure present during 1 year before the survey.

† : High molecular weight ‡ : Low molecular weight

10.3.4. Duration of Exposure Ever Reported in Industries or Occupations Defined a priori as High Risk for Occupational Asthma:

Duration of exposure ever reported in industries or occupations defined a priori as high risk for occupational asthma is shown in *Table* 10.3.4. Most of the reported exposures in these industries or occupations had a median duration of 2 to 4 years. Men reported a median exposure of half a year in the bakery industry, and 5 years in electroplating. Women reported a median exposure of 10 years in hairdressing, and 5 years in electroplating. The range of the duration was mostly 0 to 17 years, with a maximum length of 23 years.

Table 10.3.4 : Duration of ever exposure reported in industries or occupations defined a priori high risk for occupational asthma:

	Men n (%)			**Women n (%)**			**Total n (%)**		
	238 (100)			260 (100)			498 (100)		
	(N)*	**Md†**	**Rg ‡**	**(N)**	**Md.**	**Rg.**	**(N)**	**Md.**	**Rg.**
Food processing	**(25)**	2	0-14	**(20)**	2.5	0-17	**(45)**	2	0-17
Textile	**(15)**	3	0-15	**(24)**	2.5	0-17	**(39)**	3	0-17
Handling lab/ farm animals	**(22)**	3.5	0-16	**(5)**	1	0-14	**(27)**	3	0-16
Bakery	**(10)**	0.5	0-16	**(15)**	2	0-17	**(25)**	2	0-17
Carpentry/ furniture making	**(19)**	4	0-19	**(4)**	1.5	0-10	**(23)**	4	0-19
Laboratory work	**(11)**	2	0-6	**(8)**	4	0-23	**(19)**	3	0-23
Electronic equipment manufacture	**(14)**	2	0-6	**(3)**		0-4	**(17)**	2	0-6
Chemical industry	**(14)**	3	0-15	**(2)**		4-22	**(16)**	3	0-22
Soldering	**(12)**	3	0-10	**(2)**		1-4	**(14)**	3	0-10
Hairdressing	**(2)**		0-15	**(6)**	10	1-17	**(8)**	10	2-17
Pharmaceutical	**(3)**	-	2-7	**(4)**	2	0-6	**(7)**	2	0-7
Electroplating	**(5)**	5	0-6	**(0)**			**(5)**	5	0-6

* : Number of subjects
†: Median (year) of duration
‡ : Range (year) of duration

10.4. Results of Analytic Studies:

10.4.1. Association of Current Asthma Defined in 3 ways, with Various Categories of Occupational Exposure Adjusted for Age, Gender, and Smoking Habits:

Table 10.4.1 shows the associations expressed as OR's, of asthma defined in 3 ways (*current wheeze*, and *asthma symptoms and or medicine*, and *airway hyper-responsiveness* alone) with various categories of occupational exposure adjusted for age, gender, and smoking habits. *Current wheeze* was significantly associated with past exposure to LMW agents, and irritants with the odds ratios of 1.61 (1.02, 2.55), and 2.73 (1.35, 5.54), respectively, but not with current exposure to HMW agents, or LMW agents, or irritants, with odds ratios of 1.12 (0.64, 1.95), 0.74 (0.39, 1.39), and 0.44 (0.09, 2.03), respectively. *Current wheeze* was also significantly associated with past exposure to cigarette smoke, combustion smoke, excess cold, and excess heat with the odds ratios of 1.66 (1.03, 2.68), 4.74 (2.26, 9.94), 2.78 (1.43, 5.41), and 2.74 (1.38, 5.41), respectively. *Current wheeze* was not however significantly associated with current exposures. *Asthma symptoms and or medicine* was significantly associated with only combustion smoke in the past (2.38, 95% CI: 1.04, 9.03). *Airway hyper-responsiveness* was not significantly associated with any occupational exposure except for excess cold in the past, with an OR of 4.18 (1.72, 10.16).

10.4.2. Association of Current Asthma Defined in 3 ways, with Occupational Exposures Defined as Ever and Various Other Factors Known or Suspected of Being Determinants of Asthma:

Table 10.4.2 shows the association of current asthma defined in 3 ways, with ocupational exposures defined as ever and various other factors known or suspected of being determinants of asthma. Significant associations are shown in bold type in *Table* 10.4.2 These are grouped into 5 main categories and each is discussed briefly below.

Table 10.4.1: Odds ratios for associations between current asthma defined in 3 ways and category of occupational exposure adjusted for gender, age, and smoking habits:

Factor	Current wheeze OR (95%CI)	Asthma Symptom and/or Medicine OR (95%CI)	Airway Hyper-responsiveness OR (95%CI)
HMW agents*			
• **Past†**	1.43 (0.92, 2.22)	1.12 (0.65, 1.92)	1.59 (0.85, 2.98)
Current‡	1.12 (0.64, 1.95)	0.94 (0.46, 1.89)	1.20 (0.53, 2.68)
LMW agents§			
• **Past**	**1.61 (1.02, 2.55)**	1.61 (0.92, 1.81)	1.33 (0.69, 2.56)
Current	0.74 (0.39,1.39)	0.88 (0.41, 1.88)	1.13 (0.49, 2.63)
Irritants			
• **Past**	**2.73 (1.35, 5.54)**	1.17 (0.46, 2.98)	0.19 (0.02, 1.47)
Current	0.44 (0.09, 2.03)	0.92 (0.20, 4.22)	1.50 (0.30, 7.52)
Other agents:			
Inorganic dust			
• **Past**	1.20 (0.58, 2.50)	1.13 (0.45, 2.86)	0.77 (0.25, 2.41)
Current	1.12 (0.49, 2.57)	1.50 (0.59, 3.84)	1.22 (0.39, 3.85)
Cigarette smoke			
• **Past**	**1.66 (1.03, 2.68)**	1.52 (0.86, 2.70)	1.26 (0.64, 2.46)
Current	0.97 (0.62, 1.51)	0.89 (0.51, 1.56)	1.39 (0.75, 2.59)
Combustion smoke	**4.74 (2.26, 9.94)**	**2.38 (1.04, 5.43)**	0.83 (0.23, 2.95)
• **Past**	0.71 (0.27, 1.84)	1.68 (0.64, 4.37)	0.23 (0.63, 2.63)
Current			
Excess cold			
• **Past**	**2.78 (1.43, 5.41)**	1.98 (0.92, 4.26)	**4.18 (1.72, 10.16)**
Current	0.98 (0.46, 2.08)	0.86 (0.32, 2.29)	0.43 (0.10, 1.92)
Excess heat			
• **Past**	**2.74 (1.39, 5.41)**	1.39 (0.54, 3.09)	0.64 (0.18, 2.24)
Current	1.24 (0.65, 2.36)	1.06 (0.47, 2.37)	1.16 (0.45, 2.98)

List of the categories of occupational exposures relevant for the analysis is given in Table 9.3.1.

* : High molecular weight

† : Past exposure occurred more than 1 year prior to the survey

‡ :Current: exposure present during 1 year before the survey.

§ : Low molecular weight

Table 10.4.2: Association between ***Current wheeze, Asthma symptom and/or medicine, and Airway hyper-responsiveness***, and occupational exposure and other factors after adjustment for gender, age, and smoking:

Factor	**Current wheeze OR (95%CI)**	**Asthma Symptom and/or Medicine OR (95%CI)**	**Airway Hyper-responsiveness OR (95%CI)**
Occupational Exposure and Related Factors			
Exposure Ever to HMW and/or LMW Agents	1.21 (0.78, 1.89)	1.10 (0.64, 1.89)	**2.04 (1.05, 3.93)**
Exposure Ever To Irritants	1.85 (0.97, 3.52)	0.98 (0.41, 2.31)	0.47 (0.13, 1.69)
Other Work Related Exposure Ever	1.16 (0.72, 1.85)	1.03 (0.58, 1.82)	1.65 (0.77, 3.48)
Accidental Exposure	**2.18 (1.10, 4.34)**	**3.12 (1.48, 6.57)**	1.33 (0.47, 3.81)
Changing Job Ever	**3.95 (1.78, 8.73)**	**5.21 (2.33, 11.65)**	0.71 (0.15, 3.35)
Hobby including any occupational exposure	0.94 (0.50, 1.51)	1.13 (0.54, 2.35)	**2.76 (1.32, 5.78)**
Exposures and Respiratory Diseases in the Childhood			
Childhood asthma	**9.08 (4.32, 19.10)**	**11.22 (5.51, 22.86)**	**6.08 (2.43, 15.20)**
Serious Respiratory Infection Before Age 5	**5.96 (2.96, 11.99)**	**3.75 (1.84, 7.64)**	1.03 (0.29, 3.68)
Going to Playschool or Nursery Before Age 5	**1.68 (1.06, 2.66)**	**2.10 (1.22, 3.59)**	0.70 (0.34, 1.45)
Sharing Bedroom with an Elder Sib Before Age 5	**0.60 (0.39, 0.94)**	0.89 (0.52, 1.50)	1.03 (0.56, 1.88)
Having an Elder Brother	**0.48 (0.31, 0.73)**	0.76 (0.45, 1.28)	**0.52 (0.28, 0.96)**
Having an Elder Sister	**0.58 (0.38, 0.89)**	**0.45 (0.26, 0.79)**	1.39 (0.76, 2.52)
Having an Elder Sib	**0.51 (0.33, 0.78)**	0.61 (0.36, 1.01)	0.63 (0.34, 1.15)
Any Pet in Household in the Childhood	**1.81 (1.05, 3.11)**	1.01 (0.55, 1.86)	1.14 (0.56, 2.31)

/continued over

Table 10.4.2: Association between ***Current wheeze, Asthma symptom and/or medicine, and Airway hyper-responsiveness***, and occupational exposure and other factors after adjustment for gender, age, and smoking:

Factor	Current wheeze OR (95%CI)	Asthma Symptom and/or Medicine OR (95%CI)	Airway Hyper-responsiveness OR (95%CI)
Exposures in the Adulthood and Related Factors			
Smoking in the past	1.04 (0.53, 2.00)	0.96 (0.44, 2.07)	0.82 (0.32, 1.10)
Smoking currently	**3.13 (1.96, 5.00)**	1.28 (0.72, 2.26)	1.87 (0.96, 3.64)
Home Characteristics			
Electrical Heating	0.93 (0.58, 1.48)	1.20 (0.66, 2.16)	**3.28 (1.34, 8.03)**
Atopy and Family History of Allergic Diseases			
Atopy	**2.05 (1.26, 3.32)**	**2.34 (1.24, 4.38)**	1.05 (0.55, 2.00)
Asthma in the Mother	**2.87 (1.23, 6.66)**	**3.10 (1.27, 7.52)**	**3.97(1.36, 11.56)**
Asthma in the Father	**2.59 (1.11, 6.04)**	**2.87 (1.17, 7.01)**	0.46 (0.06, 3.72)
Asthma in Any Brother	**2.82 (1.34, 5.92)**	**2.32 (1.03, 5.26)**	1.98 (0.72, 5.41)
Asthma in Any Sister	1.65 (0.86, 3.19)	**2.30 (1.12, 4.70)**	1.54 (0.58, 4.06)
Asthma in the Family	**2.36 (1.48, 3.77)**	**2.23 (1.30, 3.84)**	**2.30 (1.20, 4.43)**
Allergy in the Father	**1.98 (1.20, 3.29)**	1.36 (0.74, 2.52)	1.13 (0.54, 2.38)
Allergy or Asthma in the Family	1.38 (0.89, 2.16)	**1.92 (1.07, 3.44)**	1.47 (0.78, 2.78)
Personal Factors			
Gender (Women)	**1.62 (1.06, 2.47)**	1.38 (0.82, 2.32)	1.50 (0.82, 2.73)
Age 35-39	0.76 (0.32, 1.52)	**0.34 (0.12, 0.92)**	0.90 (0.35, 2.32)

10.4.2.1. Occupational Exposures and Related Factors:

The factors examined included *exposure ever to HMW and/or LMW agents, exposure ever to irritants , other work related exposure ever, accidental exposure, changing job ever,* and *hobbies including any occupational exposure. Current wheeze,* and *asthma symptoms and/or medicine* were significantly associated with accidental exposure to occupational agents ever, and a history of ever changing job upon respiratory complaints, with OR's of 2.18 (1.10, 4.34), and 3.95 (1.78, 8.73); and 3.12 (1.48, 6.57), and 5.21 (2.33, 11.65), respectively. By contrast, *airway hyper-responsiveness* was significantly associated with occupational *exposure ever to HMW and/or LMW agents* and hobbies including any of the occupational exposures, with OR's of 2.04 (1.05, 3.93), and 2.76 (1.32, 5.78), respectively.

