EARLY CHANGES IN RESPIRATORY HEALTH IN YOUNG APPRENTICES AND PHYSICIAN UTILIZATION FOR ASTHMA AND BRONCHITIS LATER IN LIFE

by

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ABSTRACT

Introduction: The main risk factors for the development of respiratory disease have been largely established, however we still cannot predict which individuals will develop respiratory morbidity later in life. This study had two main goals: 1) to examine early working-life changes in respiratory health as risk factors for the development of asthma and bronchitis, and 2) to assess the utility of healthcare utilization data for longitudinal studies in respiratory epidemiology.

Methods: A cohort of young apprentices at entry to their trade (machining, construction painting, insulating, and electrician) was enumerated in 1988 to study prospectively the natural history of respiratory morbidity. This group (n=356) was followed-up again two years later. Subjects were linked to a provincial database of all healthcare encounters from 1991 to 2004 (linkage rate 98%). Two health outcomes were studied using physician diagnosis codes: asthma and “bronchitis”. Demographics, smoking, spirometric variables, and respiratory symptoms were assessed as predictors of both becoming a respiratory case (logistic regression), and of physician visit rate (negative binomial regression) during the administrative follow-up.

Results: There were 281 subjects available for analysis (complete data from baseline, first follow-up, administrative data). Sixteen met the case definition for asthma (2 physician visits in 1 year), and 20 met the case definition for “bronchitis” (3 visits in 1 year). Baseline bronchial responsiveness (BR), and especially a rapid increase in BR over the first 2 years was a strong risk factor for both asthma and “bronchitis”. Baseline symptoms of chronic cough or phlegm were predictive of subsequent “bronchitis” visits, and incident asthma-like symptoms were strongly related to subsequent asthma visits. Lung function variables were not important in any models. Relationships were also detected between type of physician, age, sex, job title, size of town, smoking status and the type of respiratory diagnostic code assigned at each physician visit.

Conclusions: Early changes in respiratory health may be useful markers in a surveillance program of workers who are susceptible to subsequent obstructive lung disease. Health care utilization data is a unique and promising tool in respiratory epidemiology.
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Finally I would like to acknowledge the funding support provided by the Canadian Institutes of Health Research Graduate Master's Scholarship, and WorkSafe BC. This funding has made it possible for this valuable study to continue.
CO-AUTHORSHIP STATEMENT

Chapters 2 and 3 consist of manuscripts prepared for scientific publication. The identification and design of the overall research program of which this study is a part was devised by SM Kennedy. Collection of early data on the apprentices was performed by Dr. Kennedy's research team as well before I joined the study. I performed all data preparation and research, manuscript preparation, and all analyses. My co-authors (PA Demers, J Sehmer, SM Kennedy) provided conceptual guidance and suggestions, as well as editing work.
CHAPTER 1: INTRODUCTION

Background

Asthma and Chronic Obstructive Pulmonary Disease (COPD) are chronic diseases that account for $12 billion in direct and indirect health care costs in Canada annually (1997), and COPD is the 4th leading cause of death worldwide (1). While the major risk factors for these diseases are known (smoking for COPD, and environmental exposures and host factors for asthma and COPD), predicting who will develop respiratory morbidity later in life is currently not possible. It is known that occupational exposures can contribute to more rapid development of obstructive lung diseases. If it could be shown that early indicators of lung health or changes thereof (including spirometric measures and symptom reporting) in working individuals were predictive of later morbidity, preventive measures could be taken to protect the health of susceptible individuals.

One occupation at risk for respiratory impairment from their job is machinists. Machinists work with cutting oils, or metalworking fluids, which serve as lubricants and coolants. In 1988, UBC researchers enrolled a group of 356 apprentices in four occupational groups: machinists, painters (a group with potential risk for occupational asthma should they include painters exposed to isocyanates) and two others (insulators and electricians) as controls. The apprentices were examined at baseline and after two years, and a significant association was found between machinists' exposure to metalworking fluids and the appearance of new bronchial hyperresponsiveness (BHR) (2). Table 1.1 shows how methacholine responsiveness (and changes therein) differed between machinists and other trades. In addition, 29% of the entire cohort had an annual decline in airflow of 100 mL or greater, when a decline of 0-30 mL would be considered “normal” (3), and 22% of the cohort had a rapid increase in bronchial responsiveness.

A second clinical follow-up, 16 years after inception, is currently underway. The study protocol followed at baseline and 2 years follow-up is being repeated. This includes: 1) a standardized questionnaire on job history, respiratory symptoms, and other demographic
information; 2) simple spirometry; 3) administering of a bronchial responsiveness test; and 4) a skin test for atopy.

The logistics and cost of this type of study, which includes subjects regardless of their current location or occupation in order to overcome the healthy worker effect, have led researchers to consider alternate methods of follow-up. In British Columbia, researchers have access to a comprehensive administrative database called the British Columbia Linked Health Database (BCLHD), which includes information on doctor and hospital visits and worker’s compensation claims. This database was designed for health services research, however the physician billing data is collected in a format specific for billing purposes. Therefore, it is as yet unclear how useful physician visit data will be for health researchers. A recent study by Demers et al. looked at the relationship between exposure to various fungicides in BC sawmills and respiratory morbidity (asthma, chronic obstructive pulmonary disease, and all respiratory disease) measured using mortality and hospital admissions from the BCLHD (4). While they found no relationship with exposures (either type of fungicide or duration of exposure), sawmill cohort members had a higher risk of hospitalization for all respiratory disease and COPD than the general BC population. These results are promising for my study as they demonstrate that occupational cohorts can be studied with respect to respiratory outcomes using the BCLHD; however the researchers used hospitalizations rather than physician visits.

The purpose of this research project is thus to use physician visit data contained in the BCLHD to examine questions related to the development of respiratory morbidity in young workers exposed to irritants (and/or subject to respiratory symptoms or lung function change) early in their careers. This information will later (subsequent to the present study) be used to compare the results obtained from this investigation to those collected via active follow-up of the cohort.
Respiratory morbidity in adulthood

The basic cause of respiratory morbidity in adults is airflow obstruction, and this obstruction may be fixed (as in COPD) or episodic (as in asthma). Asthma is often thought of as a “childhood disease”, however a recent American Thoracic Society panel estimated that 15-35% of all asthma in adults is linked to occupational exposures (5). In contrast, COPD is slowly progressive, and develops largely as a result of various environmental exposures, the most important of which is cigarette smoke. COPD is also mainly restricted to older adults, whereas asthma can occur at any age.

Both asthma and COPD can be triggered by environmental exposures (such as air pollution, various workplace exposures to dusts and fumes). However, the development of both diseases involves a complex interaction between external factors (environmental) and internal factors (genetics, individual susceptibility).

Individual variation is such that researchers are unable to predict who will, and who will not, develop respiratory morbidity. A schematic diagram of the natural history of the development of respiratory morbidity is shown in Figure 1.1. Note the early interaction of possible environmental and occupational factors and host factors, leading to an inflammatory response in susceptible individuals. Continued exposure to irritants or sensitizers can contribute to the ultimate development of asthma or COPD.

A potential link between rapid decline in airflow rates early in the career and later airflow obstruction has been observed in coal miners (6-8), and among workers exposed to asbestos (9,10) and grain dust (11). Unfortunately, this association was not the main focus of any of these studies; most of them were designed to tease out the relationship between a specific workplace exposure and smoking behaviours. The study of coal miners by Seixas and colleagues (7) showed that exposures prior to their start of follow-up among miners exposed for less than 5 years were the most important in predicting later airflow obstruction. However, they were not able to study this relationship directly because they did not have true baseline data. In the study by Hall and Cissik (10) on asbestos exposure as it relates to lung function decline, the researchers noted that
workers exposed to asbestos for less than 20 years lost an average of 81 mL in FEV₁ per year, while those exposed for longer than 20 years only lost an average of 1 mL/year. While this suggests that early exposures may be very important in determining long-term pulmonary function losses, the cohort was much older than the one in my study (mean age of 51) and already had significant workplace exposure histories at the start of the study (mean employment time in the asbestos industry of 29 years).

One study followed a cohort of grain workers from the start of their career until year five, and was designed to assess the differences in pulmonary function loss by duration of follow-up (12). The researchers found that workers who left the grain elevator after only one follow-up screening test had the fastest lung function decline; the longer a subject stayed, the slower their decline. However, even among those available for all 4 follow-up tests, annual lung function decline was 70 mL/year. Unfortunately, no additional follow-up was carried out to examine long-term respiratory outcomes in this group.

**Occupational agents and respiratory disease**

**Occupational asthma**

Occupational asthma is the most common work-related lung disease in the developed nations (13-16). A recent American Thoracic Society panel estimated that 15-35% of all asthma in adults is linked to occupational exposures (5). Occupational asthma (OA) is defined as:

"a disease characterized by variable airflow limitation and/or airway hyperresponsiveness due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace" (17).

It is important to note that OA is clinically identical to non-occupational asthma, except that a specific occupational exposure can be identified as the cause of the disease (18). This can make it difficult to diagnose asthma as specifically related to an occupational exposure, for example in people who may have a history of childhood wheeze. The two general types of OA are allergic and non-allergic (Figure 1.2).
Allergic OA develops in response to a sensitizing agent via immunologically-mediated pathways, and develops after a latency period (19). Within the category of allergic OA, two main groups of substances can be distinguished: generally high molecular weight compounds that act via the production of specific IgE antibodies (i.e. – animal proteins), and generally low molecular weight compounds whose mechanism is less understood, but generally not mediated by specific IgE antibodies (i.e. – plicatic acid in Western Red Cedar) (20).

Non-allergic agents of OA (or irritants) are a somewhat new category, and are unique in that no latency period for symptoms exists. This form of OA (which is sometimes called Reactive Airways Dysfunction Syndrome (RADS) or Irritant Induced Asthma) typically results after an accidental acute exposure to an irritant (i.e. – chlorine gas), and is more likely to be related to acute airway inflammation than hypersensitivity. Table 1.2 presents some of the more common agents of OA.

**Chronic airflow obstruction from workplace exposures**

COPD, which is defined clinically as non-reversible and progressive airflow obstruction due to the chronic inhalation of irritants, is less likely to be diagnosed as specifically arising from an occupational exposure (21). This is because patients have often been exposed to a number of different irritants at different points in their working lives, and their relative contribution to the disease is impossible to disentangle. In addition, there is a clear causal pathway linking cigarette smoking with the development of COPD, which may obscure the relationship with occupational exposures. Smoking and exposure to workplace dusts and fumes also tend to interact with one another; blue-collar workers in “dusty” occupations (i.e. - those likely to have inherent irritant exposures) tend to be heavier and more frequent smokers than those in other occupations (22). As another complicating factor, only a minority of smokers or exposed workers actually develop COPD (23,24).

Despite these obstacles, however, several studies have shown that chronic airflow obstruction is associated with exposure to mineral dusts, metal particulate and fumes, organic matter, combustion products, irritant gases, and combinations of these agents (19). In addition, a history of occupational exposure combined with a history of smoking
appears to have an additive effect on the risk of COPD development (24). Occupationally-induced COPD is generally the result of an intrinsic inflammatory response to irritants, although cadmium exposure has been shown to cause COPD via emphysematous mechanisms (23). A list of some of the more common occupational causes of chronic bronchitis is presented in Table 1.3; some general groupings of substances are metals, minerals, smokes, organic dusts, and irritant gases.

**Metalworking fluids and chronic respiratory disease**

One agent of occupational lung disease of particular interest to this study is *metalworking fluids* (MWF), also known as cutting or machining oils. These fluids are used as lubricants and coolants in machining operations where the cutting, boring, or grinding of metals is required. MWF are complex mixtures that contain both irritants and sensitizers, making them of particular interest in the study of the development of respiratory disease. The composition of MWF varies with manufacturer, type, and degree of recycling and contamination (25). Metalworking fluids that contain water are prone to microbial and fungal contamination; endotoxin (produced by gram negative bacteria) can also be found in MWF (26-30). Components of MWF can cause occupational asthma (31-36), and MWF has repeatedly (although inconsistently) been implicated in the development of elevated respiratory symptoms. Since the current study is the only prospective, longitudinal investigation of the long-term effects of MWF on pulmonary function, the implications for respiratory morbidity is unknown.

**Screening for respiratory disease in the workplace**

Screening is aimed at identifying those individual workers who are susceptible to developing symptoms or disease from occupational exposures, and surveillance programs (developed for prevention) often include screening as a component. Large surveillance programs (that include aspects of screening) for occupational asthma have been implemented; good examples of these initiatives are the SENSOR program in the United States (37), and the SWORD program in the United Kingdom (38). These programs have been very successful in increasing awareness of occupational causes of respiratory disease among physicians, and thus increasing the detection of existing...
cases, however prevention programs for occupational respiratory diseases, especially for occupational asthma (39), have been less well studied. An appropriate screening program would identify individuals who are at a high risk of developing a chronic respiratory condition. This is problematic for obstructive lung diseases because while the general natural histories are understood, who is at particular risk is not (40,41). Epidemiologic studies typically use physiologic measurements coupled with standardized questions on respiratory symptoms. Studies that attempt to correlate symptom reporting with physiologic measures usually do so cross-sectionally (42,43), and their utility in predicting morbidity is poorly characterized (44).

