Examining Factors Related to Diagnostic Outcomes in Shortness of Breath Patients with Prescribed Inhaler Medications

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ABSTRACT

Over 10% of deaths are attributed to lung disease. Of these, asthma and chronic obstructive pulmonary diseases (COPD) are of significant global health concern. They are the two main obstructive airway diseases (OADs) associated with shortness of breath (SOB) symptoms and accounting for over 70% of patients presenting to the family physician (FPs) or requiring breathing relief. Underdiagnoses or over-diagnosis of asthma and COPD are common in SOB patients. Recent studies have reported these as widespread misdiagnoses in family practice. Many patients with SOB symptoms presenting to their FPs are often treated with inhaled medications and sometimes without proper diagnostic workup. Pulmonary function testing (PFT) along with physical examination and patient history are recommended by the international guidelines including the Canadian Thoracic Society guideline to objectively assist in the diagnosis, differentiation, and categorization of those with OADs for proper management.

The primary objectives of this thesis are: 1) to examine care-gap in physician-diagnosed asthma and COPD in family practice (Study 1 in Chapter 3), and 2) to delineate factors associated with increased risk of spirometrically-derived diagnosis of *asthma, COPD, and the overlap syndrome or ACOS* in community patients with SOB symptoms and prescribed inhalers from FPs using pulmonary function testing (PFT) (Study #2 in Chapter 4). Understanding care gaps in clinical and individual patient's factors which are associated with a proper diagnosis or misdiagnosis of asthma and COPD in SOB patients will help FPs improve the treatment and management of community patients with SOB symptoms.

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Statement of Co-authorship

The results presented in this thesis was a secondary analysis of the Epidemiology of Shortness of Breath (EpiSOB) program. The EpiSOB study was led by Dr. William Midodzi (Memorial University) and his research team at the University of Alberta and University of Saskatoon, Canada. The two universities (that is, the University of Alberta and University of Saskatoon) funded the primary data collection and the research objectives of the EpiSOB program and are the legal custodian of EpiSOB instruments published in the appendix, the primary data and research results included in Chapter 3. The thesis was primarily conducted by Jenese Nugent (J.M.N) for training purpose to obtain her degree of Master of Science in Medicine at the Memorial University of Newfoundland under the supervision of W.K.M. J.M.N declares that, in all cases, her main contributions to this thesis are primarily: the study design, the data analysis, interpretation of the results, and the proposal submitted for the secondary analysis conducted in Chapter 4. J.M.N conceptualized the key ideas in the proposal for the study presented in Chapter 4 under the direction of W.K.M. J.M.N performed the literature search and review for the introduction section of the thesis, quality assessment and data cleaning, and the analysis of the results presented in Chapter 4. The diagnostic algorithm for asthma and COPD presented in this thesis was conducted by W.K.M and members of his research team for the EpiSOB program. W.K.M also contributed significantly to the statistical analysis presented in Chapter 4. The contributions of other committee members were generally through the provision of suggestions and corrections. Drs. Zhiwei Gao and Jamie Farrell provided feedback on refinement of ideas about clinical issues in Chapter 4 and editing of the thesis.

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List of Abbreviations

ABG	Arterial Blood Gas
ACOS	Asthma and COPD Overlap Syndrome
ACQ	Asthma Control Questionnaire
ATS	American Thoracic Society
BNP	Brain Natriuretic Peptide
BODE	Body mass index, Obstruction, Dyspnea, and Exercise
CAT	COPD Assessment Test
CCHS	Canadian Community Health Survey
CCQ	COPD Clinical Questionnaire
CDC	Centers for Disease Control and Prevention
CHMS	Canadian Health Measures Survey
CI	Confidence Interval
CIHI	Canadian Institute for Health Information
COPD	Chronic Obstructive Pulmonary Disease
CRD	Chronic Respiratory Diseases
CT	Computed Tomography
CTS	Canadian Thoracic Society
DLCO	Diffusing Capacity
ECG	Electrocardiogram
ECRHS	European Community Respiratory Health Survey
ED	Emergency Department
EPICORE	Epidemiology Coordinating and Research
EpiSOB	Epidemiology of Shortness of Breath
ERS	European Respiratory Society
FET	Forced Expiratory Time
FEV_1	Forced Expiratory Volume in one second
FP	Family Physician
FRCPL	Functional Residual Capacity Plain phase

FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Lung Disease
HF	Heart Failure
HRQL	Health-Related Quality of Life
ICS	Inhaled Corticosteroids
ICC	Intra-class Correlation Coefficient
ISAAC	International Study of Asthma and Allergies in Childhood
LAAC	Long-Acting Anticholinergic
LABA	Long-Acting Beta-Agonist
LAMA	Long-Acting Muscarinic Antagonist
MRC	Medical Research Council
NCHS	National Center for Health Statistics
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NLHEP	National Lung Health Education Program
NOAD	Non-Obstructive Airway Disease
NPHS	National Population Health Survey
OR	Odds Ratio
OAD	Obstructive Airway Disease
PAH	Pulmonary Arterial Hypertension
PDI4	Phosphodiesterase 4 Inhibitor
PEF	Peak Expiratory Flow
PFT	Pulmonary Function Testing
PHAC	Public Health Agency of Canada
QoL	Quality of Life
R	Pearson correlation coefficient
RV	Residual Volume
ROC	Receiver operating characteristic

SAAC	Short-Acting Anticholinergic
SABA	Short-Acting Beta-Agonist
SAMA	Short-Acting Muscarinic Antagonists
SD	Standard Deviation
SGRQ	St. George's Respiratory Questionnaire
SOB	Shortness of Breath
TLC	Total Lung Capacity
US	United States
VA	Alveolar Volume
VC	Vital Capacity
WAP	Written Acton Plans
WHO	World Health Organization

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List of Research Presentations

Conference Presentation

1. Jenese Nugent[1], MSc candidate, Zhiwei Gao[1], Ph.D., Deborah Gregory[1], Ph.D., Jamie Farrel[1], MD, William Midodzi[1,2], PhD
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"Epidemiology of shortness of breath in inhaler medication users"
PriFor 2016 Conference, Sheraton Hotel Newfoundland, St. John's, Newfoundland and Labrador, June 29-30, 2016.

Graduate Seminar Presentation

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[1]Memorial University, St. John's, NL, Canada. [2]University of Alberta, Edmonton, AB, Canada **"Epidemiology of shortness of breath in inhaler medication users"**
MED6400 Seminar, Memorial University of Newfoundland, November 23, 2016.

CHAPTER 1

Introduction

1.1 Background

Shortness of breath (SOB) or breathlessness also commonly referred to as dyspnea may be defined as ‘breathing discomfort’ (1). The *American Thoracic Society* (ATS) officially defines dyspnea or SOB as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity” (2). SOB is also defined as ‘an unpleasant, subjective sensation of difficult breathing’ (3).

SOB symptoms may be caused by various mechanisms related to cardio-pulmonary conditions in the body (2) and is an extremely common complaint of patients presenting to an emergency department, with these types of visits accounting for 16% to 25% of admissions that are nonsurgical (3). SOB symptoms may be due to a variety of diseases, including cardiac, pulmonary and some systemic disease, and may result in numerous detrimental outcomes.