10.4.2.2. Childhood exposures and history of asthma:

The factors examined included *childhood asthma, serious respiratory infection before age 5, parental smoking in the childhood (father or mother smoking, mother smoking in the pregnancy), going to playschool or nursery before age 5, sharing bedroom with an elder sib before age 5, having an elder brother or sister,* and *any pet in the household in the childhood. Current wheeze, asthma symptoms and/or medicine,* and *airway hyper-responsiveness* were significantly associated with childhood asthma, with OR's of 9.08 (4.32, 9.10), 11.22 (5.51, 22.86), and 6.08 (2.43, 15.20), respectively. *Current wheeze,* and *asthma symptoms and/or medicine* were significantly associated with serious respiratory infection before age 5, going to playschool or nursery before age 5, having and elder sister, with OR's of 5.96 (2.96, 11.99), and 3.75 (1.84, 7.64); 1.68 (1.06, 2.66), and 2.10 (1.22, 3.59), and 0.58 (0.38, 0.89), and 0.45 (0.26, 0.79) respectively. *Current wheeze,* and *airway hyper-responsiveness* were significantly associated with having an elder brother with OR's less than unity (0.48 (0.31, 0.73), and 0.52 (0.28, 0.96), respectively). *Current wheeze* was significantly associated with sharing bedroom with an elder sib before age 5, having an elder sib, and any pet in the household in the childhood with OR's less than unity (0.60 (0.39, 0.94), 0.51 (0.33, 0.78), and 1.81 (1.05, 3.11), respectively).

10.4.2.3. Exposures in the Adulthood and Related Factors:

The factors examined included *smoking in the past*, and *currently*, *exposure to pet (a cat, dog, birds*, or *any)*, *home characteristics* including *mold in the house ever or current, bedroom carpet, room carpet, any room carpet, electrical hating, electrical cooking.* Significant associations are shown in bold type in *Table* 10.4.3. *Current wheeze* was significantly associated with smoking currently, with an OR of 3.13 (1.96,5.00). *Airway hyper-responsiveness* was significantly associated with electrical heating, with an OR of 3.28 (1.34, 8.03).

10.4.2.4. Atopy and Family History of Allergic Diseases:

The factors examined included *atopy* as determined by any positive reaction in the skin prick testing, and *family history of asthma or allergic disease* (in the *mother, father, brother*, or *sister*). *Current wheeze*, and *asthma symptoms and or medicine* were significantly associated with atopy, with OR's of 2.05 (1.26, 3.32), and 2.34 (1.24, 4.38), respectively. *Current wheeze, asthma symptoms and or medicine*, and *airway hyper-responsiveness* were significantly associated with asthma in the mother, and asthma in the family, with OR's of 2.87 (1.23, 6.66), 3.10 (1.27, 7.52), and 3.97 (1.36, 11.56); and 2.36 (1.48, 3.77), 2.23 (1.30, 3.84), and 2.30 (1.20, 4.43), respectively. *Current wheeze*, and *asthma symptoms and or medicine* were significantly associated with asthma in the father, and asthma in any brother, with OR's of 2.59 (1.48, 3.77), and 2.87 (1.17, 7.01); and 2.82 (1.34, 5.92), and 2.32 (1.03, 5.26), respectively. *Current wheeze* was significantly associated with allergy in the father with an OR of 1.98 (1.20, 3.29). Asthma symptoms and/or medicine *wheeze* was significantly associated with allergy or asthma in the family with an OR of 1.92 (1.07, 3.44).

10.4.2.5. Personal Factors:

The factors examined included *gender, and age groups* of *25-29, 30-34, 35-39, 40-44 years* compared with *20-24 years, socioeconomic status (education: completing at least secondary school), dietary habits* including *eating fruit or vegetables regularly, eating canned food regularly, consuming soft drink soda regularly, consuming prepacked food*

or drink. Current wheeze was significantly associated with women gender with an OR of 1.62 (1.06, 3.47). Asthma symptoms and/or medicine *wheeze* was significantly associated with age group 35-39 years with an OR of 0.34 (0.12, 0.92).

10.4.3. Association Between Occupational Exposures and Occupation Related Factors and Other Potential Determinants of the Study Outcomes Adjusted for Age, Gender, and Smoking Habits:

Table 10.4.3 shows the association between occupational exposure ever to HMW or LMW agents, or irritants and other factors. Associations according to the 5 main categories of these factors are mentioned below.

10.4.3.1. Childhood Exposures and History of Asthma:

Exposure ever to irritants was significantly associated with father smoking, going to playschool or nursery before age 5, and sharing bedroom with an elder sib before age 5, with OR's of 2.1.2 (1.02, 4.42), 0.45 (0.21, 0.99), and 2.00 (1.10, 3.62), respectively. *Exposure* ever *to HMW and or LMW agents (sensitisers)* was not significantly associated with any of the childhood exposures and history of asthma used in the study.

10.4.3.2. Exposures in the Adulthood and Related Factors:

Exposure ever to irritants, and *exposure ever to HMW and or LMW agents (sensitisers)* were significantly associated with passive smoking, with OR's of 1.67 (1.12, 2.49), and 1.93 (1.00, 3.72), respectively. *Exposure ever to irritants* was also significantly associated with smoking in the past, and smoking currently, with OR's of 3.44 (1.50, 7.90), and 2.35 (1.15, 4.81), respectively. Exposure ever to HMW *and or LMW agents (sensitisers)* was significantly associated with mold in the household ever, with an OR of 1.72 (1.09, 2.69).

Table 10.4.3: Association between occupational exposure ever to sensitisers, and to irritants, and other work related exposures and other factors after adjustment for gender, age, and smoking:

Factor	Exposure Ever to HMW and/or LMW Agents OR (95% CI)	Exposure Ever to Irritants OR (95% CI)
Occupational Exposure and Related Factors		
Exposure Ever to HMW and/or LMW Agents	N/A	**8.7 (3.03, 24.97)**
Exposure Ever to Irritants	**8.7 (3.03, 24.97)**	N/A
Other Work Related Exposure Ever	**1.97 (1.30,3.00)**	**3.89 (1.49, 10.16)**
Accidental Exposure	**2.84 (1.28, 6.29)**	1.59 (0.64, 3.96)
Changing Job Ever	**7.13(2.06, 24.71)**	**3.11 (1.27, 7.60)**
Hobbies with Any Occupational Exposure	**3.85 (2.01, 7.38)**	1.47 (0.68, 3.17)
Exposures and Respiratory Diseases in the Childhood		
Father Smoking	0.85 (0.56, 1.28)	**2.12 (1.02, 4.42)**
Going to Playschool / Nursery Before Age 5	1.00 (0.65, 1.52)	**0.45 (0.21, 0.99)**
Sharing Bedroom with an Elder Sib Before Age 5	1.29 (0.88, 1.90)	**2.00 (1.10, 3.62)**
Exposures in the Adulthood and Related Factors		
Smoking in the past	1.56 (0.90, 2.69)	**3.44 (1.50, 7.90)**
Smoking currently	1.44 (0.93, 2.22)	**2.35 (1.15, 4.81)**
Passive Smoking	**1.67 (1.12, 2.49)**	**1.93 (1.00, 3.72)**
Mold in the Household Ever	**1.72 (1.09, 2.69)**	1.05 (0.53, 2.04)
Personal Factors		
Gender	**0.28 (0.18, 0.60)**	**0.25 (0.13, 0.48)**

10.4.3.3. Atopy, and Family History of Allergic Diseases:

There was no statistically significant association between Exposure ever to *irritants*, and *exposure ever to HMW and or LMW agents (sensitisers)* and atopy, and family history of allergic diseases.

10.4.3.4. Personal Factors:

Exposure ever to irritants, and *exposure ever to HMW and or LMW agents (sensitisers)* were significantly associated with female gender, with OR's of 0.28 (0.18, 0.60), and 0.25 (0.13, 0.489, respectively.

10.4.3.5. Occupational Exposures and Related Factors:

There was a strong association between occupational Exposure ever to sensitisers and to irritants with an OR of 8.70 (3.03, 24.97). Exposure ever *to HMW and or LMW agents (sensitisers)*, and *Exposure ever to irritants* were significantly associated with other work related Exposure ever, and changing job ever, with OR's of 1.97 (1.30, 3.00), and 3.89 (1.49, 10.16); and 7.13 (2.06, 24.71), and 3.11 (1.27, 7.60), respectively. Exposure ever to HMW *and or LMW agents (sensitisers)* was significantly associated with accidental exposure, and hobbies including any occupational exposure, with OR's of 2.84 (1.28, 6.29), and 3.85 (2.01, 7.85), respectively.

10.5. Multivariate Analysis of the Association of Current Asthma Defined in 3 Ways with Occupational Exposures Adjusted for Pertinent Risk Factors:

Relative risk estimates for exposure ever to occupational agents were obtained from logistic regression models, which adjusted for gender, age, and smoking habits, and other pertinent risk factors of asthma. Models using the three definitions of asthma, both in the total study population and in the study population excluding childhood asthmatics were developed. Since skin prick testing was not performed to every subject models were constructed for each study definition of asthma, one including atopy as a determinant, and one not.

10.5.1. Models Adjusting for Age, Gender, and Smoking Habits:

Table 10.5.1 shows the models for the association of current asthma defined in 3 ways with occupational exposures, adjusted for gender, age, and smoking habits. In general prevalence risk ratios expressed as odds ratios for each definition were similar, whether the study population included childhood asthmatics or not. *Exposure ever to HMW and or MW agents* slightly increased (nonsignificantly) the OR for *current wheeze*, and *asthma symptom, and or medicine* around 1.15, in the study population with or without childhood asthmatics. By contrast, *exposure ever to HMW and or LMW agents* increased the risk of *airway hyper-responsiveness* significantly with OR's of 2.28 (1.17, 4.4), and 2.46 (1.17, 5.16) in the study population with or without childhood asthmatics, respectively. The risk of *current wheeze* was increased significantly with OR's around 1.8 for female gender, and 3-3.5 for current smoking, whether or not childhood asthmatics were included. Current smoking increased the risk of *airway hyper-responsiveness*, with an OR around 2, but only when childhood asthmatics were excluded. Age group 35-39 year had significantly lower risk of *asthma symptom, and or medicine* than age group 20-24 year (reference age group), with an OR of 0.33 (0.12, 0.90). Smoking in the past was not associated with any of the three markers of asthma used in the study, although the 95% confidence intervals included 2.