The use of periodic spirometry in workplace surveillance suggests a minimum of 4-6 years of repeated measurements is required to detect a real decline in lung Function (45-47). This is due to the high variability in the spirometric method over the short-term. As time increases, the standard error of the measurements decreases, making it possible to detect a smaller, "real" decline (39). However, since many researchers do not have the luxury of studying cohorts over 6 years, particularly in young and/or transient workers (who are often the population of interest), it is important to assess shorter-term detectable changes as possible predictors of later lung trouble.

Epidemiologic use of administrative data

The universal, single payer health care system in Canada creates a useful possible tool for tracking health care utilization by individuals. In BC, the British Columbia Linked Health Database (BCLHD) is accessible to researchers. The BCLHD was developed by the Center for Health Services and Policy Research (CHSPR) at the University of British Columbia. This data set includes records for all BC residents and includes information regarding hospital discharges and deaths (~700,000 per year), patient encounters billed to the Medical Services Plan (~50,000,000 per year), drug prescriptions for the elderly (~4,500,000 per year), long term care services (~16,000 assessments per year), death certificates (~20,000 per year), and birth certificates (~40,000 per year). In addition, data on accepted workers' compensation claims for fatalities, pensions, and short-term
disabilities (~80,000 per year) are included. Almost all records within these data sets are linkable by common identifiers to a single master file. The BCLHD currently has records for the period from April of 1985 through the end of 2004, although data coverage does vary between type of file. The physician billing data (important for the current study) is optimized for billing purposes, such that a record is generated for each billed “transaction”.

Healthcare utilization data sources offer an attractive alternative to clinical follow-up because of their relatively low cost and universal coverage (48). They are often used for population-based surveillance, for example in estimating disease prevalence, however many of the studies focus on hospitalizations as their outcome (49-52). The benefit of using hospitalizations, especially for asthma, is that misdiagnosis is rather unlikely – if an individual is experiencing strong enough symptoms to attend the emergency room, we can be confident that a recorded asthma diagnosis is likely identifying an asthmatic person. However, in the case of respiratory disease, using only hospitalizations is likely to underestimate the true prevalence of people living with the disease. In the most recent National Population Health Survey (Canada) supplementary questionnaire on asthma, only 18% of those with active asthma had visited the hospital in the previous year for their asthma (53). In a study by Rosenman et al., the researchers surveyed physicians in New Jersey and assessed how many patients they saw in regular practice with an occupational lung disease and compared this list to those seen in hospital. On average, 3 to 4 times as many patients were identified from regular physician visits as through hospitalizations (54). In addition, because of differences in billing structure, emergency room visits where the patient is not admitted to the hospital are not captured in the BCLHD; therefore physician visits are an attractive alternative.

Physician visits have been used to quantify population-based estimates of asthma or COPD incidence or prevalence in several Canadian studies (55-59). In the first 2 studies, the authors were examining changes in prevalence and severity (respectively) of asthma and related conditions (including bronchitis) over time during the 1980s. Their results are useful for the present study in that they were conducted in Manitoba, which has an administrative database similar to the BCLHD, increasing confidence in
the use of respiratory diagnostic codes as a follow-up tool. In the study by Lacasse and colleagues (57), they sought to test the validity of COPD diagnoses (using various criteria) in the provincial health database in Quebec. They did not, however, have a predefined case definition; all people with at least one healthcare encounter coded as COPD were included. They found that 47% of patients over the age of 65 only had one visit in the entire 5 year follow-up, which was one finding that led to their conclusion that the diagnoses lack validity. One interesting finding that they did report was that using physician visit data among those patients they deemed to have “possible” or “probable” COPD increased the estimated prevalence of COPD in Quebec to twice the level reported by the national health survey in Canada. This intriguing finding suggests that respiratory-related physician visit data may be useful in identifying undiagnosed cases. Despite interesting findings from these Canadian studies of physician visit data, they have not addressed the issue of examining respiratory disease among a specific and at-risk group of people followed over time. To my knowledge, this is the first study to attempt this.

It would be beneficial to further examine the utility of this dataset for examining respiratory morbidity (and other occupational diseases for that matter) for a number of reasons. Firstly, administrative data research is less expensive than traditional epidemiologic methods, both in terms of money and time. Second, following patterns of physician utilization provides a way of estimating the burden of disease experienced by patients. In addition, there is a much lower potential for loss to follow-up with this type of study, and perhaps people would be more willing to participate in a study that doesn’t require much time from them after their initial intake.

**Study goal**

This study is designed as a longitudinal follow-up of an occupational cohort. The study began in 1988 when a group of young adult apprentices were recruited at entry into their first year classes (machinist, electrician, insulator, and construction painter apprentices) at the provincial technical school. Respiratory health was measured actively via pulmonary function testing, detailed in-person questionnaire, bronchial responsiveness...
tests, and allergy tests. The same group was tested again, using the same protocol, approximately 2 years later when they returned for their Year 3 training class. The participation rate at baseline was 98% (356 out of 363 agreed). In addition, we have complete information on all physician visits, hospital discharges, and workers’ compensation claims for a majority of the cohort (only 9 subjects were not linked to the database) from 1991 to 2004. The study protocol was approved in advance by the University of British Columbia Clinical Screening Committee for Research and Other Studies Involving Human Subjects, and informed written consent (including approval for accessing health care records) was provided by all participants. The UBC Research Ethics Board’s Certificates of Approval are included in Appendix I. The cohort is currently in the process of being tested again (2004 till present). The results of this follow-up will be compared to the conclusions of the present study in subsequent analyses.

We have two main research questions that will be addressed by using physician visits, hospital discharges, and WCB records in the BCLHD:

**Research Question 1:** Do early changes in lung function (FEV₁, over the first 2 years of apprenticeship) predict respiratory morbidity as measured by physician visit data?

This question will be addressed in Chapter 2 via two hypotheses:

1. An increase in bronchial responsiveness (BR) between Visit 1 (1988) and Visit 2 (~1990) is associated with an increase in physician visit rate, as well as an increased risk of becoming a case, based on 2 health outcomes (asthma and “bronchitis”).
2. A rapid decrease in forced expiratory volume in 1 second (FEV₁) between Visit 1 and Visit 2 is associated with an increase in physician visit rate, as well as an increased risk of becoming a case, based on 2 health outcomes (asthma and “bronchitis”).

**Research Question 2:** Are there any patterns of symptom reporting during the first 2 years of apprenticeship that predict respiratory morbidity?

This question will also be addressed in Chapter 2 via the following two hypotheses:

1. Reporting persistent symptoms of chronic bronchitis or asthma (present at Visit 1 and Visit 2) is associated with an increase in physician visit rate, as well as an
increased risk of becoming a case, based on 2 health outcomes (asthma and “bronchitis”).

2. The development of new symptoms of chronic bronchitis or asthma (only present at Visit 2) is associated with an increase in physician visit rate, as well as an increased risk of becoming a case, based on 2 health outcomes (asthma and “bronchitis”).

We have a secondary objective of examining the utility of the BCLHD for respiratory epidemiology, especially with respect to the potential for bias in how physicians code respiratory office visits. We will examine this issue with respect to sex, age, type of physician, and geographical location in Chapter 3.

**Study rationale**

There are three main reasons that this research project is needed. First of all, the active follow-up that constitutes the Apprentices Lung Health Study (i.e. – lung function testing, detailed in-person questionnaires, etc.) is costly. This is compounded by the fact that the study was designed to diminish the healthy worker effect by including subjects regardless of their location or occupation at the follow-up stages, requiring researchers to travel around the province and beyond to complete testing. The study design is also time-consuming, requiring that researchers wait for a sufficient time to pass to allow long-term respiratory outcomes to be addressed, and then repeating all measurements.

The second reason that this research is necessary is that the utility of the BCLHD for examining chronic disease in a cohort remains largely unexplored. Methodology for preparation of files, defining new variables, and exploring the answers that can be found within this unique dataset is not well developed. In addition, we plan to address potential bias in how physicians code respiratory office visits in this dataset.

Finally, there is very little knowledge about early predictors of respiratory disease that develops later in life. In other words, in the early stages of this study, the researchers found that workers exposed to irritants in their workplaces were more likely to develop
respiratory symptoms in the first 2 years of employment. The questions remain: What does this mean for those workers? Are they more likely to develop asthma later in life, or visit the doctor more often for respiratory complaints? Can we offer preventive recommendations to workers who exhibit these symptoms early in their working lives? None of these questions can currently be answered, and if they could be, the implications for reducing health care costs, improving quality of life for susceptible individuals, and understanding the process of respiratory disease development as a result of chronic exposure to environmental agents, are far-reaching.
Figures and Tables

Figure 1.1 The natural history of respiratory morbidity

Figure 1.2 Occupational asthma: Allergic and non-allergic types (Reactive Airways Dysfunction Syndrome), and their characteristics (adapted from Price, 2004 (18))
Table 1.1 Differences between machinists and other trades apprentices at 2 years follow-up with respect to bronchial responsiveness (adapted from Kennedy et al. (2))

<table>
<thead>
<tr>
<th></th>
<th>Machinists</th>
<th>Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>82</td>
<td>157</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Methacholine slope (ml/mg), mean ± SD</td>
<td>-18.4 ± 31.1</td>
<td>-19.7 ± 32.4</td>
<td>ns*</td>
</tr>
<tr>
<td>• PC&lt;sub&gt;20&lt;/sub&gt; ≤ 8 mg/ml, n (%)†</td>
<td>4 (5%)</td>
<td>8 (5%)</td>
<td>ns*</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Methacholine slope (ml/mg), mean ± SD</td>
<td>-35.4 ± 87.7</td>
<td>-18.5 ± 28.4</td>
<td>0.09</td>
</tr>
<tr>
<td>• PC&lt;sub&gt;20&lt;/sub&gt; ≤ 8 mg/ml, n (%)</td>
<td>8 (10%)</td>
<td>6 (4%)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Change in methacholine slope</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Slope at follow-up – slope at baseline (ml/mg), mean ± SD</td>
<td>-17.1 ± 78.8</td>
<td>+1.2 ± 31.1</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Rapid increase in BHR, n (%)</strong></td>
<td>11 (13%)</td>
<td>11 (7%)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

* Not statistically significant at the α=0.05 level
† PC<sub>20</sub> refers to the provocative concentration causing a 20% drop in forced expiratory volume in 1 second (FEV<sub>1</sub>); here, ≤8mg/mL concentration identifies hyperresponsive individuals.
Table 1.2 Substances implicated in the development of occupational asthma (adapted from Malo et al. (19))

<table>
<thead>
<tr>
<th>High molecular weight substances</th>
<th>Common sources of exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal materials</td>
<td></td>
</tr>
<tr>
<td>Dander</td>
<td>Laboratory work, fishing or fish processing, farming, etc.</td>
</tr>
<tr>
<td>Excreta</td>
<td></td>
</tr>
<tr>
<td>Secretions</td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td></td>
</tr>
<tr>
<td>Plant materials</td>
<td></td>
</tr>
<tr>
<td>Flour</td>
<td>Bakeries</td>
</tr>
<tr>
<td>Grain</td>
<td>Grain elevators or feed mills</td>
</tr>
<tr>
<td>Castor bean</td>
<td>Oil manufacture</td>
</tr>
<tr>
<td>Coffee</td>
<td>Food processing</td>
</tr>
<tr>
<td>Wood dust</td>
<td>Sawmills, carpentry, furniture work</td>
</tr>
<tr>
<td>Psyllium</td>
<td>Health care</td>
</tr>
<tr>
<td>Latex</td>
<td>Latex gloves, equipment</td>
</tr>
<tr>
<td>Enzymes</td>
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<tr>
<td>Alpha-amylase</td>
<td>Bakeries</td>
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<tr>
<td>Papain</td>
<td>Food processing</td>
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<tr>
<td>Alcalase</td>
<td>Pharmaceutical industry</td>
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<tr>
<td>Bacillus subtilis-derived enzyme</td>
<td>Detergent enzyme industry</td>
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<td>Low molecular weight substances</td>
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<tr>
<td>Spray paints</td>
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<tr>
<td>Toluene diisocyanate</td>
<td>Manufacture of plastics, foam</td>
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<tr>
<td>Dimethylphenyl diisocyanate</td>
<td>Insulation</td>
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<tr>
<td>Hexamethylene diisocyanate</td>
<td>Automobile spray paint</td>
</tr>
<tr>
<td>Woods and wood dust</td>
<td></td>
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<tr>
<td>Western Red Cedar (plicatic acid)</td>
<td>Sawmills, carpentry, furniture work</td>
</tr>
<tr>
<td>Acid anhydride</td>
<td>Users of plastics, epoxy resins</td>
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<tr>
<td>Biocides</td>
<td></td>
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<tr>
<td>Formaldehyde</td>
<td>Health care workers; also sawmills/ furniture workers for formaldehyde</td>
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<tr>
<td>Glutaraldehyde</td>
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<td>Chloramine T</td>
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<tr>
<td>Colophony fluxes</td>
<td>Electronic workers</td>
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<tr>
<td>Irritant agents</td>
<td></td>
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<tr>
<td>Irritant gases (i.e. chlorine, sulfur dioxide)</td>
<td>Pulp and paper mills</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>Hospital settings, laboratories</td>
</tr>
<tr>
<td>Isocyanates</td>
<td>Spray paint users</td>
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Table 1.3 Some common occupational irritants implicated in the development of chronic bronchitis (adapted from Balmes, 2002 (21))

<table>
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<tr>
<td>Coal</td>
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<td>Man-made vitreous fibers (MMVF)</td>
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<td>Oil mist</td>
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<td>Portland cement</td>
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<tr>
<td>Osmium</td>
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<tr>
<td>Vanadium</td>
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<td>Welding fumes</td>
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<table>
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<tr>
<th>Organic dusts</th>
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<tr>
<td>Cotton</td>
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<td>Grain</td>
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<td>Wood</td>
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<th>Smoke</th>
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<tr>
<td>Engine exhaust</td>
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<td>Environmental tobacco smoke</td>
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<td>Fire smoke</td>
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<th>Irritant gases</th>
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<tr>
<td>Chlorine</td>
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<td>Sulfur dioxide</td>
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References


CHAPTER 2: ARE EARLY CHANGES IN RESPIRATORY HEALTH IN YOUNG APPRENTICES RELATED TO RESPIRATORY PHYSICIAN VISITS FOR ASTHMA AND BRONCHITIS LATER IN LIFE?¹

Introduction

The main risk factors for the development of respiratory disease have been largely established; namely smoking, environmental exposures and host factors (1,2). Despite this, we still cannot predict which individuals will develop respiratory morbidity later in life. Consequently (and appropriately), we advise all smokers to stop smoking, and make blanket recommendations for reduction in occupational exposure to dusts, gases, and fumes. However, in the context of workplace screening, attention has also focused on the possibility that periodic respiratory health monitoring of workers may provide information that can help identify individuals at risk for the development of occupational asthma or other work-related lung disease, so that interventions can be more targeted.