1.2 Diseases of shortness of breath

The most common cardiopulmonary diseases causing SOB are asthma, chronic bronchitis, and emphysema (types of *chronic obstructive pulmonary disease* (COPD)), lung cancer, allergies reaction, hypertension, arrhythmias, coronary artery disease, and

heart failure. These diseases are classified into two main groups: *obstructive* (airway origin) or *restrictive* (non-airway origin).

1.2.1 SOB of obstructive airway origin

While the onset of asthma is diagnosed early in life (< 40 years), COPD is commonly diagnosed in late-life (>60 years) (4). Ponka et al. 2006 (5) in **Table 1.1** presents an overview of a study of community patients from family practice. As noted, COPD and asthma alone account for over half of the cardiopulmonary diseases that were found to be associated with SOB symptoms.

Table 1.1 Prevalence (%) of differential diagnosis of SOB by age group

Differential diagnosis	Under 45 years of age	Over 45 years of age
Asthma	31.8%	9.9%
Acute Bronchitis	21.5%	14.7%
COPD	1.5%	23.7%
Upper Respiratory Infection	6.7%	1.5%
Pneumonia	2.5%	3.3%
Other	36.0 %	46.9%

Table adapted from (Ponka & Kirlew, 2006) (5). SOB: shortness of breath,

Of those under 45 years old, approximately 32% have asthma, and 24% of those with COPD diagnosis are among those older than 45 years presenting to family practice (5). In asthmatic patients, SOB symptoms usually occur when the lining of the bronchial tubes swell, causing the airways to narrow and reduce the flow of air into and out of the lungs and is usually associated with an allergy history (6,7). The most common symptoms of COPD are SOB, excessive sputum production and chronic cough. During COPD

exacerbation, the airways are usually narrowed with increased resistance to exhaling air from the lung, resulting in air entrapment in the lung with a worsened SOB (8,9). Other diagnoses of SOB complications include acute bronchitis, upper respiratory infection, and pneumonia. Acute bronchitis, a type of upper respiratory infection, is the inflammation of the bronchi resulting in SOB, chest tightness, cough, and sputum production.

1.2.2 SOB Complications of restrictive origin

Unlike obstructive lung diseases, restrictive lung diseases are associated with a reduction in lung volume which is due to the alteration of the lung parenchyma (10). One major restrictive airway diseases that have SOB as a symptom is congestive heart failure (5). SOB in heart failure is caused by the decreased ability of the heart to fill and empty, producing elevated pressures in the blood vessels around the lung. Orthopnea (breathing difficulties when lying down) is the most common symptom associated with heart failure. In the majority of patients, this is usually caused by an Ischemic Heart Disease (11). However15.3% of patients, 45 years and older with SOB are often diagnosed with heart failure (5).

SOB is also common in patients with end-stage cancer as well as metastatic cancer that have spread to the lung; 1.3% of SOB patients are diagnosed with lung malignancies (5,11). Furthermore, due to the role of hemoglobin in oxygen delivery, anemia may also cause SOB in patients because of the impairment of oxygen delivery (12).

Though SOB is associated with anxiety, it can be difficult to determine whether SOB causes anxiety, as quite often the anxiety that accompanies SOB may create

diagnostic confusion as anxiety may cause SOB (7). Anxiety is reported to occur in 7.8% of patients with SOB who are under age 45 and 3.3% of those who are 45 years and older (5).

1.3 Pulmonary function testing

Pulmonary Function Testing (PFT) is a series of tests that are done to assess the if a patient has a lung disease of an obstructive origin, and effectiveness of the lungs in carrying out its function, that is, taking in and releasing air and how well oxygen is transferred from the alveoli to the bloodstream and surrounding tissues (13). PFT is the main diagnostic tool for evaluating the respiratory symptoms and detecting airway obstruction. A physician may order PFT for a number of reasons, such as to find the cause of SOB, diagnosis of asthma and or COPD, assess the effectiveness of treatment and its progression, checking of lung function before surgery is done, and to measure lung function after exposure to occupational chemicals (13). PFTs *(*commonly referred to as complete pulmonary function survey*)* may include: Spirometry *forced expiratory volume in one second* (FEV_1), *forced vital capacity* (FVC), and ratio FEV_1/FVC), formal lung volume measurement, vital capacity (VC), total lung capacity (TLC), RV, RV/TLC, and FRC PL), diffusing capacity for carbon monoxide (DLCO, VA, and DLCO Adj for VA), and arterial blood gases.

Spirometry is the most commonly used lung function screening test in detecting airflow limitation and is crucial in diagnosing COPD and asthma. In addition, the *Global Initiative for Chronic Lung Disease* (GOLD), and the *World Health Organization* (WHO) stated that spirometry is the most reproducible and objective measurement of airflow

limitation available. GOLD further stated that good quality spirometric measure was possible in any setting and therefore can be administered in the ambulatory setting, physician's office, emergency department, or inpatient setting (4). FVC and FEV_1 are the most important aspect of spirometry (14). FVC is the total maximal volume of air exhaled following a full inhalation While, FEV_1 is the maximal volume of air that a patient exhaled in the first second following a full inhalation. To clinically diagnosed COPD and asthma, spirometry is required. In addition, spirometry aids in differentiating between COPD and asthma and well as monitor the effectiveness of treatment.

1.3.1 PFT in COPD diagnosis

In diagnosing patients with COPD, spirometry is performed pre-bronchodilator and post-bronchodilator treatments in order to determine whether airflow obstruction and reversibility are present (partial or fully). If there is no reversibility post-bronchodilator treatment with an FEV_1/FVC ratio less than 70% as outlined in the GOLD guidelines is indicative of COPD. Though the FEV_1/FVC ratio is crucial in the diagnosis of COPD, the percent predicted-value for FEV_1 post-bronchodilator determines the severity of airflow limitation.

1.3.2 PFT in asthma diagnosis

In diagnosing asthma, the patient with SOB is assessed by spirometry. The FEV_1/FVC ratio is taken to determine if airflow limitation is present. If airflow limitation is present a bronchodilator is administered. An FEV_1/FVC post-bronchodilator measurement is then taken to assess the degree of reversibility of airflow limitation. That

is, spirometry is performed at baseline after which an inhaled bronchodilator is administered by metered-dose or nebulizer. Post-Bronchodilator spirometry is then repeated. As outlined by the *Global Initiative for Asthma* (GINA), a diagnosis of asthma in adults is an increase in FEV_1 by 12% and by at least 200ml post-bronchodilator, which suggests acute bronchodilator responsiveness.

1.3.3 Methacholine testing in asthma or airway hyper-responsiveness

A patient with SOB and showing mild or no airflow limitation pre-bronchodilator and/or post-bronchodilator, a bronco-provocation challenge using methacholine (or other acceptable bronco-provocative agents) is performed. A positive methacholine test is indicative of asthma (see Appendix T for methacholine test procedure summary).

1.4 Overview of diseases of obstructive airway origin

1.4.1 Asthma

Asthma is an airway inflammatory disease characterized by reversible airflow obstruction, bronchial hyper-responsiveness, submucosal edema, recurrent attacks of breathlessness and wheezing (6). In most cases, the presence of atopy or family history of allergies and the presence of wheezing in childhood are associated with the onset of asthma. However, not all wheezing symptoms are asthma related and not all asthma patients are present with wheezing.