10.5.2. Models with Pertinent Risk Factors of Asthma (Atopy not Included):

Table 10.5.2 shows the models for the association of asthma defined in three ways with pertinent risk factors of asthma included, but not atopy. The models were developed for *current wheeze* in the overall study population, and the study population excluding childhood asthmatics, were then applied to the other two study definitions of asthma, primarily for comparison of the findings using the three different study definitions of asthma. Prevalence rate ratio estimates (odds ratios) for each definition was similar in the study population whether or not childhood asthmatics were included in the analysis. *Exposure ever to HMW or LMW agents* increased the risk of asthma defined as *airway hyper-responsiveness* significantly, with an OR of 2.20 (1.10, 4.38), and 2.05 (1.00, 4.22)

Table 10.5.1: Association of ***Current Wheeze, Asthma Symptoms and/or Medicine, and Airway Hyper-responsiveness*** with occupational exposures, adjusted for gender, age, and smoking in the adult population:

	All the study population			Study Population excluding childhood asthmatics		
	W* (n=498) OR (95% CI)	Ast S/M† (n=498) OR (95% CI)	AHR‡ (n=368) OR (95% CI)	W (n=458) OR (95% CI)	Ast S/M (n=458) OR (95% CI)	AHR (n=344) OR (95% CI)
Ever Occupational Exposure to						
HMW/LMW agents	1.15 (0.73, 1.81)	1.19 (0.68, 2.07)	**2.28 (1.17, 4.44)**	1.14 (0.69, 1.88)	1.15 (0.60, 2.20)	**2.46 (1.17, 5.16)**
Irritants	1.78 (0.92, 3.45)	0.93 (0.38, 2.26)	0.35 (0.09, 1.29)	1.79 (0.86, 3.71)	0.76 (0.25, 2.33)	0.42 (0.11, 1.62)
Woman	**1.83 (1.17, 2.88)**	1.45 (0.84, 2.50)	1.65 (0.87, 3.13)	**1.83 (1.11, 3.01)**	1.37 (0.72, 2.61)	1.59 (0.79, 3.22)
Age (years)						
25-29	0.80 (0.42, 1.55)	0.66 (0.31, 1.42)	0.53 (0.21, 1.35)	0.95 (0.45, 2.01)	0.83 (0.31, 2.22)	0.61 (0.22, 1.68)
30-34	1.02 (0.54, 1.93)	0.99 (0.48, 2.02)	0.43 (0.16, 1.18)	1.31 (0.63, 2.69)	1.31 (0.53, 3.26)	0.39 (0.12, 1.24)
35-39	0.76 (0.38, 1.55)	**0.33 (0.12, 0.90)**	0.79 (0.30, 2.08)	0.90 (0.40, 2.00)	0.68 (0.22, 2.07)	0.69 (0.23, 2.08)
40-44	0.76 (0.38, 1.56)	0.66 (0.28, 1 53)	1.84 (0.74, 4.57)	1.10 (0.50, 2.40)	1.16 (0.43, 3.14)	2.26 (0.83, 6.13)
Smoked In the Past	0.96 (0.49, 1.86)	0.95 (0.43, 2.08)	0.81 (0.31, 2.14)	0.93 (0.43, 2.00)	0.89 (0.34. 2.31)	0.76 (0.25, 2.35)
Currently smoking	**2.99 (1.86, 4.79)**	1.27 (0.71, 2.26)	1.96 (0.98, 3.90)	**3.51 (2.09, 5.90)**	1.52 (0.78, 2.98)	**2.24 (1.05, 4.77)**

* : Current wheeze †: Asthma symptom and/or medicine ‡ : Airway Hyper-responsiveness

Table 10.5.2: Association of ***Current Wheeze, Asthma Symptoms and/or Medicine, and Airway Hyper-responsiveness*** with occupational exposures, adjusted for pertinent risk factors of asthma in the study population (atopy not included)

	All the study population			Study Population excluding childhood asthmatics		
	W* (n=498) OR (95% CI)	Ast S/M† (n=498) OR (95% CI)	AHR‡ (n=368) OR (95% CI)	W (n=458) OR (95% CI)	Ast S/M (n=458) OR (95% CI)	AHR (n=344) OR (95% CI)
Ever Occupational Exposure to HMW /LMW Agents	1.01 (0.62, 1.66)	1.03 (0.57, 1.86)	**2.20 (1.10, 4.38)**	1.02 (0.60, 1.72)	1.03 (0.54, 1.98)	**2.05 (1.00,4.22)**
Irritants	**2.12 (1.03, 4.34)**	0.88 (0.33, 2.31)	0.35 (0.09, 1.34)	**2.17 (1.01, 4.63)**	0.85 (0.27, 1.61)	0.52 (0.14, 1.89)
Childhood Asthma	**5.99 (2.64, 13.58)**	**8.89(4.06, 19.47)**	**8.72 (2.85,26.66)**			
Respiratory Infection Before age 5	**2.94 (1.32, 6.54)**	1.39 (0.57, 3.39)	**0.21 (0.04, 1.00)**	**5.24 (2.04, 12.98)**	2.23 (0.76, 6.52)	0.40 (0.05, 2.35)
Childhood History of Pet in the Household	**1.90 (1.05, 3.42)**	1.07 (0.54, 2.07)	0.98 (0.47, 2.03)	**2.04 (1.06, 3.91)**	0.98 (0.47, 2.05)	1.17 (0.52, 2.63)
Having an Elder Sib	**0.44 (0.27, 0.71)**	**0.56 (0.32, 0.99)**	0.54 (0.28, 1.01)	**0.52 (0.31, 0.86)**	0.60 (0.32, 1.14)	0.57 (0.29, 1.10)
Current Smoking	**3.60 (2.26, 5.76)**	1.26 (0.71, 2.24)	**2.24 (1.19, 4.21)**	**3.85 (2.35, 6.30)**	1.46 (0.78, 2.73)	**2.30 (1.19, 4.45)**
Education Level	**0.42 (0.20, 0.88)**	**0.43 (0.19, 0.98)**	1.78 (0.49, 6.50)	**0.41 (0.19, 0.88)**	**0.40 (0.17, 0.93)**	1.66 (0.46, 6.06)
Family History of Asthma	**2.26 (1.33, 3.82)**	**1.96 (1.06, 3.61)**	**2.09 (1.04, 4.20)**	**2.15 (1.23, 3.77)**	**2.24 (1.14, 2.39)**	1.79 (0.84, 3.83)
Woman	**1.74 (1.07, 2.82)**	1.23 (0.69, 2.22)	1.69 (0.87, 3.28)	**1.79 (1.07, 2.99)**	1.25 (0.65, 2.38)	1.70 (0.85, 3.40)

* : Current wheeze †: Asthma symptom and/or medicine ‡ : Airway Hyper-responsiveness

in the study population including childhood asthmatics or not, respectively. By contrast, for the other definitions of *current asthma* the OR's were not significant. *Exposure ever to irritants* increased the risk of *current wheeze*, with OR's of 2.12 (1.03, 4.34), and 2.17 (1.01, 4.63) in the study population including childhood asthmatics or not, respectively. Childhood history of asthma significantly increased the risk of all three markers of asthma in the study population, with OR's in the range of 6-8. Respiratory infection before age 5 increased the risk of *current wheeze* with OR's of 2.94 (1.32, 6.54), and 5.24 (2.04, 12.98) in the study population including childhood asthmatics or not, respectively. However, a respiratory infection before age 5 decreased the risk of *airway hyper-responsiveness* although non-significantly with OR's of 0.21 (0.04, 1.00), and 0.40 (0.05, 2.35) in the study population including childhood asthmatics or not, respectively. Childhood history of pet in the household increased the risk of asthma defined as *current wheeze* with OR's of 1.90 (1.05, 3.42), and 2.04 (1.06, 3.91) in the study population including childhood asthmatics or not, respectively, but was not associated significantly with the other two study definitions of asthma. Having an elder sib decreased the risk of all three definitions of asthma used in the study, with OR's around 0.4-0.6, though not significantly for *airway hyper-responsiveness* including childhood asthmatics or not. Current smoking increased the risk of *current wheeze* with OR's of 3.60 (2.26, 5.76), and 3.85 (2.35, 6.30) in the study population including childhood asthmatics or not, respectively. The findings were similar for *airway hyper-responsiveness* with OR's of 2.24 (1.19, 4.21), and 2.30 (1.19, 4.45). Current smoking was not however significantly associated with *asthma symptoms and or medicine*, with OR's of 1.26 (0.71, 2.24), and 1.46 (0.78, 2.73) in the study population including childhood asthmatics or not, respectively. Education level, defined as completing secondary school significantly decreased the risk of *current wheeze*, and *asthma symptoms and or medicine* with OR's of about 0.4; and decreased, but again not significantly the risk for *airway hyper-responsiveness*. Family history of asthma significantly increased the risk of all three markers of asthma used in the study, with OR's about 2, with the exception of *airway hyper-responsiveness* in the study population excluding childhood asthmatics, where the increase was not significant. Finally gender (being a woman) increased the risk of asthma but only significantly when defined as

current wheeze, with OR's of 1.74 (1.07, 2.82), and 1.79 (1.07, 2.99) population including childhood asthmatics or not, respectively.

10.5.3. Models with Pertinent Risk Factors For Asthma, with Atopy Included:

Table 10.5.3 shows the models for the association of asthma defined in three ways with other pertinent risk factors for asthma (ie. the same factors as were included in the previous models without atopy) together with atopy. All the factors had OR's similar to those in the corresponding models without atopy. As in the models without atopy, relative risk estimates for each definition was similar in the study population whether childhood asthmatics were included or not. Exposure ever *to HMW or LMW agents* only increased (though not significantly) the risk of asthma, defined as *airway hyper-responsiveness*, with OR's of 2.00 (0.98, 4.07), and 1.85 (0.88, 3.88) in the study population population including childhood asthmatics or not, respectively. Exposure ever *to irritants* increased the risk of asthma defined as *current wheeze*, with OR's of 2.23 (1.07, 4.66), and 2.20 (1.01, 4.80) in the study population including childhood asthmatics or not, respectively, but was not associated with asthma using the other two definitions. Childhood history of asthma increased the risk of all three markers of asthma in the study population, with OR's in the range of 4-7. Respiratory infection before age 5 increased the risk of *current wheeze* with OR's of 3.41 (1.48, 7.87), and 5.87 (2.19, 15.72) in the study population including childhood asthmatics or not, respectively; but was not significantly associated with *asthma symptoms and or medicine* and *airway hyper-responsiveness*, including childhood asthmatics or not, respectively. Childhood history of pet in the household also increased the risk of *current wheeze* with OR's of 2.01 (1.08, 3.74), and 1.95 (1.00, 3.80) in the study population including childhood asthmatics or not, respectively; but was not associated significantly with the other two study definitions of asthma.