Population based surveillance techniques have been developed specifically for occupational asthma (e.g. the SENSOR program in the US), however these are of use mostly for identifying existing cases (3). While this is obviously useful, there has long been interest in the development of preventive screening programs for occupational respiratory diseases (4). Many workplace screening programs suggest annual (or even more frequent) spirometry testing as best practice for identifying at-risk workers (5,6). In particular, the American College of Occupational and Environmental Medicine (ACOEM) recommends evaluating spirometric values cross-sectionally as well as longitudinally to screen workers for excessive loss over time (7).

Reports from some epidemiologic studies indicate that rapid decline in lung function is predictive of subsequent low FEV₁ (8), symptom reporting and asthma (9), and hospitalizations and death from COPD (10), however other researchers note that rapid declines in lung function early in the career are not correlated with continued decline.

¹ A version of this chapter will be submitted for publication. Peters CE, Demers PA, Sehmer J, Kennedy SM. "Are early changes in respiratory health in young apprentices related to respiratory physician visits for asthma and bronchitis later in life?"
decline, and even sometimes in recovery in the study by Seixas et al (11). In a longitudinal study of new coal miners by Wang et al.(12), they also noted that partial recovery after a rapid decline in lung function can occur. In their study of young workers, they demonstrated a sharp decline in FEV1 over the first 12 months of mining, followed by a plateau lasting through their second year, and a partial increase in their third year.

Reliability of spirometric measures may not be high enough in many studies to identify all individuals at risk (13). Due to the high variability in spirometric measures over short periods of time, most surveillance programs recommend at least 4-6 years of follow-up to obtain enough data to define the “rapid decliners” (7,14,15), and symptom screening (with or without spirometry) is more often recommended for surveillance of early occupational asthma in workplaces (5).

Studies on the predictive role of early respiratory symptoms in determining subsequent lung health have had mixed results. Respiratory symptoms (16,17), incident asthma (18), and COPD (19) have been linked to subsequent faster declines in lung function. Other studies, however, have found no such relationships (20,21). Groups at known risk for occupational asthma are sometimes surveyed regularly using symptom screenings (and often spirometry); in many countries, this is either mandated by law or undertaken voluntarily by companies (22). Examples of industries involved in regular spirometry screenings and/or more comprehensive surveillance include food and animal feed, laboratories working with animals, rubber latex, and isocyanates (23-27). These are working groups at well known risk for occupational asthma.

Airway hyperresponsiveness has been identified as a risk factor for developing occupational asthma (28), faster decline in lung function (29,30), the development of respiratory symptoms (31), asthma (32), and COPD (33). Despite these findings, others have failed to find a relationship between ‘baseline’ hyperresponsiveness and the new development of respiratory symptoms in longitudinal studies (34). This could be due to the relatively high prevalence of bronchial responsiveness in the asymptomatic general population, leading to a wide overlap between hyperresponsive people with symptoms or disease and people without (35). In addition, these studies could have conflicting
results depending on what they measure as the outcome; this is because many studies in respiratory epidemiology detect relationships between measures like symptoms, lung function and airway responsiveness, but are not designed in a way that can ascertain which one of these measures actually causes the other(s). Also, the conflicting study by Hopp et al. (34) had longitudinal data on only 52 subjects – it is possible that they did not have enough subjects to detect expected relationships.

The studies mentioned thus far have widely varying lengths of follow-up, ranging from as little as 3 years (12,28) to as much as 30 years (8,33). Many studies of respiratory health are cross-sectional or have a short length of follow-up because of the methodological and logistic difficulties associated with longitudinal studies. Of additional interest to this study is that it is quite uncommon to enumerate a cohort of workers at entry to their trade (or nearly so). We are aware of only one study that has followed workers (coal miners in this case) from job entry for an extended period of many years (11), however their analysis focused on the effect of coal dust exposure on the longitudinal decline in lung function only. They detected a non-linear relationship (i.e. early rapid decline in lung function, but no additional exposure-related loss over the next 10 to 14 years). While these results inform our study, we are interested in workers of many types and specifically how early changes affect morbidity later on (rather than specific and quantified exposures). Testing people’s respiratory health before they have participated for a substantial time in the workforce is an excellent way to assess new respiratory disease, and following such individuals over a long period of time is imperative to tracking the (not well characterized) natural history of obstructive respiratory diseases.

One of the disadvantages of the ‘ideal’ surveillance approach (i.e. routine simple spirometry over a period of 4-6 years coupled with symptom assessment) is that many workers, especially young ones, change their employment frequently; well before sufficient surveillance data has been accumulated. Few studies have examined the relationship between changes over shorter time periods (such as 6 months up to a few years) and long-term declines (8,36) and we are not aware of any study that has investigated early changes in all of spirometry, bronchial responsiveness, and respiratory symptoms in predicting the development of later respiratory illness.
We had the opportunity to study these relationships in the context of an ongoing cohort study of young trades’ apprentices, enumerated between 1988 and 1990 to address the effects of metalworking fluid exposure on machinists. We tested the apprentices at first entry into their trade and again after 2 years, including those who changed their employment. We were able to obtain comprehensive healthcare utilization data for the subsequent 13 year period (1991 to 2004) for all but 9 cohort members, and to carry out analyses to address the following specific research questions:

1. Do early changes in lung function (over the first 2 years of apprenticeship) predict a subsequent increase in respiratory-related physician visits?
2. Are there any patterns of symptom reporting during the first 2 years of apprenticeship that predict a subsequent increase in respiratory-related physician visits?

The purpose of our study, in terms of its relevance to surveillance and disease prevention, is to highlight predictors of subsequent disease in healthy young adults. In addition, some studies have shown that physician visit data can be useful in studying respiratory disease outcomes (37-41). Therefore, a secondary objective, in light of the cost and effort of typical prospective studies, is to assess the use of healthcare utilization data for follow-up of an occupational cohort.

**Methods**

The original study protocol has been described elsewhere (42). Briefly, all machining, electrician, insulator, and construction painting apprentices attending their first year at a British Columbia provincial technology school in 1988 were invited to participate (n=356, 98% participation rate). Follow-up testing was carried out approximately 2 years later, when apprentices returned for their Year 3 training class. All participants who had left the program were also invited for testing. For this study, we restricted from the cohort those apprentices who were never linked to the medical plan database (n=9), those with less than 4 years of health care utilization follow-up data (n=11), and those without complete baseline (Visit 1) and first follow-up (Visit 2) data (n=55). The
protocol was approved in advance by the University of British Columbia Clinical Screening Committee for Research and Other Studies Involving Human Subjects, and informed written consent (including approval for accessing health care records) was provided by all participants.

The same testing protocol was followed during Visit 1 and Visit 2. A modified version of the American Thoracic Society questionnaire for use in epidemiologic studies was administered (43). Each symptom (cough, phlegm, wheeze (occasionally or usually), chest tightness, and dyspnea) was considered individually first, with variables created for 'persistence' (symptom present at Visit 1 and Visit 2) and 'newly developed' (symptom present only at Visit 2). We also created a variable for chronic bronchitis symptoms (chronic cough or phlegm – for longer than 3 months of the year, present for 2 years) (44), as well as one for "asthma-like symptoms": a positive response to one or more of: usual cough (aggravated by dust or fumes), wheeze apart from colds (aggravated by dust or fumes or worse at night), or chest tightness associated with difficulty in breathing (aggravated by dust or fumes) (42).

All spirometric tests and questionnaires were administered by the same technicians. Spirometry was performed using a dry rolling seal spirometer (S&M Instruments Ltd., Doylestown, PA) following the American Thoracic Society protocol (45). Methacholine challenge tests were administered to test for bronchial responsiveness, according to the tidal breathing method (46), and the methacholine concentration associated with a 20% drop in \( \text{FEV}_1 \) (PC\(_{20}\)) was determined by linear interpolation over the full range of dose-response data. Methacholine slope was calculated as the linear slope of the least squares regression line from the relationship between \( \text{FEV}_1 \) (in ml) and methacholine concentration (in mg/ml). Rapid decline in lung function was defined as having >100mL loss in forced expiratory volume in 1 second (FEV\(_1\)) per year between Visits 1 and 2. Baseline percent predicted FEV\(_1\) was also examined via categorizing into the following 6 ranges: \( \leq 75\% \), 76-85, 86-95, 96-105, 106-115, and \( \geq 116\% \). Bronchial hyperresponsiveness (BHR) was considered present if the PC\(_{20}\) was less than 8 mg/mL. Rapid increased bronchial responsiveness (BR) was defined as having a "doubling-dose increase in PC\(_{20}\)" between Visits 1 and 2 (i.e. an increase in bronchial
responsiveness resulting in a shift in \( \text{PC}_{20} \) by more than one dose category, where dose categories are \( \text{PC}_{20} < 2 \text{ mg/mL}, 2-8, 8-16, 16-32, 32-64, >64 \).

Health care utilization data was obtained by linking participants using their personal health number to the British Columbia Linked Health Database (BCLHD). The BCLHD is an administrative database, developed by the Center for Health Services and Policy Research at the University of British Columbia (47), that includes person-specific information for all residents of the province, on all encounters with the healthcare system (births, deaths, hospital discharges, physician visits, and workers’ compensation claims). For this analysis, we included records for all encounters with physicians; we also extracted information about workers’ compensation claims and hospitalizations. The physician visit database was designed in part to be useful for billing purposes, such that a record is generated for each billed “transaction”, therefore records were collapsed to represent “visits” by deleting records with the same subject ID number, date and ICD-9 code (International Classification of Diseases, Ninth Revision) (48). We also deleted transactions for procedures related to a primary visit (such as x-rays and laboratory tests) to avoid double counting. Follow-up began on April 1, 1991 (the first day on which ICD-9 codes were required for each transaction) or the first day the participant was registered in the database, whichever was later. Follow-up ended when the participant was no longer registered (either due to leaving the province or death), or on March 31, 2004 (whichever was earlier).

An asthma case definition of 2 or more visits (coded as ICD-9 493.xx) in a sliding 365-day window was developed based on the British Columbia Clinical Practice Guideline for asthma (49). This document recommends twice-yearly physician visits for patients with asthma to review symptoms, medications, and asthma control. We also created a “bronchitis” case definition, which required 3 or more visits in a sliding 365-day window for any of the following ICD-9 codes: 466 (bronchitis, acute), 490 (bronchitis, unspecified), 491 (bronchitis, chronic), 492 (emphysema), or 786 (symptoms involving the respiratory system).
Statistical analysis was carried out using SAS-PC version 9.1 (SAS Institute, Cary, NC). Simple comparisons of means or proportions between groups were carried out using the Student's t-test, Wilcoxon rank-sum test, chi-square analysis, and Fisher's exact test. We performed manual stepwise logistic regression analyses to model the likelihood of an individual becoming a case over the 13 year follow-up period after Visit 2 (one model for each of asthma and “bronchitis”) and log-linear models (Negative Binomial distribution, which allows for overdispersion and provides more statistical power than adjusted Poisson models), to examine predictors of the physician visit rate over the follow-up time, again for asthma and “bronchitis” visits. In all models, we examined simple lung function, respiratory symptoms, and bronchial reactivity variables as potential predictors, controlling for demographic factors (age, sex, race), social factors (smoking status at each visit, trade designation, and whether or not a subject quit their trade during the first two years) and host factors associated with asthma (atopy, childhood asthma, family history, self-report of current asthma). When modeling the likelihood of becoming an asthma case, we excluded “bronchitis” cases from the comparison group (and vice versa). Risk ratios and 95% confidence intervals were calculated using Wald statistics. Variables were included or excluded based on their effect on the variance in the model, their p-value, and to keep grouped variables together. Variables were removed from the models if their inclusion did not significantly change the estimates.

Results

Participants

The cohort included 281 persons who were, on average, 26 years old, with normal lung function (FEV1 ~102%), male (~3% female) and Caucasian (~95%). There were 75 subjects that did not meet the previously described study inclusion criteria (21%); these people were more likely to be current smokers at Visit 1 (49% vs. 34% of those included, p=0.03). Excluded subjects were also more likely to be non-Caucasian, however this difference was not statistically significant (11% vs. 5% of those included, p=0.1). There were no other significant differences between included and excluded
subjects with respect to age, sex, atopic status, or childhood or family history of asthma.