The Global Initiative for Asthma (GINA, 2014) defines asthma as:

"A heterogeneous disease that is usually characterized by chronic airway inflammation. It is also defined by the history of respiratory symptoms such as

wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation" (15) (p2).

In the 2014 update, GINA reported five different phenotypes of asthma, namely, allergic asthma, non-allergic asthma, late-onset asthma, asthma with fixed airflow limitation, and asthma with obesity (15). Allergic asthma is said to be the most easily recognized asthma and often presents in childhood associating with the past and current family history of certain allergic conditions such as eczema, allergic rhinitis, and food allergies (15,16). On the other hand, non-allergic asthma usually presents itself in adults and are usually recognized by testing the sputum for allergies (cellular) markers such as neutrophils and eosinophils (15). Late-onset asthma is non-allergic which affects young and older adults, more so women than men (15), while fixed airflow limitation asthma usually occurs in a patient who has had asthma for a long period. Obesity with asthma usually manifests when patients have little or no inflammation of the airways but present with asthmatic symptoms (15).

1.4.1.1 Diagnosis

Clinical diagnosis of asthma in adult patients is based primarily on the presentation of recurrent respiratory symptoms such as SOB, wheezing, chest tightness and cough, and variable expiratory airflow limitation (15) which is often confirmed on spirometry. If spirometry results are normal (FEV_1 of 80%-120% percent predicted value) or near normal FEV_1 of >75% – 80% percent predicted value in adults) and asthma is suspected, further bronco-provocation testing by methacholine (see Appendix T), histamine, cold air or exercise is performed (15). Since other respiratory conditions may

have symptoms mimicking asthma, differential diagnostic tests may be done to rule out these conditions. Chest x-rays, allergy test (specific only to allergic asthma), biomarkers of inflammation, and defusing capacity test are usually performed (17).

1.4.1.2 Management/Treatment of Asthma

Asthma is a chronic disease that needs to be managed (6). It is often commonly under-diagnosed and undertreated (6,18,19). However, asthma is mainly treated using pharmacological methods. There are three main categories of the pharmacological treatment of asthma: controller medication, reliever medication, and add-on therapy. After diagnosis, an initial controller treatment is administered, and a stepwise approach is used in maintaining asthma control (15).

The first step in asthma management involves using an 'as-needed' inhaled Short-Acting Beta-Agonist (SABA), as a rescue inhaler. These drugs are highly effective, quick reliever of symptoms and help relieve the obstruction. Therapy is then escalated if there is evidence of persistent symptoms or uncontrolled asthma; where a regular low-dose inhaled corticosteroid (ICS) and a rescue inhaler are prescribed. The low dose ICS improves lung function, quality of life (QoL), and reduces the risk of exacerbation and asthma-related hospitalization or death. If asthma is uncontrolled a combination therapy, ICS/LABA, Long-Acting Beta-Agonist, (maintenance therapy), is given along with a SABA (as needed reliever). To control frequently exacerbated asthma, a higher level of care and add-on treatment is recommended. Nonetheless, for best management, comorbidities present must also be treated (15).

Non-pharmacological therapies play an important role in the management of asthma. The GINA states that it aims to control symptoms and minimize risks. The long-term goals are to maintain good control and normal activity levels and to minimize future risk of exacerbation, fixed airflow limitation and probable side-effects (15). Non-pharmacological asthma management is employed to reduce or remove allergen or non-allergic particles in the patient environment that may provoke a reaction or worsen/promote airway inflammation that may lead to exacerbations. Such irritants may be indoor and outdoor allergens, tobacco smoke, chemical irritants, and air pollution. The GINA indicates that to have effective asthma management, there needs to be a partnership between the asthma patient and the healthcare provider (patient-health care provider partnership) (6,15). Patients may use Written Acton Plans (WAP), a set of tailored instructions designed to help with asthma to understand their worsening symptoms and the response required. GINA recommends that asthmatic patients be provided with a written asthma action plan, appropriate for their level of asthma control and health literacy which includes: the patient's usual asthma medications; when and how to increase medications; and how to access medical care if symptoms fail to respond (15).

Parameters used in clinical practice may incorrectly classify asthma as poorly controlled or well-controlled resulting in over-treating or undertreating patients. Overestimating the severity of asthma often leads to excessive use of medication and thus increasing cost and risks by exposing patients to potential adverse drug reactions. Conversely, underestimating the severity of asthma may lead to frequent exacerbation and increased morbidity risk and death. To prevent the underestimation of asthma severity the

asthma control questionnaire (ACQ) is suggested as an assessment hence, better management of asthma.

1.4.2 Chronic obstructive pulmonary disease

Chronic Obstructive Pulmonary Disease or COPD (emphysema and chronic bronchitis) is a progressive lung disease that limits normal airflow in the lungs (20) resulting in a chronic cough, breathlessness and exercise intolerance (2,21). The Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2014) defines COPD as:

> *"A common preventable and treatable disease is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gasses"* (4) (p2).

This airflow limitation is usually irreversible in most patients with COPD. Their airflow limitation is irreversible regardless of their medication prescribed (22). GOLD further described other contributors to COPD's severity which includes frequent exacerbation and pre-existing comorbidities (4).

1.4.2.1 Diagnosis

COPD is a progressive disease and is most frequently diagnosed in people 40 years and older. To clinically diagnose COPD, it is recommended that the physician must look at the patient's history, reported symptoms, physical examination, patient predisposing factors, PFT, and radiological imaging (23). The main documented factors associated with the presence of COPD are tobacco smoking, indoor and outdoor air

pollutants and occupational dust, previous respiratory infections, family history of asthma and respiratory disease, and chemical exposures from environmental and occupational settings. Tobacco smoke, both passive and active, have been attributed to be the main cause of COPD. Since COPD develops slowly, it usually takes years of exposure (e.g., tobacco/cigarette smoking, pollutants) to develop symptoms and, therefore, the disease. Hence, the evaluation of the history of these predisposing factors is crucial (4,24,25).

There are four steps that aid in the diagnosis of COPD. PFTs, medical history, symptoms from the history and physical examination. After a diagnosis of COPD, an assessment of the disease is made by *COPD Assessment Test* (CAT), Clinical COPD Questionnaire (CCQ), *modified Medical Research Council* (mMRC) scale, and or *St George's Respiratory Questionnaire* (SGRQ) to aid determining its severity (26). GOLD advocated in the 2014 update that a clinical diagnosis of COPD be considered in any patient who has SOB, chronic cough or sputum production, and a history of the risk factor for the disease (4). Although the diagnosis cannot be based on symptoms alone as some patients are free of symptoms and/or presenting with similar symptoms to another disease (24). Therefore, patients with a history of tobacco-use/exposure and or other risk factor are recommended for further evaluated.

Spirometry is the preferred diagnostic test for diagnosis of COPD, as recommended by GOLD, along with the patients' symptoms, medical history, and physical examination (24). This confirms the presence of irreversible airflow (24–26).