Having an elder sib decreased the risk of all three markers of asthma used in the study, with OR's around 0.4-0.6, though the decrease was not significanct for asthma defined as *airway hyper-responsiveness*. Education level (defined as completing secondary school) decreased the risk of asthma defined as *current wheeze*, and *asthma symptoms and or medicine* with OR's of about 0.4; but was not significantly associated with asthma defined

Table 10.5.3: Association of ***Current Wheeze, Asthma Symptoms and/or Medicine, and Airway Hyper-responsiveness*** with occupational exposures, adjusted for pertinent risk factors of asthma in the study population (***atopy included***)

	W* (n=473) OR (95% CI)	Ast S/M† (n=473) OR (95% CI)	AHR‡ (n=353) OR (95% CI)	W (n=435) OR (95% CI)	Ast S/M (n=435) OR (95% CI)	AHR (n=331) OR (95% CI)
Ever Occupational Exposure to						
HMW or LMW Agents	0.94 (0.56, 1.59)	1.02 (0.55, 1.90)	2.00 (0.98, 4.07)	0.95 (0.55, 1.64)	0.96 (0.48, 1.90)	1.85 (0.88, 3.88)
Irritants	**2.23 (1.07, 4.66)**	0.90 (0.34, 2.38)	0.41 (0.11, 1.54)	**2.20 (1.01, 4.80)**	0.90 (0.28, 2.80)	0.58 (0.16, 2.16)
Childhood Asthma	**4.38 (1.88, 10.18)**	**7.62 (3.36, 17.31)**	**6.78 (2.05, 22.39)**			
Respiratory Infection Before Age 5	**3.41 (1.48, 7.87)**	1.52 (0.60, 3.81)	0.28 (0.06, 1.34)	**5.87 (2.19, 15.72)**	2.68 (0.89, 8.06)	0.46 (0.06, 3.90)
Childhood History of Pet in the Household	**2.01 (1.08, 3.74)**	1.09 (0.55, 2.17)	1.00 (0.46, 2.16)	**1.95 (1.00, 3.80)**	0.99 (0.47, 2.12)	1.06 (0.47, 2.41)
Having an Elder Sib	**0.40 (0.24, 0.67)**	**0.50 (0.28, 0.90)**	0.63 (0.32, 1.22)	0.48 (0.28, 1.82)	**0.51 (0.27, 0.99)**	0.64 (0.32, 1.30)
Current Smoking	**4.08 (2.48, 6.68)**	1.31 (0.72, 2.38)	**2.36 (1.23, 4.52)**	**4.27 (2.54, 7.18)**	1.53 (0.80, 2.91)	**2.35 (1.19, 4.65)**
Education Level	**0.36 (0.16, 0.79)**	**0.35 (0.15, 0.82)**	1.80 (0.48, 6.64)	**0.36 (0.16, 0.80)**	**0.31 (0.13, 0.75)**	1.73 (0.47, 6.40)
Family History of Asthma	**2.29 (1.32, 3.95)**	**2.02 (1.08, 3.80)**	**2.26 (1.10, 4.63)**	**2.24 (1.25, 3.99)**	**2.24 (1.12, 4.49)**	2.01 (0.93, 4.35)
Gender (Woman)	1.61 (0.97, 2.67)	1.13 (0.62, 2.07)	1.74 (0.87, 3.49)	1.63 (0.95, 2.78)	1.17 (0.60, 2.28)	1.73 (0.84, 3.58)
Atopy	**1.79 (1.05, 3.00)**	1.96 (0.99, 3.89)	0.83 (0.41,1.65)	**1.75 (1.02, 3.02)**	1.92 (0.93, 4.39)	0.76 (0.37, 1.54)

* : Current wheeze † : Asthma symptom and/or medicine ‡ :Airway Hyper-responsiveness

as *airway hyper-responsiveness*. Current smoking increased the risk of asthma defined as *current wheeze* with OR's of 4.08 (2.48, 6.68), and 4.27 (2.54, 7.18) in the study population including childhood asthmatics or not, respectively. Current smoking also increased the risk of *airway hyper-responsiveness* with OR's of 2.36 (1.23, 4.52), and 2.35 (1.19, 4.65), in the study population including childhood asthmatics or not, respectively. Current smoking was not significantly associated with asthma defined as *asthma symptoms and or medicine*. Family history of asthma significantly increased the risk of all three markers of asthma used in the study, with OR's about 2, except for asthma defined as *airway hyper-responsiveness* where the OR was not significant in the study population excluding childhood asthmatics. Female gender was not significantly associated with any of the three definitions of asthma.

Finally atopy increased the risk of asthma defined as current wheeze, statistically significantly, with OR's of 1.79 (1.05, 3.00), and 1.75 (1.02, 3.02) in the study population including childhood asthmatics or not, respectively. Atopy also increased, but not significantly the risk of asthma defined as *asthma symptoms and or medicine*, and *airway hyper-responsiveness* were 1.96 (0.99, 3.89), and 0.83 (0.41, 1.65) in the overall study population, and 1.92 (0.93, 4.39), and 0.76 (0.37, 1.54) in the study population excluding childhood asthmatics, respectively.

10.6. Effect Modification of Occupational Exposures in the Models with Pertinent Risk Factors of Asthma:

10.6.1. Effect Modification for Exposure Ever to HMW and/or LMW agents:

Interaction terms were tested in the models as described in the section *9.3.3.4. Model selection*. None of the interaction terms met the criteria for effect modification. To address the same issue in a different way, models were applied in the selected domains of potential effect modifiers. *Table* 10.6.1 shows the models taking the pertinent risk factors of asthma into account in selected groups of potential effect modifiers, such as *gender, age, smoking*

Table 10.6.1: Association of asthma defined in three ways with ever exposure to HMW and/or LMW agents in the models taking pertinent risk factors into account in the selected groups of potential effect modifiers such as *gender, age, smoking status, atopic status, history of changing job, other work related exposures,* and *not reporting ever asthma*:

	Current Wheeze	Asthma Symptoms and/or Medicine	Airway Hyper-responsiveness
	OR (95% CI)	OR (95% CI)	OR (95% CI)
All Study Population	1.01(0.62, 1.66)	1.03(0.57, 1.86)	**2.20(1.10, 4.38)**
Gender			
Male	0.68 (0.32, 1.48)	1.38 (0.49, 3.88)	1.13 (0.38, 3.34)*
Female	1.28 (0.68, 2.44)	0.99 (0.46, 2.12)	**3.19 (1.29, 7.91)**
Age group			
20-29 year	1.68 (0.72, 3.89)	0.95 (0.34, 2.67)	1.92 (0.64, 5.75)*
30-39 year	0.84 (0.38, 1.87)	0.91 (0.35, 2.36)	3.11 (0.71, 13.57)
40-44 year	0.85 (0.24, 3.04)	1.52 (0.27, 8.63)	**7.26 (1.11, 47.30)**
Smoking Status			
Never smoked	1.05 (0.44, 2.45)	1.40 (0.52, 3.71)	0.74 (0.24, 2.27)
Smoked in the past	0.74 (0.16, 3.39)	0.28 (0.04, 1.97)	4.01(0.45,35.61)*
Currently smoking	1.11 (0.53, 2.32)	1.04 (0.42, 2.57)	**5.32 (1.69, 16.76)**
Atopic status			
Non-atopic	0.98 (0.36, 2.69)	2.20 (0.58, 8.35)	1.70 (0.47, 6.13)*
Atopic	1.02 (0.53, 1.94)	0.76 (0.36, 1.58)	0.31 (0.61, 4.09)
History of changing or leaving job			
No	0.90 (0.54, 1.51)	0.87 (0.46, 1.63)	**2.25 (1.12, 4.53)**
Other work related exposures			
None	0.48 (0.18, 1.26)	0.40 (011, 1.46)	0.88 (0.17, 4.39)*
Any	1.23 (0.66, 2.30)	1.26 (0.60, 2.63)	**2.26 (1.01, 5.08)**
Ever asthma			
No	1.17 (0.63, 2.16)	2.43 (0.82, 7.26)	1.79 (0.83, 3.86)

* : Model fit is questionable due to cells containing no observation

status, atopic status, history of ever changing or leaving job, other work related exposures, and *ever asthma,* for *exposure ever to HMW or LMW agents.* Risk of airway hyper-responsiveness associated with exposure ever to HMW or LMW agents increased significantly in the groups of *female gender* (3.19 (1.29, 7.91)), *age group 40-44 year* (7.26 (1.11, 47.30)), currently smoking (5.32 (1.69, 16.76)), positive *history of ever changing or leaving job* (2.25 (1.12, 4.53)), and *other work related exposure* (2.26 (1.01, 5.08)). These are higher than the OR of exposure ever to HMW or LMW agents in the overall population, 2.20 (1.10, 4.38). In the groups of women, and currently smoking the OR's of exposure ever to HMW or LMW agents were 3.19 (1.29, 7.91), and 5.32 (1.69, 16.76), respectively. Relative excess risk due to interaction was calculated as 0.3 for women, and 1.88 for currently smoking (139). This suggested an interaction between exposure ever to HMW or LMW agents, and currently smoking for airway hyper-responsiveness.

10.6.2. Effect Modification for Exposure Ever to Irritants:

Table 10.6.2 shows the models taking the pertinent risk factors of asthma into account in selected groups of potential effect modifiers as listed in *Table* 10.6.1. The risk of *current wheeze* associated with *exposure ever to irritants* increased in the groups *age group 20-29 year* (3.22 (1.04, 9.85)), *never smoked* (3,87 (1.10, 13.58)), and *non-atopic* 6.52 (1.42, 29.92). These are higher than the OR of exposure ever to irritants in the overall population, 2.12 (1.03, 4.34). The association between *current wheeze* and *exposure ever to irritants* was similar to that in the total study population, when it was analysed in those who did not report ever asthma (OR: 2.44, 95% CI:1.08-5.50).

Table 10.6.2: Association of asthma defined in three ways with ever exposure to irritants in the models taking pertinent risk factors into account in the selected groups of potential effect modifiers such as *gender, age, smoking status, atopic status, history of changing job, other work related exposures* and *not reporting ever asthma*:

	Current Wheeze	Asthma Symptoms and/or Medicine	Airway Hyper-responsiveness
	OR (95% CI)	OR (95% CI)	OR (95% CI)
All Study Population	**2.12 (1.03, 4.34)**	0.88 (0.33, 2.31)	0.35 (0.09, 1.34)
Gender			
Male	1.89 (0.78, 4.56)	1.08 (0.35, 3.31)	0.32 (0.06, 1.63)*
Female	2.83 (0.77, 10.42)	0.99 (0.04, 3.71)	0.50 (0.04, 5.37)
Age group			
20-29 year	**3.22 (1.04, 9.85)**	1.68 (0.33, 7.26)	0.60 (0.10, 3.47)
30-39 year	2.23 (0.69, 7.22)	0.69 (0.15, 3.08)	0*
40-44 year	1.13 (0.19, 8.64)	0.68 (0.05, 9.64)	0.26 (0.02, 3.92)
Smoking Status			
Never smoked	**3.87 (1.10, 13.58)**	1.66 (0.32, 8.68)	0.87 (0.09, 8.02)
Smoked in the past	1.14 (0.14, 9.20)	3.39 (0.40, 28.47)	0.67 (0.03, 13.89)*
Currently smoking	2.42 (0.86, 6.82)	0.49 (0.10, 2.50)	0.15 (0.02, 1.37)
Atopic status			
Non-atopic	**6.52 (1.42, 29.92)**	0.34 (0.03, 3.81)	1.23 (0.08, 17.66)
Atopic	1.53 (0.63, 3.71)	1.08 (0.36, 3.25)	0.31 (0.06, 1.59)*
History of changing or leaving job			
No	1.89 (0.85, 4.22)	0.96 (0.32, 2.89)	0.41 (0.10, 1.58)
Other work related exposures			
None	1.37 (0.12, 15.25)	8.36 (0.62, 112.7)	0*
Any	2.18 (0.97, 4.89)	0.66 (0.23, 1.93)	0.26 (0.06, 1.17)
Ever asthma			
No	**2.44 (1.08, 5.50)**	1.11 (0.30, 4.16)	0.58 (0.15, 2.15)

* : Model fit is questionable due to cells containing no observation

10.7. Population Attributable Risk Percentages of Asthma Defined in Three Ways due to Occupational Exposures:

Population Attributable Risk Percentages of *current wheeze, asthma symptoms and or medicine,* and *airway hyper-responsiveness* due to occupational exposures were calculated according to the formula given in the section *9.3.2. Plan for the Attainment of Objectives.* The relative risk ratio estimates were prevalence rate ratios, obtained from the models with Poisson regression.