**Healthcare utilization during follow-up**

Figure 2.1 shows the distribution of types of physician visits for the study population using ICD-9 code groupings, showing number of visits per person-year of follow-up (mean years of follow-up = 12.0, and total number of visits = 21,387). The most common cause for a physician visit in this cohort was musculoskeletal problems, at 31% of all visits and a mean of 2.0 visits per person-year. Respiratory-related visits accounted for approximately 9% of all visits and a mean of 0.6 visits per person-year. Most of the study population had at least one workers' compensation claim (83%). The mean number of claims for the entire group was 2.9 over the follow-up period; none of these claims were related to respiratory disease. Only one subject was hospitalized for asthma, and one for bronchitis; however 50% of the cohort was hospitalized at least once. Hospitalizations in this database include same-day stays (where a patient is admitted but is sent home on the same day). The distribution of types of hospitalizations using ICD-9 code groupings showing the number of hospitalizations per person-year of follow-up is shown in Figure 2.2. The most common cause for hospitalization was injury (20% of total hospitalizations), and two thirds of these were overnight stays. Digestive and musculoskeletal problems were the next most common causes for hospitalization in this group.

A total of 16 subjects met our case definition for asthma during the follow-up period and 28 met the case definition for "bronchitis". Eight of these met both the asthma and the "bronchitis" case definitions, so they were classified in the 'asthma' group, rather than the "bronchitis" group as we had more confidence in the asthma case definition (being based on an established practice guideline), leaving 20 in the "bronchitis" group. Administrative follow-up data on workers' compensation claims, hospitalization admissions, and physician visits are presented in Table 2.1, grouped according to the participant's 'follow-up status' (i.e. asthma, "bronchitis", or neither). Interestingly, hospitalization rates were higher among both asthma and "bronchitis" cases.
There were 42 subjects who had at least one visit for asthma during the follow-up (15%). Over half the cohort (63%) had at least one visit for “bronchitis”. Physician visit rates for all causes among asthma and "bronchitis" cases were roughly double the rates for subjects with no respiratory disease.

**Demographic and health status information at baseline (Visit 1)**

Demographic, baseline health status, and occupation information for the study subjects, grouped according to their ‘follow-up status’, is included in Table 2.2. Subjects who met the case definition for either asthma or “bronchitis” during the follow-up were significantly more likely to have a low PC20 at baseline (p=0.02) and have self-reported asthma at baseline (p<0.0001). They were also more likely to report a family history of asthma (p=0.06) and had slightly lower lung function (p=0.07), compared to those who did not meet the respiratory-related case definitions in the follow-up period. Having a childhood history of asthma was more common only among those who met the case definition for asthma in the follow-up period (p=0.008). There were no other significant differences between groups with respect to sex, age, atopy, smoking status, or job title.

**Changes over the first 2 years of employment**

Table 2.3 contains respiratory health variables depicting changes in lung function and symptom reporting between Visit 1 and Visit 2. Twenty-two subjects (8%) had left their initial trade by Visit 2, and these people were more likely to have been machinists initially (15 of the 22 were machinists) (p=0.006). In addition, a large proportion of subjects who developed asthma quit smoking between Visits 1 and 2, and both "bronchitis" and asthma cases quit their trades more often than those who did not meet the case definitions (however, neither of these comparisons were statistically significant).

Interestingly, compared to subjects who didn’t meet the case definitions, subjects who met *either* the asthma or the "bronchitis" case definition after visit 2 were more likely to report remission of bronchitis symptoms (i.e. present at visit 1, but not present at visit 2) (p<0.001). In addition, both case groups were more likely to report persistent asthma-like symptoms (p<0.001), as well as incident asthma-like symptoms (although this result was not statistically significant – p=0.07).
Subjects who developed asthma during follow-up were more likely to have experienced a rapid increase in BHR over the first two years of employment (p=0.002), and not surprisingly had steeper methacholine slopes than the other groups. They did not differ, however, with respect to change in FEV₁.

**Multivariable analyses for predictors of asthma and “bronchitis” during follow-up**

We examined risk factors for respiratory-related physician visits during the follow-up period using multivariable modeling for each of the following dependent variables: becoming an asthma case, becoming a “bronchitis” case, number of asthma visits, and number of “bronchitis” visits. For each outcome, we modeled symptoms separately from spirometric measures because these variables were highly correlated with one another, and because we were interested in whether or not symptoms alone (i.e. data that can be gathered using only a questionnaire) were related to respiratory-related physician visits, and thus have potential as a screening tool. Similarly, two spirometry models were developed for each health outcome measure because having a rapid decrease in FEV₁ and a rapid increase in bronchial responsiveness were highly correlated and could not be modeled together. We considered all variables described in the methods section in all models. Notably, models were examined first using individual symptoms and second using the symptoms complexes described here. The models with symptom complex variables proved more informative.

In models adjusted for smoking and demographic factors but not for symptoms or spirometric measures, machinists and insulators were at increased risk for subsequent asthma (OR 2.4 for both groups), however these results were not statistically significant. In addition, machinists were more likely to have higher bronchitis visit rates; this result was marginally significant (OR 1.5, p=0.06). We did not include job designation in the full symptom and lung function adjusted models as we reasoned that if occupation was a risk factor for respiratory morbidity it would manifest itself through its impact on respiratory symptoms or reduced lung function.

The final ‘best’ model results are shown in Table 2.4. Included in all the models shown were an indicator variable to identify subjects with particularly heavy non-respiratory
physician visits (defined as greater than 12 visits per year), and variables to identify smoking behaviour at both Visit 1 and Visit 2, to control for potential confounding, as smoking was related to most of the other variables included in the models, and to the outcomes in univariate analyses.

Having a high rate of non-respiratory physician visits (>12 per year) was related to an increased risk of becoming a “bronchitis” case (OR 6.4 – 6.9 depending on the model; always statistically significant), and not surprisingly, to higher respiratory visit frequency for both health outcomes. In the multivariable models, smoking was seldom a significant risk factor, however quitting smoking between Visit 1 and Visit 2 was suggestive of a relationship with developing asthma during follow-up in spirometry models (OR 4.5, 95% CI 0.9 to 22.8), as well as in symptoms models (OR 4.2, 95% CI 0.7 – 23.2). In contrast, taking up smoking between Visit 1 and 2 was related to developing “bronchitis” during follow-up in spirometry models (odds ratios ranging from 1.2 to 1.6, although again, not statistically significant), and in symptoms models (OR 1.2 to 2.3, not significant). Results suggest that subjects who consistently smoked at Visit 1 and 2 were less likely to visit their physicians for respiratory complaints.

Results of the ‘symptoms’ models showed that reporting of new asthma-like symptoms at Visit 2 was strongly and significantly related to both asthma health outcomes (developing asthma and frequency of asthma physician visits), and marginally, to developing “bronchitis” during the follow-up. Reporting chronic bronchitis symptoms at Visit 1, but not at Visit 2 was strongly related to becoming a “bronchitis” case, and to increased visit rate for “bronchitis”.

The lung function models indicated that a large increase in bronchial responsiveness between Visit 1 and Visit 2 was strongly associated with subsequently becoming an asthma case (OR 8.2, 2.4 – 28.5) and with more frequent visits for both asthma and “bronchitis”. Baseline bronchial hyperresponsiveness was also a risk factor in all models (although not always statistically significant), especially for increased asthma visit rate. In contrast, neither baseline nor rapid decline in lung function were important risk factors for any of the outcomes modeled.
The sensitivity of having a rapid increase in BR for identifying individuals who met the asthma case definition was 38% (Positive Predictive Value 25%), and the specificity was 93% (Negative Predictive Value of 96%). For incident asthma symptoms between Visit 1 and 2, the sensitivity for identifying asthma cases was 25% (PPV 10%), and the specificity was 86% (NPV 95%). We also calculated the sensitivity of reporting symptoms of chronic bronchitis at baseline for identifying "bronchitis" cases at 50% (PPV 23%) and the specificity was 87% (NPV 96%).

**Sensitivity analyses**

We conducted several sensitivity analyses to ensure our final results were as robust as possible. Firstly, we attempted to use a “bronchitis” case definition of 2 visits in a sliding 365 day window instead of 3 (to match the asthma case definition), and 24% of the cohort met this definition. However, these models were not as informative as those where we used 3 visits in one year as the case definition. We also tried using a case definition where we removed ICD-9 code 466, in addition to one where we removed ICD-9 code 786. Again, the interpretation of the results did not change; however, with ICD-9 code 466 removed the odds ratios for the originally significant predictors increased, and in both new scenarios, there were fewer “bronchitis” cases. There was no change in odds ratios with ICD-9 code 786 removed. For these reasons, we preserved our original, more inclusive case definition for “bronchitis”.

Although symptoms and spirometric measures were highly correlated, we tried putting them together in the multivariable models. There were no substantive changes in the effect estimates, although the results indicated that baseline BHR and rapid increase in BR were the strongest predictors (i.e. more important than any respiratory symptoms).

Excluding the 10 subjects who had self-reported asthma at Visit 1 or 2 (or including indicator variables in the models to identify these subjects) did not result in any substantive changes in most effect estimates; however, confidence intervals were wider. Interestingly, only 4 of these individuals subsequently met the asthma case definition, and 3 met the “bronchitis” case definition. One notable change was that baseline BHR was no longer predictive of subsequent asthma, presumably because many of the subjects with baseline PC20 less than 8 mg/ml were excluded.
We also attempted to group asthma and "bronchitis" outcomes to model the development of either asthma or "bronchitis" and the frequency of any respiratory visits. Not surprisingly, these models had effect estimates that were intermediate for those found from asthma or "bronchitis", and the confidence intervals were narrower due to increased power. Overall, the same risk factors as we found in our separate models (i.e. increase in BR, baseline BHR, chronic bronchitis symptoms at Visit 1, asthma-like symptoms at Visit 2) were significant in the grouped models. In addition, reporting asthma-like symptoms at Visit 1 was related to an increased respiratory visit rate (OR 1.6, 95% CI 1.0 – 2.4).

Discussion

Our results suggest that early reporting of respiratory symptoms, as well as the presence of baseline airway hyperresponsiveness and a large change in bronchial responsiveness (over the first 2 years of employment), are all related to subsequently higher physician utilization for both asthma and “bronchitis”.

In particular, a rapid (clinically relevant) increase in bronchial responsiveness (BR) was related to an 8-fold increased risk of becoming an asthma case. This gives us confidence in our choice of case definition, as the presence of hyperresponsiveness is a physiologic component of asthma (34), and recommended by some researchers as the “gold standard” for asthma diagnosis (31). In addition to being a component of asthma itself, BHR is also a known risk factor for the development of asthma and related symptoms (32), however some studies have not found longitudinal relationships with respiratory symptoms (34). We cannot address the predictive power of BHR for later development of symptoms as of yet, but when the final stage of data collection is finished for the overall study, a comparison can be made. Linkages have also been made between BHR and more rapid decline in lung function (FEV₁) over time (30), in addition to the development of Chronic Obstructive Pulmonary Disease (COPD; of which chronic bronchitis is a manifestation), particularly as it relates to mortality (33). What is also interesting in this study is that while baseline BHR was a risk factor for the
development of "bronchitis"-related morbidity (and somewhat less so for asthma), the strongest predictor for both becoming an asthma case, as well as having more frequent asthma visits, was the rapid development of new BR, suggesting that early-adulthood changes in airway reactivity may be linked to subsequent respiratory morbidity.

In contrast, our results did not confirm our initial hypothesis that early rapid change in FEV₁ may also be predictive of subsequently higher respiratory-related physician utilization. The reason for this finding is unclear, however there is a growing body of research on the use of periodic simple spirometry in workplace surveillance that suggests that a minimum of 4-6 years of repeated measurements is required to detect a real decline in lung function (14,15,27). This is due to the high amount of variability in the spirometric method over the short-term. As time increases, the standard error of the measurements decreases, making it possible to detect a smaller, "real" decline (4). Decrements much higher than those experienced by our subjects may be required to detect an actual deviation from the normal distribution. This is true even though we expect a decline of approximately 30mL per year in healthy non-smokers, and approximately 40mL per year in smokers, and in our group the mean value was more than 60mL/year, and our "rapid decliners" had a decrement of at least 100mL/year (50).

This research suggests that the difference between our rapid decliners and others was perhaps more likely just an indicator of normal spirometry variability, and adds to the body of research suggesting that shorter-term simple spirometry measurements may not be as useful at detecting true decrements. However, since many researchers do not have the luxury of studying cohorts over 6 years, especially in young and/or transient workers (who are often the population of interest), we suggest more research into detecting rapid declines in lung function as early as possible, whether through new tests or combinations of tests. This is imperative if interventions are to be successful.

With respect to respiratory symptoms, we found an 8-fold increased risk of becoming an asthma case for those who reported asthma-like symptoms Visit 2, but not at Visit 1, suggesting that the new development of asthma symptoms early in working life could be a flag in workplace surveillance programs. This is especially true because of how we chose to define such symptoms in this study – namely by singling out respiratory symptoms specifically made worse by typical workplace irritants (dusts and fumes). A
similar odds ratio (OR 5.7, 95% CI 2.1 – 15.7) was detected in our asthma visit rate model. The benefit of examining respiratory-related physician visits using the rate models was that we gained more data with which to model (because many subjects who did not meet our case definitions still had some respiratory-related visits), narrowing confidence intervals substantially. The limitation is that we are less certain about whether or not these extra subjects did indeed have ongoing respiratory difficulty, and this is reflected in the lower odds ratios found in rate models as compared to case definition models.