Other strategies suggested by GOLD as part of the diagnosis and assessment of COPD include:

1. Chest x-rays used not as a diagnostic tool but to rule out another possible diagnosis
2. Lung volumes and diffusing capacity which helps to identify gas trapping and hyperinflation and may help determine the severity of COPD and the functional impact of emphysema, respectively
3. Oximetry and *arterial blood gas* (ABG), which evaluate the oxygen saturation and supplemental oxygen-need in the patient
4. Alpha-1 antitrypsin deficiency, a serum concentration of alpha-1 antitrypsin below 15-20% normal value strongly suggests a deficiency which may aid in the diagnosis
5. Exercise testing may be used to assess patients disability and the effectiveness of pulmonary rehabilitation, and
6. The composite score, including *Body mass index, Obstruction, Dyspnea, and Exercise* (or the BODE method) gives a better prediction of the subsequent survival than any other single component.

COPD patients are classified based on their phenotype (4,25). There are mainly four types of phenotype: non-exacerbator, mixed COPD-asthma, exacerbator with emphysema, and exacerbator with chronic bronchitis. Patients may be classified further based on the severity of COPD, that is, the degree of airflow limitation (4). The severity of the COPD (airflow limitation) in patients with FEV_1/FVC is based on the value of FEV_1 measured after a required dose of a short-acting inhaled bronchodilator (post-bronchodilator) (4). There are four grades of degree of severity levels of airflow limitation as stated by GOLD: GOLD stage 1 which is mild with a $FEV_1 \geq 80\%$

predicted; GOLD stage 2, moderate limitation with FEV_1 50–80% of predicted; GOLD stage 3, severe limitation with FEV_1 30–50% of predicted; GOLD stage 4, very severe airflow obstruction with FEV_1 <30% of predicted.

1.4.2.2 Management and Treatment of COPD

COPD is a progressive disease and is incurable. However, smoking cessation may slow the progression of the disease. Quitting smoking and supplemental oxygen are the only therapies that prolong survival in COPD patients) (8,26). As with asthma, there is also two aspects of COPD management, non-pharmacological and pharmacological therapy.

Pharmacologically COPD is treated based on its severity and phenotype (25). The aim of COPD pharmacological therapy as set out by the GOLD and Finnish guidelines are to control symptoms and improve QoL, reduce and prevent future risk for exacerbation, slow disease progression, increase exercise tolerance and reduce mortality (4,24). These therapies include bronchodilators, the combination of ICS and long-acting bronchodilators, phosphodiesterase 4 (PDE4) inhibitors or theophylline, and influenza and pneumococcal vaccination (24).

The main component of non-pharmacological therapy is respiratory rehabilitation (4,25,27) it is recommended that patients be asked to participate in a rehabilitation program immediately after or as late as three weeks after an exacerbated hospitalization (25). Aspects of rehabilitation are education (smoking cessation, education information on COPD, etc.), nutritional intervention, and exercise training (4,24,25). There are numerous benefits to be gained. Pulmonary rehabilitation is used to improve the patient's

QoL, reduce symptoms and the number of hospitalizations by exacerbation, improve exercise tolerance, reduce anxiety and depression, and improved survival (4). Other aspects of non-pharmacological therapy include oxygen therapy, non-invasive ventilation, surgical treatments (lung volume reduction surgery (only in select patients), lung transplant, bronchoscopic lung volume reduction not commonly used), and palliative care (4).

1.4.3 Asthma-COPD Overlap Syndrome

Until recently, COPD and asthma were thought of as separate diseases, and although they have clear differences, some manifestation of both coexist in some patients (28). However, it is unclear whether an overlap between COPD and asthma represents patients with coexisting COPD and asthma or an exclusive disease entity termed, *asthma-COPD overlap syndrome* (ACOS) (29). Until recently no definitive definition for this syndrome existed; however, GINA and GOLD recently collaborated and defined ACOS.

> *"ACOS is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified by the features that it shares with both asthma and COPD"*(30) (p4).

Additionally, Bujarski et al. 2015 (31) and Nielsen et al. 2015 (32), published review papers on the various possible criteria that may define and diagnose ACOS. This makes it even more difficult to assess due to its varying definitions (29,32). The document released by GINA/GOLD in 2014, provides features that are typical of ACOS compared with COPD and asthma (**Table 1.2**).

1.4.3.1 Pathophysiology

The pathophysiology of ACOS, based on the definition above, is very similar to that of both COPD and asthma. The patient may have more physiological features of COPD with reversibility in airflow obstruction post-bronchodilator or more features of asthma with irreversible airflow obstruction post-bronchodilator (physiology of both COPD and asthma discussed above).

1.4.3.2 Diagnosis

Because ACOS is currently identified by the features that it shares with both COPD and asthma, GOLD/GINA recommends a stepwise approach to its diagnosis. The initial step involves the patient being assessed for or diagnosed with the presence of chronic airway disease. The clinical history is taken, a physical examination is conducted, a chest x-ray or a CT scan is performed to rule out other lung diseases, and a screening questionnaire is administered to help the physician identify other potential risk factors. In the second step, the physician first checks the history of the patient to determine if the patient has a clear diagnosis of COPD or asthma. Second, the physician may compare the features to see the number that favors COPD or that of asthma (**Table 1.2**). After this physician looks at the level of evidence pointing towards the diagnosis of COPD, asthma or if there are features of both COPD and asthma, hence ACOS. At Step 3, spirometry is performed, with results reviewed to confirm a diagnosis of ACOS. Airflow obstruction must be present to diagnose ACOS. However, this does not differentiate between the three phenotypes (asthma, COPD, and ACOS) (see **Table 1.2**). Step 4 treatment is

initiated, which based mainly on the prominent syndrome. Finally, at step 5 a referral to a pulmonary expert for advice and diagnostic evaluation may be considered (30).

Table 1.2: Review summary of the similarities and dissimilarities of features of obstructive airway diseases

Feature	Asthma	COPD	ACOS
Age of onset	Usually childhood onset but can commence at any age.	Usually > 40 years of age	Usually age ≥40 years, but may have had symptoms in childhood or early adulthood
Pattern of respiratory symptoms	Symptoms may vary over time (day to day, or over longer periods), often limiting activity. Often triggered by exercise, emotions including laughter, dust or exposure to allergens	Chronic usually continuous symptoms, particularly during exercise, with 'better' and 'worse' days	Respiratory symptoms including exertional dyspnea are persistent but variability may be prominent
Lung function	Current and/or historical variable airflow limitation, e.g. BD reversibility, AHR	FEV1 may be improved by therapy, but post-BD FEV1/FVC < 0.7 persists	Airflow limitation not fully reversible, but often with current or historical variability
Lung function between symptoms	May be normal between symptoms	Persistent airflow limitation	Persistent airflow limitations
Past history or the family history	Many patients have allergies and a personal history of asthma in childhood, and/or family history of asthma	History of exposure to noxious particles and gases (mainly tobacco smoking and biomass fuels)	Frequently a history of doctor-diagnosed asthma (current or previous), allergies and a family history of asthma, and/or a history of noxious exposures
Time course	Often improves spontaneously or with treatment, but may result in fixed airflow limitation	Generally, slowly progressive over years despite treatment	Symptoms are partly but significantly reduced by treatment. Progression is usual and treatment

			needs are high
Chest X-ray	Usually normal	Severe hyperinflation & other changes of COPD	Similar to COPD
Exacerbations	Exacerbations occur, but the risk of exacerbations can be considerably reduced by treatment	Exacerbations can be reduced by treatment. If present, comorbidities contribute to impairment	Exacerbations may be more common than in COPD but are reduced by treatment. Comorbidities can contribute to impairment
Typical airwayinflammation	Eosinophils and/or neutrophils	Neutrophils in sputum,lymphocytes in airways,may have systemic inflammation	Eosinophils and/or neutrophils in sputum.