10.7.1. Population Attributable Risk Percentages of Asthma in the Models Adjusting for Age, Gender, and Smoking Habits:

Table 10.7.1 shows Population Attributable Risk Percentage (PARP) in the models adjusting for age, gender, smoking for asthma defined in 3 ways in the overall study population, and in the study population excluding childhood asthmatics. These estimates were not different in the study population whether or not the childhood asthmatics were excluded. Population Attributable Risk Percentage for *exposure ever to HMW or LMW agents* was of the order of 5% for *current wheeze*, and 6% to 7% for *asthma symptoms and or medicine,* and 30% for airway hyper-responsiveness. Population Attributable Risk Percentages for *exposure ever to irritants* of the order of 5% for *current wheeze*, and below 0 for *asthma symptoms and or medicine,* and *airway hyper-responsiveness.*

10.7.2. Population Attributable Risk Percentages in the Models Adjusting for Pertinent Risk Factors of Asthma, but not for Atopy:

Table 10.7.2 shows Population Attributable Risk Percentage (PARP) in the models adjusting for pertinent risk factors of asthma, but not for atopy, for asthma defined in 3 ways in the overall study population, and the study population excluding childhood asthmatics. The estimates were not different in the study population whether or not the

Table 10.7.1: Parameter estimates, prevalence rate ratios, and Population Attributable Risk Percentages of occupational exposures with three study definitions of asthma in the models adjusting for gender, age, smoking in the adult population:

	All the study population			Study Population excluding childhood asthmatics		
	Current Wheeze (n=498)	Asthma Symptoms and or Medicine (n=498)	Airway Hyper-responsiveness (n=368)	Current Wheeze (n=458)	Asthma Symp. and or Medicine (n=458)	Airway Hyper-responsiveness (n=344)
Ever Exposure to HMW or LMW Agents						
P*	58.46	57.14	64 81	58.25	56.25	0.65.91
β†	0.0892	0.1470	0.6448	0.0831	0.1216	0.7063
SE (β) ‡	0.1924	0.2597	0.3005	0.2155	0.3114	0.3345
PRR§	1.09	1.16	1.90	1.09	1.13	2.03
PARP¶	4.99	7.81	30 80	4.64	6.44	33.38
95% CI	‖	‖	(13.26, 71.56)	‖	‖	(13.30, 71.52)
Ever Exposure to Irritants						
P*	14.62	10.00	5.56	14.56	8.33	6.82
β†	0.3743	-0.0611	-0.8602	0.3936	-0.2393	-0.6905
SE (β) ‡	0.2652	0.4172	0.6179	0.2968	0.5415	0.6262
PRR§	1.45	0.94	0.42	1.48	0.79	0.50
PARP¶	4.56	-0.63	-7.58	4.74	-2.25	-6.78
95% CI	(0.97, 21.51)	‖	(-2.59, -22.19)	‖	‖	(-6.68, -6.88)

* : Percentage of occupational exposure among cases † : Parameter estimate obtained in the model for Prevalence Rate Ratio
‡ : Standard error of the parameter estimate § : Prevalence Rate Ratio ¶ : Population Attributable Risk Percentage
‖ : 95% confidence interval too wide

Table 10.7.2: Parameter estimates, prevalence rate ratios, and Population Attributable Risk Percentages of occupational exposures with three study definitions of asthma in the models adjusting for pertinent risk factors, but not for atopy:

	All the study population			Study Population excluding childhood asthmatics		
	Current Wheeze (n=498)	Asthma Symptoms and or Medicine (n=498)	Airway Hyper-responsiveness (n=368)	Current Wheeze (n=458)	Asthma Symp. and or Medicine (n=458)	Airway Hyper-responsiveness (n=344)
Ever Exposure to HMW or LMW Agents						
P*	58.46	57.14	64.81	58.25	56.25	0.65.91
β†	0.0412	0.0335	0.6092	0.0543	0.0346	0.5952
SE (β) ‡	0.1914	0.2577	0.3055	0.2146	0.3073	0.3341
PRR§	1.04	1.03	1.84	1.06	1.04	1.81
PARP¶ 95% CI	2.36 ¶	1.88 ¶	29.57 (12.04, 72.65)	3.08 ¶	1.91 ¶	29.56 (10.74, 81.39)
Ever Exposure to Irritants						
P*	14.62	10.00	5.56	14.56	8.33	6.82
β†	0.4463	-0.0875	-0.8163	0.4776	-0.1509	-0.5532
SE (β) ‡	0.2671	0.4208	0.6159	0.2969	0.0506	0.6176
PRR§	1.56	0.92	0.44	1.61	0.86	0.58
PARP¶	5.26 (1.39, 19.89)	-0.91 ¶	-7.02 ¶	5.53 (1.36, 22.49)	-1.36 N/A	-5.04 (-0.79, -31.88)

* : Percentage of occupational exposure among cases
† : Parameter estimate obtained in the model for Prevalence Rate Ratio
‡ : Standard error of the parameter estimate
§ : Prevalence Rate Ratio
¶ : Population Attributable Risk Percentage
¶:95% confidence interval too wide

childhood asthmatics were excluded. Exposure ever *to HMW or LMW agents* had PARP's of about 2-3% for *current wheeze*, 2% for *asthma symptoms and/or medicine*, and 30% for *airway hyper-responsiveness*. *Exposure ever to irritants* had PARP's of about 5% for *current wheeze*, and below 0 for *asthma symptoms and/or medicine*, and *airway hyper-responsiveness*.

10.7.3. Population Attributable Risk Percentages in the Models Adjusting for Pertinent Risk Factors of Asthma, and Atopy:

Table 10.7.3 shows Population Attributable Risk Percentage (PARP) in the models adjusting for pertinent risk factors of asthma, including atopy, for asthma defined in 3 ways different study definitions of asthma in the overall study population, and the study population excluding childhood asthmatics. The estimates were not different in the study population whether or not the childhood asthmatics were excluded. *Exposure ever to HMW or LMW agents* had PARP's of the order of 0% for *current wheeze*, and 2% for *asthma symptoms and/or medicine*, and 26% for *airway hyper-responsiveness* in the overall study population, and of the order of 0%, minus 2%, and 26% in the study population excluding childhood asthmatics, respectively. Exposure ever *to irritants* had PARP's of the order of 5% for *current wheeze*, and below 0 for *asthma symptoms and/or medicine*, and minus 6% for *airway hyper-responsiveness*, and there was little change when the study population excluded childhood asthmatics.

10.8. Summary:

In a cross-sectional study conducted to investigate the prevalence of asthma, and role of occupational exposures in the development of asthma in the adult population (20-44 year aged) of Montreal, using a standardised protocol and questionnaires, 2460 subjects (1196 men, 1633 women) completed a screening questionnaire including questions on asthma, smoking behaviour, and occupational exposures. The second stage of the study included

Table 10.7.3: Parameter estimates, prevalence rate ratios, and Population Attributable Risk Percentages of occupational exposures with three study definitions of asthma in the models adjusting for pertinent risk factors, including atopy:

	All the study population			Study Population excluding childhood asthmatics		
	Current Wheeze (n=473)	Asthma Symptoms and or Medicine (n=473)	Airway Hyper-responsiveness (n=353)	Current Wheeze (n=435)	Asthma Symptoms and or Medicine (n=435)	Airway Hyper-responsiveness (n=331)
Ever Exposure to HMW or LMW Agents						
P*	59.02	58.21	63.27	58.76	56.52	65.91
β†	0.0047	0.0304	0.5379	-0.0086	-0.0364	0.5124
SE (β) ‡	0.2002	0.2659	0.3158	0.2248	0.3187	0.3426
PRR§	1.00	1.03	1.71	0.99	0.96	1.67
PARP¶	0.28	1.74	26.32	-0.51	-2.10	26.43
95% CI	N/A	‖	(8.99, 7.08)	‖	‖	(7.76, ,89.93)
Ever Exposure to Irritants						
P*	15.57	10.45	6.12	15.46	8.70	6.82
β†	0.4809	-0.0732	-0.6984	0.4927	-0.0932	-0.4492
SE (β) ‡	0.2702	0.4243	0.6199	0.3002	0.5453	0.6238
PRR§	1.62	0.93	0.50	1.64	0.91	0.64
PARP¶	5.94 (1.70, 20.65)	-0.79 ‖	-6.18 ‖	6.01 (1.53, 23.52)	-0.85 ‖	-3.87 (-0.36, -41.31)

* : Percentage of occupational exposure among cases
† : Parameter estimate obtained in the model for Prevalence Rate Ratio
‡ : Standard error of the parameter estimate
§ : Prevalence Rate Ratio
¶ : Population Attributable Risk Percentage
‖ : 95% confidence interval too wide

interviewer administered questionnaires of asthma in 498 subjects (238 men, 260 women), and of occupational exposures, skin prick testing, and airway challenge with methacholine. Comparison of the study population that participated in the second stage of the study with that who did not suggested a problem in representativeness of the study population (see *Table* 10.1.1). Thus, the prevalence percentages of asthma were obtained from the first stage of the study as: *current wheeze:* 23.72 (22.19, 25.26) *asthma symptoms and or medicine:* 12.81 (11.60, 14.01). Prevalence percentages from the second stage of the study were: *airway hyper-responsiveness:* 14.67 (11.06, 18.29), *airway hyper-responsiveness* combined with *current wheeze:* 6.79 (4.22, 9.36). Imputation of airway hyper-responsiveness using the information available in the first stage of the study gave estimates ranging from 13.89 to 15.24, and 4.77 to 5.41 for *airway hyper-responsiveness*, and *airway hyper-responsiveness* combined with *current wheeze*, respectively.