Interestingly, we did not find a relationship between wheeze alone and becoming an asthma case (data not shown). This may have been due to the low number of cases and wheeze reporters in our cohort, or perhaps wheeze in young adults is not as important as a predictor as it is in children (among whom much of asthma and symptoms research takes place) (51). Alternatively, it may be because asthma in young adulthood presents with a more diverse spectrum of symptoms including cough and chest tightness, or it could be related to the fact that we used work exacerbation as part of our ‘asthma-like’ symptoms definitions.

Subjects who reported symptoms of chronic bronchitis (cough and phlegm) at baseline were approximately seven times more likely to meet our “bronchitis” case definition, however these symptoms at Visit 2 were not important, and in fact had an odds ratio below 1.0 (not significant). This is also highlighted in Table 2.3, where we see that people who developed “bronchitis” during the follow-up were more likely to report remission of chronic bronchitis symptoms (i.e. present at Visit 1 but not at Visit 2). This is an unexpected finding – it is unclear why these subjects reported their symptoms resolved when they obviously still had enough respiratory trouble to visit their physicians for “bronchitis” subsequently. It could be the nature of the study – we initially tested the group before they had any substantial work experience in their chosen fields, and perhaps the culture of the workplaces they entered during those 2 years made them less likely to report any continuing trouble when they returned at Visit 2. This question can potentially be addressed when the results of the second follow-up are available.
That we found relationships with our “bronchitis” case definition is encouraging, given that it was largely exploratory and aimed at capturing some of the variability in how physicians code respiratory complaints. This shows that phlegm and cough are strong predictors of physician utilization for “bronchitis” (and perhaps also asthma). The importance of this finding has also very recently been demonstrated in a study by de Marco and colleagues (52). They found a two-fold risk for the development of COPD among those young adults who reported chronic bronchitis symptoms; this increased to a three-fold risk among those who reported chronic bronchitis symptoms both at baseline and at the 9-year follow-up visit. This relationship between symptom reporting and subsequent development of COPD is particularly applicable to our cohort because de Marco’s study was also done on relatively young adults, and thus aimed at finding earlier-life predictors that may be useful in prevention of chronic bronchitis.

With respect to occupational risk factors, we did not see any statistically significant associations between the job held in the first 2 years and subsequent respiratory-related physician visits, although the analyses did suggest a relationship between exposure to metalworking fluids (MWF), as well as being in the insulating trade in the first 2 years of employment and increased risk of subsequent asthma. Also, machinists were marginally more likely to have higher visit rates for “bronchitis”. Exposure to machining oil has been linked to faster decline in lung function (53), occupational asthma (54), and symptoms of chronic bronchitis (55) in previous studies. Our results suggest that workers exposed to MWF are visiting their physicians more frequently for respiratory complaints; however, we are not able to examine the full effect of exposure on our health outcomes as we do not yet have information on employment during the follow-up period. These limitations will be addressed when the results of this analysis are able to be compared to the final follow-up study, currently underway.

We defined subjects as asthma cases as a priority over “bronchitis” cases, even if they would have met both definitions, because we were more confident in our asthma case definition (as it was based on a practice guideline). In addition, our “bronchitis” case definition included several non-specific ICD-9 codes (most notably code 786: symptoms involving the respiratory system). It is possible that we captured physician visits for common colds, or upper respiratory tract infections. However, there are other specific ICD codes for these diagnoses that were commonly used by physicians in this
cohort. We also included ICD-9 code 466 (acute bronchitis) in our "bronchitis" codes, which could have increased the potential for misclassification. However, we included this code because we anticipated that in our young cohort, physicians would be unlikely to assign a diagnosis of chronic bronchitis or obstruction. Also, each bronchitis episode, even if it were a manifestation of a chronic problem, would still present the same as an acute bronchitis infection. In addition, our sensitivity analysis comparing "bronchitis" defined with and without codes 786 and 466 did not change the interpretation of any results. By requiring a rather restrictive three "bronchitis"-related visits in one year to become a case, we have helped to mitigate the potential for bias.

Interestingly, 8 of the 16 asthma cases would also have met the "bronchitis" case definition. This highlights the difficulty of distinguishing asthma and bronchitis (which includes a longer list of respiratory-related diagnoses) in young adults, especially when using coded administrative data. This is not surprising, given that asthma and chronic bronchitis can cause similar symptoms, and that physicians are not necessarily trained nor motivated to use all available and specific ICD-9 codes for coding respiratory-related office visits. However, encouragingly, we did detect diagnosis-specific relationships, most notably for respiratory symptoms. Subjects who reported asthma-like symptoms (at least at Visit 2) were more likely to become asthma cases, and subjects who reported symptoms of bronchitis were more likely to become "bronchitis" cases.

Using physician visit ICD-9 coding and the specified case definitions, we found an approximate annual incidence rate of 4.7 per 1000 for asthma and 5.9 per 1000 for bronchitis in following up this cohort of young industrial and construction workers. When we excluded subjects who reported asthma at baseline, this resulted in a 'new' asthma incidence rate of 3.6 per 1000. This rate is similar to the adult asthma incidence rate identified by Sama and colleagues (of 3.8 per 1000 for new asthma) in an large Health Maintenance Organization (HMO) cohort in which asthma was identified using a computer algorithm to search administrative records followed by manual chart review (56).
The potential for using rapid increases in BR, new reporting of asthma-like symptoms, or baseline reporting of chronic bronchitis symptoms to identify those who went on to meet the case definitions yielded low sensitivities and moderate specificities. This suggests that even though strong relationships between these risk factors and subsequent respiratory-related physician visits exist, many of our cases would not have been flagged as “at risk” using these criteria.

**Strengths and limitations**

Ours is one of few prospective studies aimed at discerning the complicated natural history of chronic obstructive lung diseases (COPD and asthma). These studies are important because they seek to follow the same group over time and can therefore assess incidence of disease. We are limited in this study by our small number of cases, however the prevalence of each matches what we would expect in a young, generally healthy population. Larger studies would be required to increase case numbers.

There are also several limitations to using administrative data, including potential physician coding bias, geographical access of remote individuals, and varying patterns of use among people, especially young adults (57). However, we are given some confidence in our techniques, given that we found some expected relationships. In addition, our case definitions were quite conservative compared to the few other studies that have used physician visit data (40,41). While these relationships offer hypotheses as to why our subjects visited their physicians more, we cannot be entirely sure which of these outcomes (or perhaps another) provided the impetus for physician utilization (i.e. low lung function, respiratory symptoms, asthmatic experiences). This requires more research into healthcare utilization patterns and validation studies among individuals.

It should be emphasized that this cohort is relatively young. Therefore, we are likely not detecting true chronic bronchitis, but rather general respiratory troubles related to bronchitis symptoms. Our asthma case definition, however, is more likely to capture individuals who have asthma, or at least an asthma-like syndrome. We did not have access to prescription information for this group; if we did, we could have included a
validation step where we required some number of prescriptions for bronchodilators or corticosteroids, for example.

Interestingly, this cohort visited their physicians often, approximately six times per year. Intuitively, we expected lower physician visit and hospitalization rates for a young, male, generally healthy population. Unfortunately, to our knowledge, there are no published studies examining typical rates by age and/or sex to compare to. In the Public Use Microdata File of the Canadian Community Health Survey (CCHS) administered in 2003, information on the self-reported frequency of physician visits in the year previous to the survey is available, stratified by 5-year age groups and sex (58). Given that the average age of the apprentices in 1988 was 26, their average age in 2002 (the year for which the population in the CCHS was reporting on) would have been approximately 40. The visit rate for 2002 reported for 35 to 39 year old males in the CCHS was 2.6 (SD 68.7), and for 40 to 44 year old males was 2.8 (SD 70.9). It is difficult to make a direct comparison to our data, as the number of physician visits allowable was 31 (i.e. answers above this number were assigned a value of 31), and our visit rates were averaged over the entire follow-up period rather than just for one year. However, this does suggest that our group may be more frequent visitors to their physicians than might be expected. Since the majority of physician visits were for injuries and musculoskeletal problems, we can speculate that these young male adults were involved in physical accidents fairly often (i.e. sporting injuries, perhaps workplace injuries). Our estimate for physician visit rate may have been a slight overestimate due to how we defined one “visit”; we counted a separate visit for each encounter with a different date and ICD-9 code. Therefore, in some cases, 2 visits were counted on the same day where the diagnosis code was different. However, we did this so that we would not delete diagnostic information and miss respiratory visits, and if we limit the dataset to only one visit allowed per day, we only decrease our rate estimates by approximately 12%. Further research should be done to quantify typical rates among specified populations in the BCHLD.

While it would appear that we are limited in our knowledge of confounding factors that may exist during the follow-up period during which we have no contact with subjects, this is actually a main goal of the study. One of our goals was to assess the utility of
using an administrative database to follow the same group over time; our results suggest that this may be possible. Statistically significant results were found for many expected relationships, and thus are unlikely to have arisen by chance.

In summary, we have found that early signs of respiratory trouble among young adults, including baseline and rapid change in bronchial responsiveness and respiratory symptoms, are related to the development of asthma and bronchitis later in life. This has broad implications for the use of workplace screening programs to help prevent obstructive lung diseases. We plan to compare these results to our final follow-up of this cohort, currently underway, in order to draw conclusions about the extent to which administrative data analysis identifies those with true respiratory disease. Our results suggest that individuals at risk of respiratory disease can be follow-up over time using respiratory-related physician visits, and future research should focus on examining this potential in other similar databases.
Figures and Tables

Figure 2.1 Distribution of physician visit type using ICD-9* code groups, by body system£

* International Classification of Diseases, 9th revision.
£ 'Other' category includes neoplasms, endocrine disorders, diseases of the blood & circulatory system, congenital anomalies, complications of pregnancy, as well as ill-defined ICD9-codes. Total number of physician visits represented = 21,387 over a mean follow-up time of 12 years for 281 subjects.
Figure 2.2 Distribution of hospital admission type (overnight or same day)† using ICD-9* code groups, by body system

† 'Same day' here refers to hospitalizations that have the same admission and discharge date. Overnight means the patient stayed for at least one night in hospital. There were 307 total hospitalizations for a cohort of n=281.

* International Classification of Diseases, 9th revision.
Table 2.1 Physician visit, hospitalization, and workers' compensation follow-up results (1991 – 2004)

<table>
<thead>
<tr>
<th></th>
<th>No respiratory disease during follow-up</th>
<th>Met asthma case definition during follow-up†</th>
<th>Met “bronchitis” case definition during follow-up¶</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n of subjects</td>
<td>245</td>
<td>16</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Duration of follow-up, years (mean, range)</td>
<td>12.0 (4.7-13)</td>
<td>12.2 (6.8-13)</td>
<td>12.1 (8.3-13)</td>
<td>0.7</td>
</tr>
<tr>
<td>Workers' compensation claims, n (mean, range)*</td>
<td>2.9 (0-15)</td>
<td>3.3 (1-6)</td>
<td>2.8 (0-5)</td>
<td>0.3</td>
</tr>
<tr>
<td>Hospital admissions, all causes (mean, range)*</td>
<td>0.9 (0-7)</td>
<td>2.4 (0-23)</td>
<td>2.4 (0-7)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Physician visits, all cause, n (mean, range)</td>
<td>69 (1-428)</td>
<td>105 (24-451)</td>
<td>158 (24-442)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physician visit rate, all causes, visits/year (SD)</td>
<td>5.8 (5.6)</td>
<td>8.4 (7.7)</td>
<td>14 (12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asthma visits, n (mean, range)</td>
<td>0.09 (0-3)</td>
<td>7.8 (2-21)</td>
<td>0.7 (0-3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asthma visit rate, visits/year (SD)</td>
<td>6.3 x 10⁻³ (0.03)</td>
<td>0.6 (0.5)</td>
<td>0.06 (0.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bronchitis visits, n (mean, range)</td>
<td>1.3 (0-8)</td>
<td>6.1 (0-17)</td>
<td>8.3 (3-44)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bronchitis visit rate, visits/year (SD)</td>
<td>0.11 (0.14)</td>
<td>0.5 (0.4)</td>
<td>0.8 (1.1)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

† Refers to those people who met the case definition of at least 2 asthma physician visits in a one-year sliding window.
¶ Refers to those people who met the case definition of at least 3 "bronchitis"-related physician visits in a one-year sliding window.
*There were no respiratory-related workers' compensation claims. 1 subject had 1 asthma hospitalization, and 1 subject had 1 "bronchitis" hospitalization.
Table 2.2 Baseline (Visit 1*, V1) characteristics of respiratory cases compared to those who did not develop respiratory disease during follow-up (1991 – 2004)