Adapted from GINA, 2014

1.4.3.3 Management/Treatment of ACOS

The 'Joint project of GINA and GOLD (2015)' (30) recognizes ACOS as asthma with symptoms of COPD. They recommended that the initial stage of treatment for a patient suspected of ACOS is to treat asthma. This is recommended until a definite diagnosis is established. An ICS (low/ moderate dose) is first prescribed followed by a LABA and or a LAMA depending on the severity of the patient's symptoms.

The 2014 Spanish Guidelines and the Finnish Guidelines recognizes ACOS as a phenotype of COPD (25,33). In addition, they also recommended prescribing ICS and a LABA at stage I and II of this phenotype and for patients with frequent exacerbation, ICS/LABA plus LAMA with the addition of theophylline or phosphodiesterase four inhibitors (PDI4) (25,33).

The GINA/GOLD also recommends smoking cessation, pulmonary rehabilitation, vaccination, and the treatment of comorbidities.

1.5 Review of the burden and the epidemiology of asthma and COPD

1.5.1 Search strategy used for the literature review

Several medical databases PubMed (Medline), CINAHL, Cochrane Collection, EMBASE, and Google Scholar were to search the literature presented in this thesis. Three major searches were conducted in the period of September 2015 and March 2017. The first search was conducted to gather the information on the background and literature review presented in Chapter 1. The second and third searches were done based on the objectives of research studies presented in Chapter 3 and Chapter 4. As the population of interest in this study was SOB patients with prescribed inhalers, a specific search was done on the topic. Also, the family physicians were thought to underuse PFT and so information was also needed to be presented on the use of PFT in the diagnosis of airway diseases. With these in mind, the literature search for the review presented in Chapter 1 was conducted on subject-specific databases where keywords combined by Boolean operators such as '**AND/ OR'** commands were used. Additionally, in order for the reader to get a full understanding of what asthma, COPD, and asthma-COPD overlap syndrome (ACOS) are, information on disease presentation, signs and symptoms, diagnosis and disease management were presented along with literature on the global and domestic burden of asthma and COPD. The following sites and reports were searched: the World Health Organization (WHO) website; *Centre for Disease Control and Prevention* (CDC) website; Statistics Canada website; Up-To-Date; the Global Initiative for Chronic Obstructive Lung Disease (GOLD); the Global Initiative for Asthma (GINA); and Spanish Guideline for COPD (GesEPOC).

In addition to the general information presented in Chapter 1, based on the premise of both research studies presented, specific searches needed to be conducted. Aimed at research Study 1 (Chapter 3) a search was done on PFT and their use in family practice and the prevalence of asthma and COPD in community patients. And, aimed at research Study 2 (Chapter 4) a search was done on the factors associated with an increased risk of asthma, COPD, and ACOS. All searches were conducted in Medline through PubMed; CINAHL; google scholar, and the Cochrane library) laterally using keywords combined by Boolean operators such as '**AND/ OR'** commands. Keywords were identifying using the PICO (Population-Intervention-Comparison-Outcome) acronym and Medical Subject Headings (MeSH terms). The first stage of the literature searches was sensitive (broad). For example, 'Asthma AND Risk AND Adults'. This was followed by more specific searches; for example, '((*Asthma) AND (Risk OR environmental exposure OR Occupational Exposure OR smoking) AND (Adult) AND Humans [Mesh]'. Truncations (*) were also used to identify all possible endings of keywords when necessary, for example, '*adult', whose base does not change when used differently (e.g. Adult, adulthood, adult's). Reference-lists were also used to identify additional articles.

1.5.2 Asthma

1.5.2..1 Global burden

Asthma is one of the most common diseases worldwide. In 2013, the WHO estimated that 235 million people suffer from asthma (6). Although asthma is prevalent in

all countries (both low and high-income countries) 80% of all asthma death occurs in low and lower-middle income countries (6). The Public Health Agency of Canada (PHAC) reported that asthma accounts for approximately 80% of chronic respiratory diseases in Canada (34). Also, Statistics Canada reported in 2013 that approximately 7.9% of the population, aged 12 and over (i.e., about 2.4 million people), have been diagnosed with asthma by a health professional (35). This is a decrease from 8.6% in 2011 and 8.1% in 2012 (35).

1.5.2.2 United States

Asthma affects approximately 18.7 million adults 18 years and older in the United States, (36). The prevalence has increased significantly over the last three decades from 3.1% in 1980 to 5.5% in 1996 and 7.3% in 2001 to 8.4% in 2010 (37). Blacks were more likely to have asthma than both Whites and Hispanics. In a document published by Centers for Disease Control and Prevention (CDC) in collaboration with National Center for Health Statistics (NCHS) and the National Health Interview Survey (NHIS) asthma prevalence was found to be higher among blacks (11.2%) and was lower among Asian (5.2%) and Hispanic persons (6.5%) compared with white persons (7.7%). Among Hispanics, Puerto Ricans (16.1%) were more likely to have asthma compared with Mexican persons (5.4%). Asthma prevalence was also found to increase with decreasing annual household income (36,37).

Geographically, asthma prevalence was higher in the Northeast (8.8%) than in the South (7.6%) or the West (8.0%), and was higher in the Midwest (8.7%) than in the South

(7.6%); however, the prevalence between metropolitan and nonmetropolitan areas did not differ.

1.5.2.3 Canada

An estimated 8.4% (>2 million people) of the population aged 12 and older (9.6% of females and 7.1% of males) have reported being diagnosed with asthma according to the 2003 *Canadian Community Health Survey* (CCHS). The prevalence rates of asthma in teenage boys and girls were 12.2% and 12.6%, respectively. However, this difference was not statistically sided44iujunificant. Conversely, the rates of asthma decreased with age with women being more likely to report asthma than men. In the same survey, approximately 80,000 people were admitted to hospital for asthma with admissions highest among young children and seniors (16). Current data published by Statistics Canada revealed that 6.96% of Canada's populations have asthma, 4% percent of which are females compared to males (2.96%). **Table 1.3** shows the recent number of people with asthma in Canada.