Occupational exposures were grouped as high molecular weight agents, low molecular weight agents, and irritants reported by 181, 161, and 41 subjects in the past (exposure occurred more than one year before the survey), and 82, 78, and 16 subjects within the year before the survey, respectively (see *Table*'s 9.3.1, 10.3.3). Exposure ever to HMW and/or LMW agents (sensitisers) was significantly associated with other work related exposures, accidental exposure, changing job ever, hobbies including any occupational exposure, passive smoking, mold in the house ever, and female gender. Exposure ever to irritants was significantly associated with other work related exposures, changing job ever, father smoking, going to playschool/nursery or sharing bedroom with an elder before age 5, smoking in the past or currently, passive smoking, and female gender (see *Table* 10.4.3). All these associations except for those with going to playschool/nursery, and female gender were positive. Associations adjusted for age, gender, and smoking suggested a significant association between *current wheeze* and past exposure to LMW agents, and to irritants, with OR's of 1.61 (1.02, 2.55), 2.73 (1.35, 5.54) (see *Table* 10.4.2). Association of asthma defined in 3 ways and exposure ever to HMW and/or LMW agents, and to irritants were adjusted for age, gender, smoking, and pertinent risk factors of asthma. Prevalence OR's were not changed in models whether or not the

childhood ashmatics (asthma attack reported before age 15), or atopy were included. *Current wheeze* was significantly associated with exposure ever to irritants (OR's: 2.12-2.23), whereas *airway hyper-responsiveness* was significantly associated with exposure ever to HMW and/or LMW agents (sensitisers) (OR's: 2.05-2.28) (see *Table's* 10.5.1-3). In the models testing for interaction, women, current smokers, older subjects aged 40-44 years had significantly higher risk of *airway hyper-responsiveness* with exposure ever to HMW and/or LMW agents, compared to the corresponding reference categories (see *Table* 10.6.1). In contrast men, never smoked, and younger subjects aged 20-29 years had significantly higher risk of *current wheeze* with exposure ever to irritants (see *Table* 10.6.2). Exposure ever to HMW and/or LMW agents had population attributable risk percentages (PARP's) in the order of 30% for *airway hyper-responsiveness*. Exposure ever to irritants had population attributable risk percentages (PARP's) in the order of 5% for *current wheeze* (see *Table's* 10.7.1-3).

11. DISCUSSION

11.1. Potential Sources of Bias: This study being a cross-sectional study is subject to all the potential sources of bias to which a cross-sectional study is. This probably represents the most important source of bias in terms of exposure response relationship (139).

11.1.1. Selection Bias:

The characteristic feature of selection bias is the difference in the relation between exposure and disease for those who participate in the study and those who would be theoretically eligible for the study, but do not participate (139). This study which provided the material for this thesis was a community-based study conducted to investigate the prevalence and determinants of asthma in the young adult population of Montreal, with two stages. Response rate was good (84%) in the first stage, but poor in the second stage (35%). Since the study was not introduced to participants as a study particularly related to asthma or to occupational exposures, participation of subjects was not likely to be affected by their asthma status or their occupational exposures. Participants involved in the second stage of the study (and the study population for this thesis) had a lower prevalence of smokers, and respiratory symptoms, including current wheeze (one of the study definitions of asthma) than the subjects involved only in the first stage of the study (*Table* 10.1.1). Thus, representativeness of the study population was questionable, which could threaten the inferences made for the prevalence of asthma in the general population. Prevalence estimates were based on the findings from the first stage of the study to deal with this problem. As the two study populations had similar distributions of occupational exposures, this would not threaten the inferences made for occupational asthma, which was investigated by analytic studies based on data gathered in the second stage of the study. Among those exposed to dust, chemicals, gases or fumes, a higher proportion reported changing or leaving job upon respiratory complaint in the second stage (10.7%) than that in the first stage (6.3%), which raises the question of selection bias. Four definitions of asthma were used to establish its current presence: *"current wheeze"*, *"asthma symptoms and/or medicine in the last 12 months"*, *"airway hyper-responsiveness"* and *"current wheeze and airway hyper-responsiveness"*. These had previously been validated and found appropriate for epidemiological studies, and in addition had the advantage of legitimising

comparison of the study findings with other published studies. As measurement of airway hyper-responsiveness was not available for the first stage of the study, so its prevalence in the target population was obtained by multiple imputation technique (see *section* 9.2.2). Results of imputation were not so different from the prevalence of airway hyper-responsiveness, which suggested that selection bias if present was not so strong (see *Table* 10.2.2). Because subjects with poor lung function were excluded from airway challenge testing, this would give an underestimate of the prevalence of airway hyper-responsiveness in the Montreal adult population.

11.1.2. Information Bias:

Information bias refers to errors in the classification of subjects (139). Information bias may occur in the response or exposure variables, both of which were measured by questionnaire in this study.

11.1.2.1. Study Instruments:

This study used the standardised study instruments developed and validated for the ECRHS. Usage of a standardised study protocol and study instrument by a trained study team was a feature that would help to minimise the information bias.

11.1.2.2. Translation of the Questionnaire:

In such a multicentre study translation of the original questionnaires to other languages might also be another source of bias. This possibility is especially important, as the word "*wheeze*" (central for one of the study definition of asthma) does not have a direct translation into French. French as one of the official languages of Québec, was cited as the home language in close to 70% of study subjects in this study. Findings from validation studies showed that sensitivity and discriminative power (measured by Youden's index) of wheeze was not as good in France as in Nottingham, UK (sensitivity: 0.73 vs. 0.89, Youden's index: 0.38 vs. 0.51) (132).

Table 11.1.2: Prevalence of respiratory symptoms and airway hyper-responsiveness in some countries. which used the ECRHS protocol (7. 131. 143):

	Respiratory symptoms			**AHR†**	
Country (Number of centres)	**Wheeze (%)**	Waking with SOB*	Asthma attack (%)	**AHR† (%)**	Mean slope
Australia (1)	**28.8**	11.4	9.7	**22.0**	6.97
USA (1)	**25.7**	7.3	3.1	**18.3**	7.10
UK (5)	**25.2-29.8**	7.9-8.8	4.8-5.7	**15.5-27.6**	6.66-7.69
Norway (1)	**24.6**	5.0	3.1	**8.0**	7.68
New Zealand (4)	**24.2-27.3**	9.9-14	6.8-8.6	**22.7-27.6**	6.68-7.07
Denmark (1)	**24.1**	N/A	3.4	**23.5**	7.28
Netherlands (3)	**19.7-21.1**	7.6-8.9	2.3-3.0	**18-14.3**	7.40-7.60
Sweden (3)	**19.2-23.2**	4.4-7.1	3.1-3.3	**7.7-11.8**	7.65-8.05
Iceland (1)	**18.0**	1.5	2.2	**7.2**	8.34
Switzerland (1)	**16.9**	7.6	3.9	**9.8**	7.97
Spain (6)	**16.2-29.2**	3.7-9.5	1.5-3.1	**3.4-21.3**	7.07-8.44
France (5)	**13.6-15.7**	3.7-4.7	2.7-4.6	**12.0-23.2**	6.77-7.85
Germany (2)	**13.3-21.1**	4.3-5.0	1.3-3.0	**12.0-17.5**	7.21-7.44
Italy (3)	**8.5-17**	6.2-8.1	2.6-4.2	**9.3-11.6**	7.67-8.17
Median‡	**27**	7.3	3.1	**13.0**	7.6
Canada (6)	**23.5-33.3**	**7.5-12**	**5.2-7.9**	**4.8-22.0**	**6.8-8.1**
Montreal	**23.5**	**7.5**	**6.7**	**12.1**	**7.7**
Vancouver	23.7	7.9	5.7	16.9	7.2
Winnipeg	28.8	8.6	6.9	8.4	7.9
Hamilton	31	12	7.2	22.0	6.8
Halifax	33.3	12	7.9	4.8	8.1
Prince Edward	26.3	7.9	5.2	9.4	7.8

*: Shortness of breath †: Airway hyperrresponsiveness standardised for age, and gender (provocative dose of methacholine causing a 20% fall in FEV1 of 1 mg)

‡ : Median given for all the centres in ECRHS

Prevalence of respiratory symptoms and airway hyper-responsiveness in some countries, which used the ECRHS protocol are shown in *Table* 11.1.2 (131, 143). As indicated in the section 6.3, Validation of the questionnaires, prevalence of current wheeze was higher in English speaking countries than the other countries. Airway hyper-responsiveness determined as the dose of methacholine producing a 20% fall in FEV1 (PD20), and the regression coefficient of percentage decline in FEV1 (slope) was also higher in English speaking countries, and France, Denmark, and Germany than the other countries. The prevalence of wheeze was similar to that of airway hyper-responsiveness, in most of the English speaking countries, but there was a higher prevalence of both conditions than that of the other participant countries. Prevalence of waking with a shortness of breath, and attack of asthma in the last 12 months were also higher in English speaking countries than the other countries. Four of the six Canadian centres Montreal, Winnipeg, Halifax, and Prince Edward Island showed a trend similar to most North European countries with prevalence of *current wheeze* almost twice or more than that of *airway hyper-responsiveness*. Thus, although translation of the questionnaire might have resulted in an under-reporting of asthma symptoms, evidence does not indicate such a possibility. In fact, comparison of the reported prevalence of wheeze with airway hyper-responsiveness, suggests that Montreal might be among the centres with a higher reporting of current wheeze relative to airway hyper-responsiveness.

11.1.3. Bias due to "Healthy" Worker Effect:

As mentioned in the *section 5* on "healthy" worker effect, community-based studies have the advantage of reaching the individuals who left or changed their jobs upon developing respiratory complaints, and thus less subject to bias by "healthy" worker effect. This study being a community-based study with detailed information on occupational exposure provided a means to control the "healthy" worker effect, and some evidence documenting the presence of "Healthy" worker effect, due to leaving or changing job upon respiratory complaint. The association between *current wheeze* and past occupational exposures in all categories was stronger than with current exposures (see *Table*'s 10.4.1, and 10.4.2), which suggested that individuals with *current wheeze* had avoided these exposures.

Findings with *asthma symptoms and/or medicine*, and *airway hyper-responsiveness* were mostly inconsistent.

11.1.4. Recall Bias:

Recall bias is a major concern in the present study since the presence of both the occupational exposure and asthma symptoms were assessed through self-reporting by the study population. The stronger association between current wheeze and past exposure to asthmagenic agents (see *Table*'s 10.4.1 and 10.4.2), and non-specific irritants, and lack of association with current exposures (see *Table*'s 10.6.1 and 10.6.2) found in the present study could be regarded as evidence against the presence of significant recall bias; if present one would expect the associations to be stronger between current wheeze and current exposure. In a study in Montreal in 297 subjects, agreement between the reported and recorded jobs were 83% and 81% agreement in the more recent period and in the earlier period, respectively (152). In another study of 145 female garment workers employed in 5 factories in Montreal, work histories collected by interview was compared to yearly job information in public and union records, and found valid for 81% of the person years. The average validity was 89% and 74% for the recent period (1972-1983), and more distant past (1955-1971) (153). These findings suggest that recall of the recent exposure is better than that for the past exposure. There would be a recall bias if the subjects with asthma (defined in 3 ways for this study) had a predilection to selectively recall the past occupational exposure. However analysis excluding those, who changed or left their jobs, or who reported asthma as ever did not change the results (see *Table* 10.6.1-2). This can be regarded as evidence against the presence of a significant recall bias, which would have weakened the associations found.

11.1.5. Misclassification of the Occupational Exposure:

In the present study, undoubtedly there was some misclassification in placing the occupational exposures into the broad categories used for analysis. As an example, work in pharmaceuticals and hairdressing could include exposure to both HMW and LMW agents, so could have been classified under LMW or HMW agents, or both. Thus, formaldehyde (71), and toluene di-isocyanate (TDI) (154), both classified as "immunologically acting LMW agents", could act as an irritants at higher concentrations.

However, the number of individuals in these categories was small (11 in hairdressing, 9 in pharmaceuticals, see *Table* 10.3.1), and unlikely to have changed much the risk estimates obtained for the general exposure category of exposure ever to HMW and/or LMW agents. Absence of the job title "health professionals" in the questionnaire is a weakness, but the result most likely would be underestimation of the relative risk, if the related exposures were not covered in the other questionnaire items such as pharmaceuticals.