<table>
<thead>
<tr>
<th></th>
<th>No respiratory disease during follow-up</th>
<th>Met asthma case definition during follow-up†</th>
<th>Met “bronchitis” case definition during follow-up‡</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n of subjects (total=281)</td>
<td>245</td>
<td>16</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>% female</td>
<td>2%</td>
<td>6%</td>
<td>10%</td>
<td>0.09</td>
</tr>
<tr>
<td>Age at Visit 1 (mean)</td>
<td>25 yr.</td>
<td>26 yr.</td>
<td>29 yr.</td>
<td>0.2</td>
</tr>
<tr>
<td>% non-Caucasian</td>
<td>5%</td>
<td>6%</td>
<td>5%</td>
<td>0.8</td>
</tr>
<tr>
<td>% atopic</td>
<td>42%</td>
<td>63%</td>
<td>45%</td>
<td>0.3</td>
</tr>
<tr>
<td>% predicted FEV₁ (mean)</td>
<td>102%</td>
<td>98%</td>
<td>97%</td>
<td>0.07</td>
</tr>
<tr>
<td>% with PC₂₀ ≤ 8 mg/mL</td>
<td>10%</td>
<td>19%</td>
<td>30%</td>
<td>0.02</td>
</tr>
<tr>
<td>History of asthma (%) :</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Current asthma (self-report, V1)</td>
<td>1%</td>
<td>25%</td>
<td>15%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>▪ Family history §</td>
<td>7%</td>
<td>13%</td>
<td>20%</td>
<td>0.06</td>
</tr>
<tr>
<td>▪ Childhood history £</td>
<td>7%</td>
<td>31%</td>
<td>5%</td>
<td>0.008</td>
</tr>
<tr>
<td>Smoking status:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Current smoker (V1)</td>
<td>35%</td>
<td>31%</td>
<td>30%</td>
<td>0.9</td>
</tr>
<tr>
<td>▪ Ex-smoker (V1)</td>
<td>17%</td>
<td>25%</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Job title:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Machinist</td>
<td>33%</td>
<td>50%</td>
<td>30%</td>
<td>0.6</td>
</tr>
<tr>
<td>▪ Electrician</td>
<td>29%</td>
<td>19%</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>▪ Insulator</td>
<td>17%</td>
<td>25%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>▪ Construction painter</td>
<td>21%</td>
<td>6%</td>
<td>20%</td>
<td></td>
</tr>
</tbody>
</table>

* Visit 1 (V1) refers to the first testing time, which occurred in 1988.
† Refers to those people who met the case definition of at least 2 asthma physician visits in a one-year sliding window.
‡ Refers to those people who met the case definition of at least 3 “bronchitis”-related physician visits in a one-year sliding window.
§ Self-report of either parent having ever had asthma.
£ Self-report of asthma before age 16.
Table 2.3 Early changes in respiratory health and behaviors over the first two years of apprenticeship

<table>
<thead>
<tr>
<th>n of subjects (total=281)</th>
<th>No respiratory disease during follow-up</th>
<th>Met asthma case definition during follow-up</th>
<th>Met “bronchitis” case definition during follow-up</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>245</td>
<td>16</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

**Behaviours**

- Quit smoking\(^*\) 3% 19% 0% 0.2
- Left the trade before V2 (%) 7% 13% 15% 0.2

**Symptoms**

- **Chronic bronchitis\(^*\)**
  - Persistent (%) 5% 6% 15% 0.1
  - Incident (%) 10% 13% 5% 0.7
  - Remission (%) 7% 13% 35% <0.001

- **Asthma-like\(^*\)** (%)
  - Persistent (%) 7% 38% 20% <0.001
  - Incident (%) 12% 25% 25% 0.07
  - Remission (%) 9% 0% 10% 0.6

**Pulmonary function variables**

- Rapid decline in FEV\(_1\)\(^\|\|\) (%): 32% 38% 35% 0.9
- Change in FEV\(_1\), V1 to V2: -65mL/yr. -80mL/yr. -65mL/yr. 0.8
- Rapid increase in BHR\(^\|$\) (%): 7% 38% 10% 0.002
- Change in methacholine slope, V1 to V2\(^\|\) -8 mg/mL -420mg/mL 19mg/mL 0.01

\(^*\) 9 subjects took up smoking. 1 subject took up smoking and then quit before V2.
\(^\|\) Decline in FEV1 between Visit 1 and Visit 2 of ≥100mL/yr
\(|\|\) An increase in bronchial responsiveness resulting in a shift in PC\(_{20}\) by more than one dose category
\(^*\) 'Yes' to chronic cough or phlegm – for longer than 3 months of the year, present for 2 years
\(^\|\) 'Yes' to one or more of: usual cough (aggravated by dust or fumes), wheeze apart from colds (aggravated by dust or fumes or worse at night), or chest tightness associated with shortness of breath (aggravated by dust or fumes)
\(|\) Larger negative numbers mean a subject was more responsive to methacholine at Visit 2. A positive number indicates that they became less responsive.
Table 2.4 Odds ratios from multivariable models* examining asthma and “bronchitis” defined in two different ways

<table>
<thead>
<tr>
<th>Symptom models</th>
<th>Asthma</th>
<th>“Bronchitis”</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case definition</td>
<td>Visit rate</td>
</tr>
<tr>
<td><strong>Symptom models</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Chronic bronchitis symptoms ‡</td>
<td>2.0 (0.4 – 10.7)</td>
<td>3.5 (0.8 – 15.2)</td>
</tr>
<tr>
<td>o V1</td>
<td>1.5 (0.3 – 6.9)</td>
<td>1.5 (0.5 – 4.8)</td>
</tr>
<tr>
<td>• Asthma-like symptoms §</td>
<td>1.2 (0.3 – 4.5)</td>
<td>1.1 (0.4 – 3.6)</td>
</tr>
<tr>
<td>o V1</td>
<td>7.8 (2.2 – 27.1)</td>
<td>5.7 (2.1 – 15.7)</td>
</tr>
<tr>
<td><strong>Spirometry models</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• FEV₁ decile, V1</td>
<td>0.8 (0.4 – 1.2)</td>
<td>0.9 (0.5 – 1.4)</td>
</tr>
<tr>
<td>• PC20 ≤ 8mg/mL, V1</td>
<td>2.9 (0.7 – 12.6)</td>
<td>4.5 (1.3 – 14.9)</td>
</tr>
<tr>
<td>• Rapid increase in BR OR †</td>
<td>8.2 (2.4 – 28.5)</td>
<td>6.5 (1.7 – 24.9)</td>
</tr>
<tr>
<td>• Rapid decline in FEV₁</td>
<td>1.4 (0.4 – 4.5)</td>
<td>0.7 (0.3 – 1.9)</td>
</tr>
</tbody>
</table>

*All models also included current smoking (V1 & V2), and an indicator variable for high physician visit rate. No other potential predictor variables described in the methods had a significant effect on the estimates.

‡ ‘Yes’ to chronic cough or phlegm – for longer than 3 months of the year, present for 2 years
§ 'Yes' to one or more of: usual cough (aggravated by dust or fumes), wheeze apart from colds (aggravated by dust or fumes or worse at night), or chest tightness associated with shortness of breath (aggravated by dust or fumes)
† Rapid increase in bronchial responsiveness (BR) and rapid decline in FEV₁ (forced expiratory volume in 1 second) were highly correlated and could not be modeled together. Estimates for covariates presented are from the model with rapid increase in BR; they did not change substantially when rapid decline in FEV₁ was modeled instead.
References


**CHAPTER 3: THE POTENTIAL FOR BIAS IN PHYSICIAN CODING OF RESPIRATORY DISEASE²**

**Introduction**

The purpose of this section is to present the results of some basic exploratory analyses on the relationships between types of respiratory-related physician diagnoses and demographic and geographic variables. These were not examined in detail via multivariable models because the dependent nature of these data (correlation between visits by the same subjects) was not compatible with the analysis chosen for the larger study.

Two other broad analyses regarding the patterns of physician utilization were completed. For the first, it was hypothesized that there may be differences in how physicians code respiratory visits. For example, we may expect that a pulmonary specialist would apply more specific codes than a general practitioner who may have only broad knowledge of the diagnosis and treatment of respiratory illness. More specifically, some researchers have noted diagnostic biases between Chronic Obstructive Pulmonary Disease (COPD) and asthma based on gender; physicians are more likely to assign a diagnosis of COPD to men (1) and asthma to women (2). In addition, COPD is generally regarded as a disease of older adulthood; therefore we may expect to see reluctance in physicians to apply the diagnosis in younger adults.

Secondly, we hypothesized that geography may play a part in how respiratory visits are coded. This may manifest in a number of ways. In a small community, many people may visit the same physician, who may have a specific set of codes that he or she is familiar with. This could lead to the same respiratory diagnostic codes being applied to varying manifestations of disease and/or symptoms. Although this example is related to a bias on the part of the physician, there may also be real reasons for geographical differences in respiratory disease. Exposure to air pollutants common in large cities is

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² A version of this chapter will be submitted for publication. Peters CE, Demers PA, Sehmer J, Kennedy SM. "The potential for bias in physician coding for respiratory disease".

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other hand, it has been reported that rural dwellers may experience more asthma and chronic bronchitis, potentially due to differences in occupation, health behaviours such as smoking and diet, varying allergen exposures, or higher particulate exposure from industrial activities or wood smoke (4).

**Methods**

**Physician visits examined individually**

Our first step was to examine predictors of receiving specific diagnostic codes at each visit individually. For example, in this manner, we could examine age at time of each visit as it relates to type of code received, rather than just age of a person at a fixed point in time. In order to examine relationships between demographic characteristics and how respiratory diagnostic codes are assigned, we grouped ICD-9 codes (International Classification of Diseases, 9th Revision) into four main categories: acute bronchitis, asthma, other bronchitis and obstruction, and miscellaneous respiratory symptoms.

The ICD-9 respiratory codes included in each category are shown in Table 3.1. We looked at the relationship between respiratory diagnostic code and age, sex, atopic status, race, year and season of diagnosis, job title, and smoking status (at Visit 2 to have the latest possible known status). Descriptive statistics, including Chi-squared or Fisher's exact test, and the Wilcoxon rank-sum test (depending on the comparison) were performed using SAS-PC version 9.1 (SAS Institute, Cary, NC).

**Respiratory visit diagnoses grouped into categories**

As we were also interested in patterns of physician coding at the subject level, we limited our study group to those individuals who had at least 2 respiratory visits at any time during their follow-up. Subjects were “assigned” to a category of codes if greater than 50% of their respiratory visits fell into that category. If no one category comprised more than 50% of the codes, then subjects were assigned to a “mixed” diagnosis class. This analysis is a slightly different way of examining the potential for bias in respiratory code assignment — it allows us to look at the distribution of codes assigned to each
person. For example, we can see if there are particular characteristics of a subject that is almost always coded as ‘asthma’, versus one who may receive many different and mixed diagnosis codes. Again, we were interested in the effects of age, sex, race, atopic status, job title at Visit 1, and smoking status, in addition to spirometric measures, and family and personal history of asthma.

Geographic influences on respiratory diagnosis

In order to investigate if accessing healthcare in different areas of British Columbia had an effect on what kind of respiratory code a subject was assigned, we used the first 3 digits of their postal code at the time of each visit. In this way, we examined each visit individually, rather than each subject. We matched each 3 digit postal code (which denotes a ‘Forward Sorting Area’ for Canada Post mailing system purposes), with its corresponding city. We intuitively grouped towns and cities into 3 categories (urban, rural, and medium-sized or ‘mixed’). We assigned towns that may not be exceptionally large themselves, but were in close proximity to an urban centre, as urban (for example, Sidney or Port Coquitlam). We placed towns that might be rather large, but were relatively far from urban centres in the medium or ‘mixed’ category (for example, Abbotsford, Penticton). A full listing of the categorization is provided in the Results.

Results

For our analysis of predictors of respiratory diagnosis code category, 347 of a possible 356 subjects were linked to the healthcare utilization database and thus were available for analysis (97%). There were 216 subjects with at least one respiratory-related visit, and 132 had at least 2 visits (40% of subjects).

Results from examining visits individually

First, we attempted to examine physician’s specialty as it related to the type of code used. Although only 41 visits (out of 762 total) were attended by an internal medicine specialty (where most pulmonary specialists would be coded), we noted some interesting relationships (refer to Table 3.1). Our numbers are small, but specialists
were significantly more likely to code a visit as chronic bronchitis (ICD-9 code 491) or asthma (ICD-9 code 493) than any other code type (p<0.0001).

Results examining individual visits with respect to type of respiratory code are shown in Table 3.2. Although it must be kept in mind that each visit may not be an independent observation (as subjects may have more than one visit, introducing correlation between those visits), several interesting trends arise. Other bronchitis and obstructive diagnoses are more common among slightly older individuals (36 years old versus ~34 for other coding groups). Non-Caucasian subjects received a diagnosis of acute bronchitis more often than Caucasians, however this result was not statistically significant (p=0.1). Atopic individuals were more likely to be assigned an asthma diagnostic code than non-atopic individuals (p<0.0001). In addition, women were more likely to receive asthma diagnoses than men, in addition to “miscellaneous” diagnoses, however men’s diagnoses were spread rather evenly throughout the 4 possible diagnostic code groups. Miscellaneous diagnoses were more likely to be used in earlier years, although the difference was slight (mean year of 1996 versus 1997 for all other diagnoses, p=0.043). We did not detect a significant effect with respect to the time of year (season). Painters received asthma diagnoses more often than any other job title; we can speculate that perhaps some physicians are aware of the link between painting exposures and the development of asthma (although these painters were largely construction painters and thus unlikely to be exposed to isocyanates). Conversely, painters received other bronchitis and obstruction diagnoses least often (8% of diagnoses versus ~23% for other trades).