Table 1.3: Number and (%) of people in the total population that has asthma and by male and female

	2010	2011	2012	2013	2014
Canada	2,446,467 (8.5%)	2,511,890 (8.6%)	2,385,833 (8.1%)	2,363,010 (7.9%)	2,448,817 (8.1%)
Males	1,016,082 (7.1%)	1,066,427 (7.4%)	983,434 (6.8%)	1,020,626 (6.9%)	1,041,211 (7.0%)
Females	1,430,386 (9.8%)	1,445,463 (9.8%)	1,402,399 (9.4%)	1,342,383 (9.4%)	1,407,606 (9.2%)

Table adapted from Statistics Canada website http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health50a-eng.htm
Note: Population aged 12 and over who report that they have been diagnosed by a health professional as having asthma.
Source: Statistics Canada, CANSIM,

1.5.2.4 Risk of Asthma onset

The causes of asthma are poorly understood, but multiple factors are believed to play a role in the development and the exacerbation of symptoms. It is reported that genetics/family history, exposure to environmental factors, and genetics and environment interaction are the main factors influencing its development. Besides the aforementioned, the following host-related factors are also believed to play a major role in the development and severity of symptoms; age, sex, race/ethnicity, marital status, socioeconomic status, smoking status, obesity, viral/bacterial infections, occupational exposure, and comorbidities (16,38,39).

The presence of allergies has been described as the primary risk factor for developing early childhood asthma following atopy (6). Approximately 90% of children with asthma have allergies, compared with 30 to 50% of adults with asthma (40,41). Prevention of known allergen is advised to prevent asthma exacerbations. Common indoor triggers include tobacco smoke, dust mites, furry animals, cockroaches, and fungi. Outdoor triggers include aeroallergens and air pollution (15). Those who are exposed to allergens or irritants have an increased risk of developing adult-onset asthma (40). In a case-control study by Pollart et al. the results showed that in adults younger than 50 years of age, the prevalence of immunoglobin E antibodies (IgE Abs) was four times greater among patients with asthma than among control subjects (68.7% versus 14.8%; OR, 10.1; 95% CI, 4.9 to 20.7) (42). **Table 1.4** summarizes individual characteristics that are associated with asthma onset (43–62)

Table 1.4: Summary review of characteristic associated with risk of asthma

	Author	Year	country	Study design	Study Population and Methods	Study objectives	Results
Socio-economic status	Ospina et al. (43)	2012	Canada	Systematic review and metanalysis	MEDLINE, EMBASE, specialized databases and the grey literature up to October 2011 were searched to identify epidemiological studies comparing asthma and COPD prevalence between Aboriginal and non-Aboriginal adult populations. Prevalence ORs (PORs) and 95% CIs were calculated in a random-effects meta-analysis.	To evaluate differences in asthma and COPD prevalence between adult Aboriginal and non-Aboriginal populations.	Of 132 studies, eight contained relevant data. Aboriginal populations included Native Americans, Canadian Aboriginals, Australian Aboriginals, and New Zealand Maori. Overall, Aboriginals were more likely to report having asthma than non-Aboriginals (POR 1.41 [95% CI 1.23 to 1.60]), particularly among Canadian Aboriginals (POR 1.80 [95% CI 1.68 to 1.93]), Native Americans (POR 1.41 [95% CI 1.13 to 1.76]) and Maori (POR 1.64 [95% CI 1.40 to 1.91]). Australian Aboriginals were less likely to report asthma (POR 0.49 [95% CI 0.28 to 0.86]).
	Boudreaux et al. (44)	2003	USA	Prospective cohort	A total of 1,847 patients enrolled in the study. Prospective cohort studies. Sixty-four North American EDs participated.	To investigate racial/ethnic differences in acute asthma among adults presenting to the emergency department (ED), and to determine whether	Black and Hispanic asthma patients had a history of more hospitalizations than did whites (ever-hospitalized patients: black, 66%; Hispanic, 63%; white, 54%; $p < 0.001$; patients hospitalized in the past year: black, 31%; Hispanic, 33%; white, 25%; $p < 0.05$) and more frequent ED use (median use in past year: black, three visits; Hispanic, three visits; white, one visit; $p < 0.001$white, 52%; $p < 0.001$). Blacks and Hispanics also were more likely to report continued severe symptoms 2 weeks after

					observed differences are attributable to socioeconomic status (SES).	hospital discharge (blacks, 24%; Hispanic, 31%; white, 19%; $p < 0.01$). After adjusting for sociodemographic factors, the race/ethnicity differences in initial PEFR and post-hospital discharge symptoms were markedly reduced.
Basagaña et al. (45)	2004	Spain	Cross-sectional	Included were 10,971 subjects aged 20–44 years selected from the general population and interviewed in 1991–1992.	The authors assessed the association between asthma prevalence and socioeconomic status at both the individual and center levels simultaneously .by using data from 32 centers in 15 countries	Asthma prevalence was higher in lower socioeconomic groups, whether defined by educational level (odds ratio for finishing full-time studies—<16 vs. >19 years = 1.28, 95% confidence interval: 1.00, 1.64) or social class (odds ratio for semiskilled and unskilled manual workers vs. professional/ managerial = 1.51, 95% confidence interval: 1.20, 1.90), regardless of atopic status. Irrespective of individual socioeconomic status, subjects living in areas in which educational levels were lower had a higher risk of asthma ($p< 0.05$).
Cunningham, J (46)	2010	Australia		This study analyzed weighted data on self-reported current diagnosed asthma and a range of socio-economic and demographic measures for 5,417 Indigenous and 15,432 non-Indigenous adults aged 18-64 years from two nationally representative surveys conducted in	The aim of the study was to examine the relationships between indicators of socioeconomic status and self-reported asthma among a nationally representative sample of Indigenous Australian	Current asthma prevalence was higher for Indigenous than non-Indigenous people in every age group. After adjusting for age and sex, main language and place of residence were significantly associated with asthma prevalence in both populations. Traditional SES variables such as education, income, and employment status were significantly associated with asthma in the non-Indigenous but not the Indigenous population. For example, age- and sex-adjusted relative odds of asthma among those who did not complete Year 10 (versus those who did) were 1.2 (95% confidence interval (CI) 1.0-1.5)

					parallel by the Australian Bureau of Statistics in 2004-05.	adults and to compare these with corresponding patterns in the non- Indigenous population.	in the non-Indigenous population versus 1.0 (95% CI 0.8-1.3) in the Indigenous population.
	Ekerljung et al. (47)	2010		longitudinal and cross-sectional data	A postal questionnaire was sent on two occasions, 1996 and 2006, to a randomly selected sample of subjects aged 20-69 years in 1996. In total, 4479 subjects participated in both surveys.	Incidence and prevalence of adult asthma is associated with low socio-economic status	Manual workers in service had the highest prevalence and cumulative incidence for all investigated symptoms and asthma. Despite a large decrease in smokers, the increase in incident bronchitic symptoms was higher than the increase of incident asthma and incident asthmatic symptoms. Low socio-economic status, rhinitis and a family history of asthma were risk factors for having and developing asthma and respiratory symptoms.
Family History	Anto et al. (48)	2010	Spain	Longitudinal cohort	A longitudinal analysis of 9175 young adults who participated in two surveys of the European Community Respiratory Health Survey (ECRHS) conducted 9 years apart.	To assess the risk factors for the development of new-onset asthma in middle-aged adults and to compare them according to atopy.	179 cases of new-onset asthma among 4588 participants who were free of asthma and reported at the beginning of the follow-up that they had never had asthma (4.5 per 1000 person-years). In a logistic regression, the following risk factors were found to increase the risk of new-onset asthma: female gender (OR: 1.97; 95% CI: 1.38, 2.81), bronchial hyperresponsiveness (3.25; 2.19, 4.83), atopy (1.55; 1.08, 2.21), FEV_1 < 100 % predicted (1.87; 1.34, 2.62), nasal allergy (1.98;1.39,2.84) and maternal asthma (1.91; 1.13; 3.21). Obesity, respiratory infections in early life and high-risk occupations increased the risk of new-onset