Thus, in the present study misclassification of exposure is likely to have been non-differential and to have resulted in an underestimation of the association between occupational exposure and asthma.

11.2. Findings of the Analysis:

The role of occupational exposures in the development of asthma was assessed in models taking pertinent factors into account. The following are the main findings of the analysis:
a) The relative risk estimates obtained in the overall study population were similar whether or not the study population excluded the childhood asthmatics. This applies for all three definitions of asthma and both for the models with age, gender, and smoking, and models with the pertinent risk factors and risk indicators. The presence of childhood asthma was strongly associated with all three markers of asthma, but did not change the risk of developing asthma related to occupational exposures. If the presence of childhood asthma lead to avoidance of the occupational exposures which could precipitate an attack of asthma, then the proportion of adults who had asthma in childhood who also had current wheeze and reported occupational exposure would be less than the proportion in those who did not report childhood asthma. Thus, the relative risk estimate for the development of asthma in adulthood due to occupational exposure would be higher in the study population excluding childhood asthmatics than that found in the overall study population.

b) Relative risk estimates for occupational exposure to sensitisers and to irritants were similar in the uni-variate analysis and multi-variate analysis. This suggested that association

of occupational exposures with current wheeze, asthma symptoms and/or medicine, and airway hyper-responsiveness was independent of the factors included in the analysis.

c) Women had lower prevalence of occupational exposure than men, but had higher prevalence of current wheeze, airway hyper-responsiveness, and stronger association between occupational exposures and current wheeze or airway hyper-responsiveness. The higher prevalence of airway hyper-responsiveness in women than men is objective evidence against the possibility of diagnostic bias, or information bias. Lower prevalence of occupational exposures in women suggests that the difference between women and men can not be due to numbers. Because other risk factors like current smoking are almost equally distributed in both men and women, this difference is not likely to be due to the fact that occupational exposure is relatively a more important environmental exposure in women. Separate analysis in women and men suggested that women had about 3 times higher risk of airway hyper-responsiveness than men due to exposure ever to HMW and/or LMW agents. This is consistent with other data showing that during their reproductive years (i.e. age 20 to 44, the age of subjects in this study), the prevalence of asthma is higher in women than men (between 20-50 years age women:men ratio was nearly 3:1 in hospital admissions from 67 hospitals in south-eastern Pennsylvania (155).

d) Age groups were not associated with current wheeze or airway hyper-responsiveness. As the study population had a rather homogeneous age distribution, this was not surprising. Separate analysis in different age groups suggested that 40-44 year age group had an increased risk of airway hyper-responsiveness (about 7 times) due to Exposure ever to HMW and/or LMW agents; and 20-29 year age group had an increased risk of current wheeze (about 3 times) due to exposure ever to irritants.

e) Current smoking was the only adulthood exposure other than occupational exposure that was strongly associated with current wheeze and airway hyper-responsiveness. Smoking in the past was not a significant risk factor. Lower relative risk estimates were found for asthma symptom and or medication, and could be due to the clinical tendency of

avoiding the diagnosis of asthma for smokers. Separate analysis in never smoked, smoked in the past, and currently smoking suggested that currently smoking had an increased risk of (about 5 times) airway hyper-responsiveness due to exposure ever to HMW and/or LMW agents. By contrast, never smoked had an increased risk of (about 4 times) current wheeze due to exposure ever to irritants. Evidence for smoked in the past was not consistent, for any of the 3 definitions of asthma with exposure ever to HMW and/or LMW agents, or to irritants (see *Table*'s 10.6.1, and 10.6.2).

f) The level of education was used to assess socioeconomic status. Individuals who completed secondary school education were considered to have a higher socioeconomic status than those, who did not. Higher socioeconomic status was found protective for current wheeze, and asthma symptoms and/or medicine, but not for airway hyper-responsiveness.

g) Family history of asthma was associated with current wheeze, asthma symptoms and/or medicine, and airway hyper-responsiveness. Atopy determined by skin prick test (at least one positive reaction to one of the 14 aerollergens tested) was associated with current wheeze and asthma symptoms and/or medicine, but not with airway hyper-responsiveness. Avoidance by atopic subjects of occupational exposures ever to HMW and/or LMW agents, and irritants could be an explanation. However, the absence of negative association between atopy and the occupational exposures did not suggest this (see *Table*'s 10.4.3, 10.5.2, and 10.5.3).

h) Pertinent risk factors and indicators mostly included exposures in the childhood. Childhood history of pet in the household increased the risk of current wheeze, but was not significantly associated with airway hyper-responsiveness. Though respiratory infection before age 5 was not a precise characterisation of an infection in childhood, which might lead to difficulties in the interpretation of the findings, it was kept in the models as it was a strong risk factor for current wheeze. Association with airway hyper-responsiveness was almost negative. This could be due to chance, recall bias, or a real

difference. Avoidance by those who had respiratory infection before age 5, of exposures related to airway hyper-responsiveness could be an explanation. However absence of a negative association with occupational exposure ever to HMW and/or LMW agents does not suggest that this occurred. Having an elder sib decreased the risk of both conditions to about 0.5-0.6. This is consistent with published data and has been interpreted as evidence that certain infections in the first year of life results in patterning the immune system towards a T1 (non-asthma) vs. a T2 (asthmatic) response to antigens (156).

11.3. Association of Asthma with Occupational Exposures via Different Study Definitions:

In this study the relative risk estimates of occupational exposures obtained for the three markers of asthma were different. Exposure ever to sensitisers increased the risk of airway hyper-responsiveness, but was not significantly associated with current wheeze, suggesting no effect or a slightly protective effect. On the other hand, exposure ever to irritants increased the risk of current wheeze, but was not significantly associated with airway hyper-responsiveness, suggesting no effect or a slight protective effect. The discrepancy may be due to the sample size, differences between the study populations, or differences between these two markers. The first is a possibility, but does seems unlikely, even though the model with airway hyper-responsiveness was based on a in a smaller sample. This is because the prevalences of current smoking, asthmatic symptoms, physician diagnosed asthma, childhood asthma, and history of leaving, or changing job upon respiratory symptom were all higher in those who did not undergo methacholine challenge test. Individuals who reported current wheeze might have a tendency to recall exposure to irritants, and this could be the reason for the association between the two.

Problems in the definition of asthma have long been recognised, and related to the fact that "the primary cause remains unknown, pathology is rarely available, and clinical presentation can be quite variable" (157). There is also no single objective marker for asthma (158). For this reason, comparisons of prevalence and determinants of the disease

asthma (158). For this reason, comparisons of prevalence and determinants of the disease between populations and over time will be subject to differences in the definitions used to establish the presence of disease. This study used the study definitions and methodology, which were standardised through the efforts of ECRHS and used in their multi-centre studies.

In this study *airway hyper-responsiveness* was used as an objective marker of asthma. Previous studies of the association between airway hyper-responsiveness and current wheeze have found low sensitivity and high specificity for current wheeze. For example, sensitivity and specificity of airway hyper-responsiveness for wheeze (present in most days or nights) was 51% and 79% in a random population sample of 339 subjects in Vlaardingen, Netherlands. Airway hyper-responsiveness was defined as PD20 of histamine at 16 mg/ml or less in "obstructives", and 32 mg/ml or less in "hypersecretives" (159). A study of the association between airway hyper-responsiveness and asthma symptoms in 1392 Canadian male workers from various industries, found 29% sensitivity and 85% specificity for wheeze alone or with breathlessness. Airway hyper-responsiveness was defined as a PC20 of less than 8 mg/ml of methacholine (160). The predictive value of items from a French translation of ATS-DLD standardised questionnaire, administered by an interviewer was studied in 200 Québec insulation workers (134). Airway hyper-responsiveness was defined as the 15% fall FEV1 in response to a provocative concentration (PC15) of less than 16 mg/ml methacholine. Sensitivity, specificity, positive predictive value, and overall agreement of current wheeze for airway hyper-responsiveness were 26%, 87%, 35%, and 74%, respectively, similar to 31.5%, 81.8%, 22.9%, and 74.4% found in the present study, with PC20 of less than 16 mg/ml. Lack of a good association between airway hyper-responsiveness and current wheeze may be one of the reasons for the discrepancy in the findings with these two definitions.

In this study an interesting finding was the difference in the associations of asthma defined as airway hyper-responsiveness and current wheeze with occupational exposures to sensitisers and irritants (see Table's 10.5.1-3). The strong association between *airway*

hyper-responsiveness and occupational exposure to sensitisers found in this study is consistent with the substantive knowledge, and supports the distinction between sensitisers and irritants as inducers of airway hyper-responsiveness and inciters of asthma in the hyper-responsive airway (76). Thus, a widely held view considers occupational exposure only to sensitisers as causative for occupational asthma. Some legal jurisdictions accept occupational asthma for compensation only if there has been work exposure to sensitisers included in a validated the list (161). However, this a priori list has been put in question by the findings of voluntary based surveillance schemes, which suggest that at least 12% of occupational asthma in Québec (4), and 39% in the UK (2) are the result of exposures not covered by their respective workers compensation boards. It has been suggested that irritants might be responsible for the major burden of occupationally related asthma (162).

A difference between the relevant time frame for the 2 conditions included in these two definitions may also be important. Improvement of airway hyper-responsiveness may take a shorter time interval after cessation of exposure than that of current wheeze. Asthma patients who avoided the exposure to allergens have been able to improve their symptoms, and decrease their airway hyper-responsiveness. For instance, in a study of 9 asthma patients sensitive to D. pteronyssinus, both symptoms and airway hyper-responsiveness decreased after staying two months or more in almost dust-free hospital rooms (163). In a study of 31 snow-crab processing workers with occupational asthma followed after the cessation of exposure, 26 workers (84%) still had airway hyper-responsiveness (PC20 of <16 mg/ml), all reported wheezing, and 15 (48%) still needed asthma medicine, two years after the cessation of exposure (115). The authors attributed the persistence of symptoms as due to the concern of workers for compensation, and suggested that symptoms might persist for a long time even after the cessation of exposure, whereas airway hyper-responsiveness disappeared after an average time period of 1 year. *Table* 11.3.1 shows findings of some of the follow-up studies of patients with occupational exposure. Except for the study of electronic workers (164), persistence of airway hyper-responsiveness was more frequent than that of symptoms, and in some studies prevalence of airway hyper-responsiveness even increased at the follow-up. Although these findings might be biased,

Table 11.3.1: Follow-up studies of patients with occupational exposure

	First survey			Second survey	
Workforce, Reference, Publication Year	Symptom %	AHR (%)	Mean follow-up (months)	Symptom %	AHR (%)
Electronic workers, (164), 1982	20/20 (100)	9/20 (45)	24	18/20 (90)	5/20 (25)
Red cedar, (165), 1982	75/75 (100)	33/33 (100)	42	37/75 (49)	22/33 (67)
Isocyanates, (166), 1987	50/50 (100)	16/32 (50)	At least 48	41/50 (82)	14/21 (67)
TDI, (167), 1984	12/12 (100)	8/12 (67)	24	8/12 (67)	7/12 (58)
Snow crab, (168), 1985	31/31 (100)	31/31 (100)	12.3±5.5	19/31 (61)	28/31 (90)

due to availability of more severe cases, these results do not support the view that persistence of symptoms might be higher due to the concern of workers for compensation. Persistence of asthma symptoms and airway hyper-responsiveness long after the cessation of occupational exposure suggests that occupational exposure defined as ever might be relevant for current asthma, as used in this study.