Results from assigning subjects to respiratory code groups

Demographic information for our subject-level analysis (among those people with at least 2 respiratory visits, n=132) is presented in Table 3.3. The largest number of people fell into the “mixed” diagnoses category (37%). There were no significant differences between the respiratory code categories with respect to sex, age, race, atopy, family history of asthma, smoking status, or job title at Visit 1. Although not statistically significant, those with mostly asthma diagnoses (>50% of visits coded as asthma) had lower baseline percent-predicted FEV₁ than any other group (94% predicted versus ~101% for all others). As seen in the analyses presented in the
previous chapter, those in the asthma group were also more likely to have baseline bronchial hyperresponsiveness, physician diagnosed asthma at Visit 1, and a childhood history of asthma.

**Results from investigation of geographic role in respiratory diagnosis type**

It should be noted that in this analysis, the fact that we analyzed on the level of individual visit rather than on the subjects themselves will have introduced some bias in these results due to correlation between visits by the same person and/or to the same physician. Three of the respiratory physician visits did not have a postal code recorded; therefore 759 visits were available for investigation and these visits took place in 37 different cities and towns in BC. Results for this analysis are shown in Table 3.4. Most visits took place in urban areas (75%). In both small and medium sized towns, the most common diagnosis was asthma, and the proportion was significantly higher in these areas than in the cities (p=0.03). The most common diagnosis in urban areas was miscellaneous respiratory symptoms.

**Discussion**

We detected many interesting relationships (both expected and unexpected) in our analysis of potential bias in diagnostic coding. There has not been much research into these issues; most of the existing knowledge on bias and/or validity in coding practices comes from the pharmaco-epidemiologic literature, where researchers attempt to follow patients with confirmed disease to assess an intervention, for example. Validity of asthma diagnoses in the Medical Services database in Quebec (compared to chart review) has been assessed in this literature as well, and found to be satisfactory (6).

We detected an expected gender difference in how individual visits were coded, but not when we examined at the subject level with 'most common' diagnosis. In the individual visit analysis, women were more likely to be diagnosed with asthma than men, and were 3 times less likely than men to be diagnosed with bronchitis. We didn’t detect this relationship when examining at the subject level (i.e. women were no more likely to have asthma as their most common diagnosis than any other respiratory code) – this
could be because women were also more likely than men to be given a miscellaneous respiratory diagnosis (ICD-9 786) than men, which may have obscured the relationship with asthma, or possibly because of the small number of women in the study. This bias in diagnosis has been noted in studies of COPD before, where women are consistently less likely to receive the diagnosis\(^1\), as well as in studies of emergency departments, where women present more with physician-diagnosed asthma than men (2).

There was a slight, but significant effect of age on diagnosis type – other bronchitis and obstruction was diagnosed more often in older people than other respiratory diagnoses. This was an expected outcome, as chronic bronchitis / COPD is typically thought of as a disease of older adulthood (7). This could mean either (or both) that older people are more likely to have chronic bronchitis, and that physicians are more likely to diagnose chronic bronchitis in older people. We did not have a large age range in our cohort (by design) – we might see more of an age effect if we had older individuals in our study group. However, we are encouraged by the fact that we only saw one diagnosis code for emphysema, and that chronic bronchitis was not diagnosed often – our cohort is quite young and while they may be experiencing early indicators of disease, it is not likely that they have COPD as of yet.

We found that internal medicine specialists were more likely to use more ‘specialized’ ICD-9 codes than general practitioners, especially with bronchitis-related codes. Specifically, none of the specialists used ICD code 490 (bronchitis, not specified as acute or chronic), whereas general practitioners used this code fairly often. This is not surprising – we would expect that a person who has some specialization with the respiratory system would be able to provide a more confident, specific diagnosis. In addition, since specialists work on a referral basis, they do not participate in primary care, and patients presenting to a specialist may be more likely to have specific disease.

We noted several promising observations that increase our confidence in using the physician visit database in the BCHLD for longitudinal follow-up studies of respiratory disease. First of all, there was no evidence of a temporal shift in how respiratory visits were coded, which could hamper our ability to detect differences between subgroups
and draw meaningful conclusions. We also did not detect a difference in the choice of ICD-9 code by season, which has been noted before among hospitalizations for respiratory problems in a Health Maintenance Organization (HMO) study in the Pacific Northwest (8).

In an administrative population-based study by Kraut and colleagues in Manitoba, rural residents were less likely to have physician-diagnosed asthma than city-dwellers (9). In our analysis, we found the opposite effect, where asthma diagnoses were used more often in medium and small towns more than in the city. This could be partly due to the fact that urban physicians use ICD code 786 (miscellaneous respiratory symptoms) more often than rural physicians. The reasons for these coding choices are not clear — they could reflect a greater knowledge of varied respiratory diseases in smaller, more blue-collar areas than in the cities. The higher prevalence of asthma diagnoses in rural areas could also reflect higher particulate exposures (i.e. from wood smoke or oil and gas operations).

Another factor is that codes are assigned differently in the physician visit database compared to the hospital admissions database. Physician visits are coded by a variety of different people – the code may be chosen by the attending physician, or by a nurse or assistant who attempts to match the billing information with the closest diagnostic code. In addition, only one code can be assigned for each billed transaction in the physician visit files. Hospital visits, however, are assigned codes by trained coders, and they are permitted up to 16 different codes corresponding to primary, secondary, and complicating factors during the hospital stay. Therefore, we would expect more coding inaccuracies in physician visit codes than we would in hospital codes. This provides another potential reason for the urban/rural split in the accuracy of diagnostic codes in our study – perhaps in a clinic in a smaller town, physicians themselves are more likely to assign diagnostic codes and therefore be more accurate. Urban clinics may be larger and busier, increasing the potential that an assistant, or someone who only sees the chart and not the patient, coded the transaction. These are questions that should be addressed in future research using the BCLHD.
Many interesting patterns emerged in this data with respect to respiratory diagnosis type among subjects in our study, including more frequent diagnosis of bronchitis and other obstruction among men and older people. Further research is needed to investigate the reasons for these patterns, using large BC-based populations. We cannot distinguish whether the source of “bias” or “noise” in ICD coding patterns are due to incorrect clinical diagnoses, incorrect codes even in the presence of a correct diagnosis, or clerical error, and we recommend more research into these issues in administrative database research (10). We were limited by our small cohort, especially our small number of women, in addition to our lack of postal code detail for more meaningful spatial comparisons.
### Tables

Table 3.1 ICD-9 code groupings devised to examine factors influencing how physician visits are coded, 1991 – 2004

<table>
<thead>
<tr>
<th>Type of diagnosis</th>
<th>ICD-9 codes included</th>
<th>Family physician visits n (% of total)</th>
<th>Specialist visits n (% of total*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total n visits</strong></td>
<td></td>
<td>721</td>
<td>41</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>466.x: Acute bronchitis and bronchiolitis</td>
<td>181 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>Other bronchitis and obstruction</td>
<td>490.x: Bronchitis not specified as acute or chronic</td>
<td>4 (0.6%)</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td></td>
<td>491.x: Chronic bronchitis</td>
<td>146 (20%)</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td></td>
<td>492.x: Emphysema</td>
<td>4 (0.6%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>496.x: Chronic airway obstruction, not otherwise specified</td>
<td>11 (1.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Asthma</td>
<td>493.x: Asthma</td>
<td>171 (24%)</td>
<td>23 (56%)</td>
</tr>
<tr>
<td>Miscellaneous respiratory symptoms</td>
<td>786.x: Symptoms involving the respiratory system and other chest symptoms</td>
<td>207 (29%)</td>
<td>14 (34%)</td>
</tr>
</tbody>
</table>

*% specialist refers to the percentage of visits in each category attended by an internal medicine specialist (which is how pulmonary specialists are usually coded). Significant difference was noted (p<0.0001).
Table 3.2 Results from examining physician visits with respiratory diagnostic codes individually* (numbers in brackets are ICD-9 codes)

<table>
<thead>
<tr>
<th></th>
<th>n visits</th>
<th>Asthma (493)</th>
<th>Acute bronchitis (466)</th>
<th>Other bronchitis/obstruction (490-492, 496)</th>
<th>Misc. respiratory symptoms (786)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n of visits</td>
<td>762</td>
<td>194</td>
<td>181</td>
<td>166</td>
<td>221</td>
<td>-</td>
</tr>
<tr>
<td>Age at each visit, mean</td>
<td></td>
<td>35</td>
<td>34</td>
<td>36</td>
<td>34</td>
<td>0.02</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Caucasian</td>
<td>703</td>
<td>26%</td>
<td>23%</td>
<td>22%</td>
<td>29%</td>
<td>0.1</td>
</tr>
<tr>
<td>• Non-Caucasian</td>
<td>59</td>
<td>19%</td>
<td>36%</td>
<td>15%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Atopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>• Atopic</td>
<td>385</td>
<td>33%</td>
<td>22%</td>
<td>19%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>• Non-atopic</td>
<td>377</td>
<td>18%</td>
<td>25%</td>
<td>25%</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>• Females</td>
<td>52</td>
<td>38%</td>
<td>17%</td>
<td>8%</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>• Males</td>
<td>710</td>
<td>25%</td>
<td>24%</td>
<td>23%</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Year of visit (mean)</td>
<td>-</td>
<td>1997</td>
<td>1997</td>
<td>1997</td>
<td>1996</td>
<td>0.04</td>
</tr>
<tr>
<td>Season</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Winter</td>
<td>244</td>
<td>24%</td>
<td>22%</td>
<td>20%</td>
<td>34%</td>
<td>0.2</td>
</tr>
<tr>
<td>• Spring</td>
<td>193</td>
<td>22%</td>
<td>30%</td>
<td>21%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>• Summer</td>
<td>130</td>
<td>32%</td>
<td>21%</td>
<td>22%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>• Fall</td>
<td>195</td>
<td>26%</td>
<td>23%</td>
<td>25%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Job title</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>• Machinist</td>
<td>289</td>
<td>21%</td>
<td>25%</td>
<td>29%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>• Electrician</td>
<td>212</td>
<td>26%</td>
<td>27%</td>
<td>21%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>• Insulator</td>
<td>136</td>
<td>23%</td>
<td>20%</td>
<td>20%</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>• Painter</td>
<td>125</td>
<td>37%</td>
<td>18%</td>
<td>8%</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>Smoking status (V2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>• Current smoker</td>
<td>263</td>
<td>20%</td>
<td>24%</td>
<td>29%</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>• Ex-smoker</td>
<td>140</td>
<td>45%</td>
<td>16%</td>
<td>14%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>• Non-smoker</td>
<td>304</td>
<td>21%</td>
<td>29%</td>
<td>18%</td>
<td>32%</td>
<td></td>
</tr>
</tbody>
</table>

*"Individually" refers to the fact that each physician visit was examined as an independent observation. 12 people missing V2 data for a total of 55 missing visits; therefore n subjects=335, n visits=707
Table 3.3 Demographic information by most common respiratory diagnosis code (among subjects with ≥2 respiratory visits*, numbers in brackets are ICD-9 codes)

<table>
<thead>
<tr>
<th>Respiratory code category most often diagnosed</th>
<th>Asthma (493)</th>
<th>Acute bronchitis (466)</th>
<th>Other bronchitis/obstruction (490-492, 496)</th>
<th>Misc. respiratory symptoms (786)</th>
<th>Mixed† diagnoses</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n of subjects (total=132)</td>
<td>16 (12%)</td>
<td>23 (17%)</td>
<td>12 (9%)</td>
<td>32 (24%)</td>
<td>49 (37%)</td>
<td>-</td>
</tr>
<tr>
<td>% Female</td>
<td>6%</td>
<td>13%</td>
<td>8%</td>
<td>6%</td>
<td>2%</td>
<td>0.3</td>
</tr>
<tr>
<td>Age at Visit 1, mean (yrs.)</td>
<td>26</td>
<td>25</td>
<td>27</td>
<td>25</td>
<td>26</td>
<td>0.8</td>
</tr>
<tr>
<td>% non-Caucasian</td>
<td>6%</td>
<td>13%</td>
<td>0%</td>
<td>13%</td>
<td>6%</td>
<td>0.6</td>
</tr>
<tr>
<td>% atopic</td>
<td>69%</td>
<td>35%</td>
<td>42%</td>
<td>38%</td>
<td>45%</td>
<td>0.3</td>
</tr>
<tr>
<td>% predicted FEV₁ (mean)</td>
<td>94%</td>
<td>100%</td>
<td>103%</td>
<td>102%</td>
<td>100%</td>
<td>0.3</td>
</tr>
<tr>
<td>% with PC20 ≤ 8mg/mL</td>
<td>50%</td>
<td>22%</td>
<td>25%</td>
<td>9%</td>
<td>10%</td>
<td>0.006</td>
</tr>
<tr>
<td>History of asthma (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Current asthma (V1)</td>
<td>44%</td>
<td>9%</td>
<td>0%</td>
<td>9%</td>
<td>4%</td>
<td>0.001</td>
</tr>
<tr>
<td>• Family history</td>
<td>19%</td>
<td>13%</td>
<td>8%</td>
<td>6%</td>
<td>12%</td>
<td>0.8</td>
</tr>
<tr>
<td>• Childhood history</td>
<td>44%</td>
<td>13%</td>
<td>0%</td>
<td>13%</td>
<td>10%</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoking status:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Current smoker (V1)</td>
<td>38%</td>
<td>43%</td>
<td>33%</td>
<td>38%</td>
<td>27%</td>
<td>0.9</td>
</tr>
<tr>
<td>• Ex-smoker (V1)</td>
<td>13%</td>
<td>9%</td>
<td>8%</td>
<td>13%</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Job title:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Machinist</td>
<td>31%</td>
<td>44%</td>
<td>33%</td>
<td>28%</td>
<td>39%</td>
<td>0.9</td>
</tr>
<tr>
<td>• Electrician</td>
<td>38%</td>
<td>26%</td>
<td>50%</td>
<td>35%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>• Insulator</td>
<td>19%</td>
<td>13%</td>
<td>17%</td>
<td>19%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>• Painter</td>
<td>12%</td>
<td>17%</td>
<td>0%</td>
<td>19%</td>
<td>18%</td>
<td></td>
</tr>
</tbody>
</table>