Paaso et al. (49)	2014	Finland	Cohort	The study assessed the effect of the family history of asthma and allergic diseases on persistent vs. transient, and early- vs. late-onset persistent asthma in The Espoo Cohort Study 1991–2011, a population-based cohort study of 1623 subjects (follow-up rate 63.2%). The determinants were any family history (any parent or sibling); maternal; paternal; siblings only; parents only; and both siblings and parents.	Allergic diseases and asthma in the family predict the persistence and onset-age of asthma	Family history was associated with the different subtypes but the magnitude of effect varied quantitatively. Any family history of asthma was a stronger determinant of persistent (adjusted RR = 2.82, 95% CI 1.99-4.00) than transient asthma (1.65, 1.03-2.65) (heterogeneity: P = 0.07) and on early-onset than late-onset persistent asthma. Also, any family history of allergic diseases was a stronger determinant of persistent and early-onset asthma. The impact of paternal asthma continued to young adulthood (early-onset: 3.33, 1.57-7.06 vs. late-onset 2.04, 0.75-5.52) while the influence of maternal asthma decreased with age (Early-onset 3.94, 2.11-7.36 vs. Late-onset 0.88, 0.28-2.81). Paternal allergic diseases did not follow the pattern of paternal asthma since they showed no association with late-onset asthma.
Mahdi et al. (50)	2010	India	Cohort	A total of 200 families, 100 index children and 100 index adults with clinically diagnosed asthma, along with 400 non-asthmatic children and adults as controls were selected for the present study.	To investigate the inheritance patterns of asthma and the effect of family history and consanguineous marriage on asthma inheritance.	A history of asthma in any member of the family was observed in 44.5 percent of cases and 5.3 percent of controls (P < 0.001). A differential risk of developing asthma was noted in the family history of asthma in different first and second-degree relatives of children and adult patients. Consanguineous marriage was also noted in parents in 24.5 percent of cases and 12.3 percent of controls (P< 0.001). The most common mode of asthma inheritance was recessive.

Occupational / Environmental factors	White et al. (51)	2015	USA	Cross-sectional	The study examined 2010 National Health Interview Survey data	To determine the proportion of employed adults with asthma who had frequent workplace exposures.	Among adults with current asthma, 19.6% frequently worked outdoors, 17.5% were frequently exposed to workplace second-hand smoke and 28.1% were frequently exposed to workplace vapors, gas, dust or fumes. Adults ever told by a health professional that asthma is probably work-related, when compared to adults who were not, had increased odds of frequent work outdoors [prevalence odds ratio (POR) = 2.76], frequent workplace exposure to second-hand smoke (POR = 3.08) and frequent workplace exposure to vapors, gas, dust or fumes (POR = 3.56).
	Simpson et al. (52)	2014	Australia	Cross-sectional	Sixty-six participants with refractory asthma were characterized. Occupational exposure to asthma-causing or worsening agents were identified with an asthma-specific job exposure matrix. Exposure to passive cigarette smoke was determined by questionnaire and exhaled carbon monoxide assessment.	The aim of this study was to examine the relationship between occupation, past smoking, and current passive smoking and airway inflammation in a population of adults with refractory asthma.	Nineteen participants had smoked previously with low smoking pack-years (median 1.7 years). Ex-smokers more commonly lived with a current smoker (26% vs. 9%, p = 0.11) and were more likely to allow smoking inside their home (26% vs. 4%, p = 0.02) compared to never smokers. Twenty participants had occupations with an identified exposure risk to an asthmagen; thirteen had exposures to irritants such as motor vehicle exhaust and environmental tobacco smoke. Sputum neutrophils were elevated in participants with asthma who had occupational exposures, particularly those who were diagnosed with asthma at a more than 30 years of age.
	Agrawal et al. (53)	2014	India	Cross-sectional	The analysis is based on 64 725 men aged 15–54 years and 52	Occupations with an increased	The prevalence of asthma among the working population was 1.9%. The highest odds ratios for asthma were found among men in the plant

				994 women aged 15–49 years who participated in India's third National Family Health Survey, 2005–2006, and reported their current occupation.	prevalence of self-reported asthma among adult men and women in India were studied.	and machine operators and assemblers major occupation category (OR: 1.67; 95% CI: 1.14–2.45; p¼0.009). Men working in occupation subcategories of machine operators and assemblers (OR: 1.85; 95% CI: 1.24–2.76; p¼0.002) and mining, construction, manufacturing and transport (OR: 1.33; 95% CI: 1.00–1.77; p¼0.051) were at the highest risk of asthma. Reduced odds of asthma prevalence in men was observed among extraction and building trades workers (OR: 0.72; 95% CI: 0.53–0.97; p¼0.029). Among women, none of the occupation categories or subcategories was found significant for asthma risk. Men and women employed in high-risk occupations were not at a higher risk of asthma when compared with those in low- risk occupations.
Lillienberg et al. (55)	2013	Sweden	Population-based cohort	The study comprised 13 284 subjects born between 1945 and 1973, who answered a questionnaire 1989–1992 and again 1999–2001. Asthma was defined as 'Asthma diagnosed by a physician' with a reported year of diagnosing	The relation between occupational exposure and new-onset asthma was studied.	During the observation period, there were 429 subjects with new-onset asthma with an asthma incidence of 1.3 cases per 1000 person-years for men and 2.4 for women. A significant increase in new-onset asthma was seen for men exposed to plant-associated antigens (HR = 3.6; 95% CI [confidence interval] = 1.4–9.0), epoxy (HR = 2.4; 95% CI = 1.3–4.5), diisocyanates (HR = 2.1; 95% CI = 1.2–3.7) and accidental peak exposures to irritants (HR = 2.4; 95% CI = 1.3–4.7). Both men and women exposed to cleaning agents had an increased asthma risk.
Lillienberg et al. (54)	2014	Sweden	Population-based cohort	The study comprised 6253 men and 7031 women from northern Europe, born 1945-1973, who had	The aim was to investigate how the N-JEM differs in exposure	Significantly increased asthma risks were seen for men exposed to isocyanates and accidental peak exposure with both JEMs. With the N-JEM, increased asthma risks were seen for men exposed to plant-associated antigens (all and