11.4. Effect Modification for Occupational Exposures:

An interesting finding of the study was the almost opposite behaviours of the occupational exposures to HMW and/or LMW agents, and to irritants in their association with different definitions of asthma. This is also observed for the effect modification (see *Table's* 10.6.1-2). Cigarette smoking, and age group 40-44 year increased the risk of *airway hyper-responsiveness* due to ever exposure to HMW and/or LMW agents, whereas not smoking, and age group 20-29 year increased the risk of *current wheeze* due to ever exposure to irritants. Higher incidence of occupational asthma with age was reported in surveillnace based schemes (80), as discussed in section 4.4. In addition to the possible explanations of "higher likelihood of referral of older individuals to a chest physician, when they develop symptoms, and the preference of older individuals to stay in their jobs for security reasons, resulting in late application for medical help", one can also state accumulated effect of exposures as an explanation. Smoking might enhance the action of occupational exposure on the lungs through sensitisation by increasing the mucosal permeability (104). For instance, in a factory of 300 workers, the prevalence of specific IgE antibody to tetrachloropthalic anhydride (used as an epoxy resin curing agent) was higher among smokers (13%) than never or ex-smokers (3%) (169). Thus there is biological plausability of the interaction between smoking and occupational exposures for the development of asthma. The effect modification observed in the study would highly likely be an underestimate, because of the non-differential misclassification of exposure. However temporal relationship between the occupational exposure and smoking is not clear, as this is a cross-sectional study. Longitudinal studies with more precise exposure assessment are needed to establish the effect modification of the association between

airway hyper-responsiveness and ever occupational exposure to HMW and/or LMW agents.

11.5. Population Attributable Risk Percentages in Different Models:

Population Attributable Risk Percentage was the parameter used to measure the role of occupational exposures in the development of asthma in the adult population. As explained above, the asthma symptoms used in the analysis were not rare and thus, prevalence rate ratio was preferred to odds ratio in the calculations. Again similar to the findings of the models adjusting for pertinent risk factors, PARP's were not different whether or not the childhood asthmatics were included (see *Tables* 10.5.1-3). Others have also reported that there was no difference between airway hyper-responsiveness in atopic and non-atopic subjects with ocupational asthma (113). By contrast in a study carried out in Spain using ECRHS protocol, PARP's increased in the models excluding childhood asthmatics (170).

Lack of important differences between the models with and without atopic subjects could be due to some of the atopic subjects changing or leaving their jobs due to asthma symptoms at work leading to an improvement in their asthma symptoms and airway hyper-responsiveness. However, one should be careful in interpreting the results of a cross-sectional study as the temporal association between these factors cannot be established.

11.6. Comparison of the Study Findings with the Other Two Studies which Used the Same Protocol and had Published Their Results:

Table 11.6 shows the findings of this study and the two studies from Spain, and New Zealand, which used similar protocol with this study, and published their results (170, 171). Response rates were similar for stage 1 in the three studies, but lower in Montreal for stage II study. Cumulative dose of methacholine used to define *airway hyper-responsiveness* in the Spain, New Zealand, and Montreal studies were 8, 5.12 or 10.24, and 10.24 micromoles, respectively. Risk of asthma for different definitions of asthma were assessed by prevalence rate ratios for the current occupational exposures in models adjusting for age, gender, and smoking habit. Odds ratios were calculated in specific occupational groups in the studies from Spain, and New Zealand, but could not be calculated in the study from Montreal study due to low numbers of subjects in most of the occupational groups. Current occupational exposure to HMW and/or LMW agents in Montreal study (as shown in the *Table* 9.31) was comparable with the other studies which used a list of high risk occupations as the occupational exposure.

There are considerable differences between the findings of these studies. In the Montreal study prevalence of asthma using four different definitions was almost half of the other studies, and reached to almost tenfold for asthma symptoms and/or medicine combined with airway hyper-responsiveness, whereas occupational exposure among those who reported current wheeze was almost two times that of the other two studies. Population Attributable Risk Percentages were not so different between these studies for current wheeze, and asthma symptoms and/or medicine, and these increased in the study population excluding childhood asthmatics, except for the definition of *asthma symptoms and/or medicine* in the Montreal study. Population Attributable Risk Percentages for *airway hyper-responsiveness* was only available in the Montreal study. Similarity of the prevalence rate ratios suggested that selection bias was not the explanation for these differences. None of the prevalence rate ratios were statistically significant in the Montreal study. This could be due to smaller size of the study population in this study compared to that of the other two studies.

Table 11.6: Comparison of the findings of this study with the two other studies, which used similar protocol with this study, and published their results:

	Kogevinas (Spain) (170) n (%)	Fishwick (New Zeland) (171) n (%)	Montreal (Canada) n (%)
Response rate			
Stage I	14269/16884 (84.5)	11978/14318 (83.7)	2959/3454 (85.7)
Stage II	2646/4342 (69)	1609/2519 (63.9)	499/1369 (36.4)
Prevalence			
Current Wheeze	823/2345 (35.1)	633/1542 (41.3)	130/498 (26.1)
Asthma Symptom / Medicine	555/2354 (23.6)	NA	85/498 (17.1)
Airway Hyper-responsiveness	NA	376/1128 (33)	54/368 (14.7)
Current Wheeze + Airway Hyper-responsiveness	208/1424 (14.6)	234/940 (24.7)	25/368 (6.8)
Asthma Symptom / Medicine + Airway Hyper-responsiveness	136/1415 (9.6)	176/940 (18.7)	9/368 (1.8)
Prevalence Rate Ratio			
Current Wheeze	1.37	NA	1.11/1.17
Asthma Symptom / Medicine	1.81	NA	1.16/0.99
Airway Hyper- responsiveness	NA	NA	1.27/1.31
Occupational exposure among cases			
Current Wheeze	9.6	7.3	23.1/23.3
Asthma Symptom / Medicine	15	NA	24.3/28
Airway Hyper- responsiveness	NA	5.0	24.1/25
Population Attributable Risk Percentage (all/adult onset)			
Current Wheeze	2.6/2.9	NA/3.1	2.3/3.4
Asthma Symptom / Medicine	4.7/5.3	NA	3.4/NA
Airway Hyper-responsiveness	NA	NA	5.1/5.9

11.7. Summary and Conclusions:

11.7.1. Summary of the Methods and Results:

Increases in the prevalence and morbidity and mortality related to asthma in the last two decades have been a cause for public concern and have highlighted the need for the investigation of prevalence and determinants of asthma in various regions and using standard methodologies. Efforts to develop and standardise the study instruments started in the European Community, who initiated multicentre studies in selected countries in Europe, studies then extended outside Europe to various countries including US, Australia, New Zealand and Canada. This thesis is based on data collected in a cross sectional study conducted in Montreal, one of the centres in Canada that took part in a studt of Lung Health and the Canadian Environment conducted using the methodology and design of the ECRHS. The main objective of the research thesis was to determine the prevalence of asthma in the adult population, and the contribution of the occupational exposures to the burden of adult asthma.

A two staged community-based study was used. In stage 1, a randomly selected group of adults aged 20 to 44 years (n= 2959) completed a screening questionnaire, and in stage 2 a randomly selected subgroup of those who were invited to the laboratory (n=498), where they answered a detailed questionnaire on asthma symptoms and associated factors, and a second detailed occupational questionnaire, skin prick testing, lung function testing, and methacholine airway challenge. Since the study was community-based bias due to "healthy" worker was minimized. Because the sampled would include workers who left or changed their jobs upon respiratory complaint.

However the study population, which participated in the laboratory stage of the study (stage 2) could not be considered representative of the source population, because of the low response rate (35.4%). Prevalence figures were obtained from the first stage of the study using the 4 different definitons of asthma as follows: *current wheeze:* 23.72% (22.19%, 25.26%) *asthma symptoms and/or medicine:* 12.81% (11.60%, 14.01%), *airway*

hyper-responsiveness: 14.67% (11.06%, 18.29%), *airway hyper-responsiveness* with *current wheeze:* 6.79% (4.22%, 9.36%). They (stage2 population), also exhibited higher prevalence of symptoms, and there were more who never smoked in the stage 2 population who participated in the laboratory stage of the study than in the stage 1 study population.

To minimise selection bias due to low exposure rates imputation was performed for the definitions using *airway hyper-responsiveness* with a predictive model which included all the information available for the first stage of the study. Estimates obtained from the imputation did not, in fact differ much from the prevalence figures obtained from the second stage of the study. Women had higher prevalence of asthma than men using all the definitions of asthma, even when standardised for age.

Occupational exposures were defined as ever present for at least 3 months and grouped into sensitisers and irritants based on the substantive knowledge. Justification of this grouping was based on: the different mechanisms of action, other study findings which indicated that asthma symptoms and *airway hyper-responsiveness* might persist for a long time after the cessation of exposure, and validation of self reported occupational exposures. Ever exposure to sensitisers and to irritants were reported by 56.9, and 10.8% of subjects, respectively. In the models taking pertinent risk factors of asthma into account, asthma defined as *current wheeze* was associated with exposure ever to irritants (OR: 2.12 (1.03, 4.34)), and *airway hyper-responsiveness* with exposure ever to sensitisers (OR: 2.20 (1.10, 4.38)), while *asthma symptoms and/or medicine* was not associated with occupational exposures. Most of the risk factors were exposures and conditions that took place in the childhood (see *Table* 10.5.2).

The association between *airway hyper-responsiveness* and occupational exposure to sensitisers was increased in current smokers, and in those 40-44 years aged, while an association between *current wheeze* and exposure ever to irritants was increased in men, those who had never smoked, were non-atopics, and 20-29 years of age.

The population attributable risk percentages were in the order of 30% for *airway hyper-responsiveness* with exposure ever to sensitisers, and 5% for *current wheeze* with exposure ever to irritants.

11.7.2. Conclusions and Areas for Further Research:

The prevalence of asthma in the present study was comparable to those reported in other English speaking countries, and these in turn were higher than in some other countries. Examination of the figures using asthma defined by symptoms and by *airway hyper-responsiveness* suggested that language bias was not likely to have resulted in an underestimation of the prevalence of asthma defined as *current wheeze*. Comparison of the findings with two other studies which used a similar study design and protocol showed, that in the Montreal study, current occupational exposure to sensitisers (comparable to the study definition of occupational exposure in two other studies) increased the risk of asthma by similar magnitude, but without statistical significance. This could be due to the smaller sample size and the lower power in the Montreal study.
Lack of association between current occupational exposures and asthma defined in three ways suggested that the study findings were not likely to be influenced by recall bias, but could be due to the "healthy" worker effect.

This study showed the importance of occupational exposure to sensitisers for the development of asthma in adults. The study findings were supported the findings of many of the previous community-based studies.

As a cross sectional study this study had some limitations, mainly in the assessment of exposure and determining the causality of any associations demonstrated between asthma markers and occupational exposures. The study findings were not specific to any group of occupational exposures since broad categories of occupational exposures were used in the analysis. Studies with higher statistical power, which would also allow the use of *current wheeze and airway hyper-responsiveness* as a definition of asthma in the analysis would

help to give more precise estimates of relative risk and PARP. This would also help to explore the differences observed in this study between *current wheeze*, and *airway hyper-responsiveness* in their associations with occupational exposures. Longitudinal studies with more precise assessment of exposure would also help to elucidate the association between occupational exposures and smoking, atopy, and childhood asthma. Role of multiple occupational exposures in the development of asthma was not addressed is another important area of further research.

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