*We do not include subjects with <2 visits because we are examining here the proportion of respiratory diagnostic codes that a person receives; if they had only one visit, it would always be 100%. Therefore, we are examining here on the subject level, rather than at each individual visit.
† 'Mixed diagnoses' means that no one code category was assigned more than 50% of the time for an individual.
Table 3.4 Respiratory diagnosis type by city/town size*

<table>
<thead>
<tr>
<th>Size of town/city</th>
<th>n visits</th>
<th>Asthma (493)</th>
<th>Acute bronchitis (466)</th>
<th>Other bronchitis/obstruction (490-492, 496)</th>
<th>Misc. respiratory symptoms (786)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rural £ (% of visits)</td>
<td>45</td>
<td>31%</td>
<td>22%</td>
<td>20%</td>
<td>27%</td>
<td>0.03</td>
</tr>
<tr>
<td>Medium † or mixed</td>
<td>142</td>
<td>37%</td>
<td>22%</td>
<td>16%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Urban §</td>
<td>572</td>
<td>22%</td>
<td>24%</td>
<td>24%</td>
<td>30%</td>
<td></td>
</tr>
</tbody>
</table>

*3 physician visits did not have a postal code recorded; not included here (therefore n=759 visits)
£ Rural (Castlegar, Cranbrook, Dawson Creek, Fort St. John, Kitimat, Nelson, Powell River, Terrace)
† Medium or mixed (Abbotsford, Chilliwack, Duncan, Lake Country, Langley, Maple Ridge, Mission, Penticton, Pitt Meadows, Vernon, Williams Lake)
§ Urban (Burnaby, Coquitlam, Delta, Kamloops, Kelowna, Nanaimo, New Westminster, North Vancouver, Port Coquitlam, Port Moody, Prince George, Richmond, Sidney, Surrey, Vancouver, Victoria, West Vancouver, White Rock)
References


CHAPTER 4: DISCUSSION & SUMMARY

New findings and context

In this study, we have demonstrated that early-adulthood changes in lung health and respiratory symptoms are both related to respirator-related physician visits later in life. We add to the literature on respiratory epidemiology in two main ways: 1) prospective studies of occupational cohorts with substantial follow-up times are rare – and are essential for designing effective surveillance and prevention strategies for young adults; and 2) healthcare utilization data is a relatively new tool for studying respiratory disease, and we have found that it is a useful tool for this purpose.

Research as it relates to the natural history of obstructive lung diseases

One finding of particular interest is that young people (in their 20's) who report chronic cough or phlegm were at an increased risk of more frequent physician visits for "bronchitis" later in life (through their 30's, on average). A recent study by de Marco and colleagues (1) noted a similar relationship between young adults who reported chronic bronchitis symptoms eventually going on to develop COPD, a debilitating and life-threatening disease. We also found no relationship with reporting dyspnea and subsequent disease (asthma or bronchitis), and this is likely because dyspnea is a non-specific symptom, and is usually associated with advanced disease in the case of COPD\(^1\). Subjects with respiratory symptoms (including chronic cough and phlegm) were also more likely to develop obstructive lung disease in a prospective Swedish study of older adults (2). Other studies attempting to examine symptoms have not found a relationship with the development of COPD, including the classic study by Fletcher and Peto (3).

We chose to examine asthma symptoms in our study as they related to workplace exposures by specifying that the symptom must be made worse by dust or fumes. We did not detect any relationship with the more traditional hallmark symptoms of asthma (wheeze and dyspnea). However, it is possible that by specifying that a symptom was
made worse while at work (i.e. by dust or fumes) we were able to examine subjects who were truly having regular breathing troubles. It is also possible that wheeze and dyspnea are simply not specific enough to predict long term lung trouble, as was also reported in a study by Sherman and colleagues (4). It is interesting that the new development of asthma-like symptoms was a risk factor for subsequent morbidity. This could be because at Visit 1, many of the apprentices had not had enough workplace exposures to note any relationship of symptoms to work, whereas at Visit 2 they did, suggesting that their subsequent respiratory-related physician visits may be work-related. Alternatively (or perhaps in addition), it could also be that early changes, as we postulated, have had an adverse outcome on their long-term respiratory health.

Bronchial responsiveness at baseline, and in particular a rapid increase in BR over the first 2 years, was a strong risk factor for asthma, as well as “bronchitis”, diagnoses during the follow-up. Several studies have noted a relationship between BR and accelerated decline in lung function, both among initially healthy subjects (5,6), and those with COPD (7), which could explain the relationship we found with increased respiratory-related physician visits. Bronchial responsiveness itself is a hallmark of asthma, but is problematic because it can be present in non-asthmatics as well (8). We are not aware of any studies that use rapid changes in BR as predictors of subsequent disease, therefore our results are a substantial addition to the literature in this respect.

Research as it relates to using physician visits as a tool for respiratory epidemiology

Administrative databases have many potential benefits to researchers, including minimizing selection bias and increasing sample size (9), being cost-effective, and being easy to repeat, making time trend studies less challenging (10). In our study, we were interested in using administrative data to follow the same group over time, rather than the traditional use of these data to study very large populations. We have shown that it is feasible to study an at-risk occupational cohort over time with respect to their respiratory-related physician visits. In particular, we achieved a very high linkage rate for our subjects with the BCLHD (97%). We did not detect any serious biases in how respiratory visits were coded by physicians (i.e. temporal shifts or strong seasonal
patterns), which lends more credence to its utility as a sound resource. We showed that even among a relatively small group of healthy young adults, high enough respiratory visit rates and variability therein exist to detect risk factors for respiratory morbidity.

**Suggestions for future research**

This study should stimulate research in a number of different manners and fields, including policy and education with respect to the use of physician billing data and their accuracy, non-specific occupational exposures and their effect on early life changes in lung health, and surveillance methods for occupational respiratory disease. Outlined below are several suggestions in more detail.

**Comparison with active follow-up methods**

This the same occupational cohort is being tested currently with respect to their lung health in exactly the same manner as at Visits 1 and 2 in the late 1980's. We plan to compare the results and conclusions of this study with those of the active follow-up in the near future. From this comparison, we will assess our hypotheses about the benefits and limitations of using respiratory-related physician visit data. For example, we will be able to see if our case definitions for asthma and “bronchitis” have identified subjects with those diseases as measured by clinical means (i.e. spirometry and methacholine challenge testing, respiratory symptoms, and/or self-reported diagnosis). We will be able to see how sensitive and specific our methods are for diagnosis as well.

We will also be able to add a longitudinal dimension to our risk factors. As of right now, we have only had contact with the apprentices at the start of their career, and have no knowledge regarding their place of residence, smoking habits, or occupational exposures between Visit 2 and the current follow-up. We may be able to look at finer details in the respiratory-related physician utilization data with this kind of information; for example, we might be able to assess incident asthma from a workplace exposure if we know when that job was started and when the subject met our case definition.
One particular aspect that we are interested in examining is the relationship between early rapid decline in lung function and lung function later in life. We did not identify rapid decline in lung function as a risk factor for subsequent respiratory morbidity, however we are still unsure of how this may have affected subsequent lung function in our subjects. Other studies have noted a non-linear effect in lung function decline in young workers; Wang and colleagues report on a cohort of new young coal miners, many of whom experienced a rapid decline in $\text{FEV}_1$ during their first year of mining, a plateau during their second year, and a partial recovery starting in their third year (11). These findings are corroborated by the coal mining study done by Seixas et al (12). Although our study is not about coal mining exposures in particular, we can still speculate that perhaps a similar phenomenon has occurred among our cohort (i.e. rapid declines in lung function early in the working life may level off after a few years). We can make this connection because, as Wang notes, coal miners are not developing mining-related diseases over the time span of the study (i.e. pneumoconioses or emphysema) – these diseases have very long latencies. Early adulthood exposures to dusts or fumes (that occur in many varied working environments) may cause an inflammatory response in the large or small airways, leading to a reduction in the caliber of the airway early on, however this could be at least partly reversible (11).

When we have complete follow-up lung function data from our current study, we can examine whether early decrements, that seem unrelated to any specific workplace exposure, are related to subsequent low lung function.

**New studies on healthcare utilization data for epidemiology**

Our research suggests that there is the potential to examine more fully why individuals do or do not access the healthcare system for respiratory complaints. There could be many subjects in this study with respiratory problems who never decide to go to their physician for help, and we haven’t been able to capture those people in our current analysis. In addition, it seems that this particular cohort has an unusually high physician visit rate (mean of 6 visits per year); however, we are not aware of any peer-reviewed studies that have characterized the patterns of use, especially among young men. We have also detected other interesting patterns among our subjects (i.e. high utilization rates for injury and mental health issues) that could be examined as well. We suggest
that more research into physician visit patterns, especially among young adults, is
needed in order to assess the true burden of disease using the BCLHD.

Our study has shown that we likely chose a reasonable case definition for our disease
outcomes (because we did detect expected relationships), but we are not sure to what
extent physicians follow the clinical practices guideline for asthma treatment, nor if
there is a better way to capture chronic bronchitis in a young population. There have
been few studies that have attempted to assess asthma via administrative databases,
and those that do have used many different case definitions (13,14). For example,
many studies use prescriptions of asthma medication, hospitalizations, and/or
physician visits in many different combinations to decide who has “true” asthma.
However, there isn’t a gold standard for asthma diagnosis in clinical practice, let alone
in database research. A large scale research program that was able to validate disease
on several measurement scales would be ideal in assessing the validity of case
definitions in this type of research. This would also be an ideal study for assessing
validity of physician diagnosis codes in the BCLHD with respect to obstructive lung
diseases.

**Screening, surveillance and prevention studies**

Our study suggests that more research is needed into the use of screening programs
for identifying workers at risk for developing respiratory disease. For example, we have
shown that people who experience a rapid increase in bronchial responsiveness (BR)
are at a substantially higher risk of developing asthma and “bronchitis” than other
people. What we don’t know is if and how this could be prevented. For example, if we
undertake a targeted intervention to prevent the development of respiratory disease
among those at-risk individuals, would it be effective? Since we haven’t linked these
early changes to specific exposures, what would we do to actually intervene?

Questions about the necessity of monitoring changes in FEV₁ over time among at-risk
workers have been raised before (15,16). These stem mostly from the problem of
detecting a real and clinically relevant decline in lung function, especially over short
time periods, when there is so much variation both within and between people with
respect to spirometric testing (17). In fact, the American Thoracic Society (ATS)
position paper on serial lung function measurement interpretation strategies notes that "test variability will usually far exceed the true annual decline, and reliable rates of change for an individual subject cannot be calculated without prolonged follow-up" (18). They also suggest that a lung function loss of at least 15% over one year is required before any confidence in an actual short-term loss can be ascertained. The usefulness of such a restrictive criterion is debatable - this kind of decrement in lung function over just one year is massive, and there are many subjects who would never lose lung function this fast – however this does not mean that they are not at risk of developing respiratory disease. Other researchers have had success applying the concept of the LLN (lower limit of normal) decline – flagging those individuals whose one-time FEV₁ measurement is at or below the 5th percentile of the distribution, or whose decline in lung function is in the lowest 5th percentile (19). Research also suggests that a follow-up time of 4 to 6 years is required to detect any real decline in lung function (17). This makes it especially difficult to monitor young workers, who may not remain in one workplace for such a long time, and are the prime targets for intervention. Our study indicates that better and more sensitive methods for assessing lung function may be necessary so that we can detect meaningful declines over shorter time periods. In addition, our study should spur more research into the reasons behind early rapid decline in FEV₁ noticed in studies of wide variety workplaces. This suggests that it is not one exposure that is responsible, but perhaps a non-specific response. One hypothesis suggested by Wang and colleagues is that dust exposures in early adulthood may preclude the attainment of full ventilatory capacity.
Summary

The natural histories of obstructive lung diseases (including asthma and COPD) are not well characterized. While risk factors for both conditions are well known, we still cannot predict who will go on to develop respiratory disease, given a specific set of risk factors. This study has added to current knowledge in this respect; we have shown that early career changes in bronchial responsiveness, in addition to patterns of respiratory symptom reporting, are related to respiratory-related physician visits later in life in a young, working population.

We have demonstrated that healthcare utilization data, in particular physician visit data, is of use for following a cohort over time with respect to their respiratory health. This is very encouraging, given the ease of gathering this type of data, and reduction in cost compared to traditional epidemiologic methods.

In summary, asthma and COPD are chronic diseases that are responsible for a considerable burden on the healthcare system and people of Canada. The severity of both of these diseases can be lessened by early diagnosis and treatment. Changes in lung health and respiratory symptoms early in working life may put people at risk for subsequent respiratory disease.
References