				answered both a screening (1989–1992) and a follow-up questionnaire (1999–2001). During the study period (1980–2000), there were 136 men and 293 women with new-onset asthma.	assignment and asthma risks from an already established JEM.	non-atopic), epoxy compounds (all and non-atopic), and acrylates (non-atopic). With the other JEM, increased asthma risks were seen in men and women exposed to 'possible exposure to irritant gases or fumes' (all and non-atopic), a group classified as having low asthma risk. Men and women exposed to cleaning agents also showed significant asthma risks with both JEMs. PAR with the N-JEM was 14.3% for men and 6.6% for women, compared with 12.9% and 8.3% with the other JEM.
Knoeller et al. (56)	2013	USA	Cross-sectional	We used data from questions asked in the 2010 NHIS core and Occupational Health Supplement. Data were from the 2010 NHIS sample adult dataset for 27,15 7 randomly selected participants aged ≥18 years. The 201 0 NHIS sample adult response rate was 60.8% [Centers for Disease Control and Prevention, 2011].	To determine the occupation held when individuals first developed asthma symptoms, we examined the 2010 National Health Interview Survey data for working adults with current asthma.	Overall 37.1% of working adults with current asthma developed asthma while employed. Of these, the highest proportions of individuals identified office and administrative support (13.3%), sales and related (9.4%), and management (8.5%) as the occupation held when asthma first developed; 37.8% had a different current occupation than at asthma onset, and estimates of a change in occupation were highest for those who developed asthma while working in business and financial operations (49.3%), sales and related (48.6%), and healthcare support (43.8%) occupations.
Beach et al. (63)	2013	Canada	Observational	1 118 239 eligible participants. WCB claims for any reason 1995–2004 were linked to physician billing data. NOAA	The aim of this study was to extend this method to data from British Columbia (BC)	Among 1 118 239 eligible WCB claims the incidence of NOAA was 1.4%. 16 occupations and 44 industries had a significantly increased risk; six industries had a decreased risk. The JEM identified wood dust [odds ratio (OR) 1.55, 95% confidence interval (CI) 1.08– 2.24]

					was defined as billing for asthma (ICD-9 493) in the 12 months before a WCB claim without asthma in the previous 3 years.	so as to compare the two provinces and to incorporate Bayesian	and animal antigens (OR 1.66, 95% CI 1.17–2.36) as related to an increased risk of NOAA. Exposure to isocyanates was associated with decreased risk (OR 0.57, 95% CI 0.39– 0.85).
Comorbidities	Gao et al. (57)	2015	Japan	Met-analysis of prospective studies	Only comparative prospective studies with reported risk estimates of the association between depression and asthma were included. In order to investigate whether one of these conditions was predictive of the other, studies were excluded if enrolled participants had pre-existing depression or asthma.	To determine whether depression predicts asthma and, conversely, whether asthma predicts depression.	Seven citations, derived from 8 cohort studies, met our inclusion criteria. Of these, six studies reported that depression predicted incident adult-onset asthma, including 83684 participants and 2334 incident cases followed for 8 to 20 years. Conversely, two studies reported that asthma predicted incident depression. These studies involved 25566 participants and 2655 incident cases followed for 10 and 20 years, respectively. The pooled adjusted relative risks (RRs) of acquiring asthma associated with baseline depression was 1.43 (95% CI, 1.28–1.61) (P<0.001). The adjusted RRs for acquiring depression associated with baseline asthma was 1.23 (95% CI, 0.72–2.10) (P = 0.45).
	Brunner et al. (58)	2014	USA	Cohort	The study examined the longitudinal association between asthma and depressive symptoms bidirectionally in the Coronary Artery Risk Development in Young Adults (CARDIA) cohort.	To examine the association between prevalent elevated depressive symptoms and incident asthma, and between prevalent asthma and	The relative hazard of incident asthma among those with elevated depressive symptoms was 1.26 (95% confidence interval [CI] = 1.02–1.56) after adjustment for covariates. When depressive status was modeled as the total number of reports of elevated depressive symptoms before the onset of asthma, the adjusted hazard ratio was 1.15 (95% CI = 1.02–1.29). The hazard of incident elevated depressive symptoms for those with asthma was no different than the hazard in those without

					incident elevated depressive symptoms in a cohort of young and middle-aged adults.	asthma (adjusted hazard ratio = 0.92; 95% CI = 0.70–1.20).
Patel et al. (59)	2013	USA	Cross-sectional	Cross-sectional interview data from the National Health and Nutrition Examination Survey were analyzed (n = 22,172) between 2003 and 2010.	To examine the prevalence and demographic distribution of five common chronic conditions (arthritis, heart disease, cancer, diabetes, and hypertension) in adults with and without asthma and the adverse asthma outcomes associated with multiple chronic conditions.	Of the 10% of subjects with asthma, 54% had one or more coexisting health condition(s). The prevalence of two or three or more other chronic conditions was greater among those with asthma compared with those without (P, 0.001). Common comorbidities with asthma were hypertension (34%) and arthritis (31%). For every additional comorbid chronic condition, there was an increase in the prevalence of reported asthma symptom episodes (prevalence ratio [PR], 1.06; 95% confidence interval [CI], 1.00–1.13), frequent activity limitation (PR, 1.14; 95% CI, 1.04–1.25), sleep disturbances (PR, 1.22; 95% CI, 1.04–1.43), and emergency department visit for asthma (PR, 1.45; 95%CI, 1.19–1.76) when adjusted for socioeconomic and demographic factors and body mass index. The population-attributable risk for emergency department visits for asthma among individuals with asthma who have other chronic comorbidities was 19.5%.
Aubas et al. (60)	2013	France	Prospective	1122 patients. d'Information (PMSI) data records from 2009 were sorted using selected	The aim was to characterize and describe risk factors associated with hospitalizations	One thousand two hundred and eighty-nine hospitalizations due to asthma exacerbation were found, concerning 1122 patients. We observed significant differences within the groups, using univariate analysis, concerning duration of hospitalizations (mean ± SD, 4.9 ±

				International Classification of Diseases (ICD10) codes eliciting three groups of asthma hospitalizations according to acute severity.	due to asthma in the Languedoc-Roussillon region (France) in 2009.	5.9 days vs 6.4 ± 6.8 vs 15.8 ± 16.8, P < 0.001), deaths (percentage, 0.03% vs 1.50% vs 9.20%, P < 0.001) and numbers of comorbid conditions Recurrent admissions for asthma during the period 2006–2008 were significantly more frequent in the more severe group (1.93 ± 3.91 vs 2.56 ± 4.47 vs 2.81 ± 3.97, P = 0.006).
Brumpton et al. (61)	2013	Norway	Prospective cohort	This study was conducted as a prospective cohort study of 23 599 adults who were 19–55 years old and free from asthma at baseline in the Norwegian Nord-Trøndelag Health Study. The Hospital Anxiety and Depression Scale was used to measure anxiety or depression symptoms. Obesity was defined as a body mass index530.0 kg/m2.	The aim was to assess the association of anxiety or depression symptoms and the joint association of these symptoms and obesity with incident asthma.	Having anxiety or depression symptoms were associated with incident asthma [odds ratio (OR) 1.39, 95% confidence interval (CI) 1.09–1.78). Obese participants with anxiety or depression symptoms had a substantially higher risk of incident asthma (OR 2.93, 95% CI 2.20–3.91) than any other group (non-obese participants without anxiety or depression symptoms [reference], non-obese participants with anxiety or depression symptoms (OR 1.20, 95% CI 1.00–1.45) and obese participants without anxiety or depression symptoms (OR 1.47, 95% CI 1.19–1.82)]. The relative excess risk for incident asthma due to the interaction between anxiety or depression symptoms and obesity was 1.26 (95% CI 0.39–2.12).
Steppuhn et al. (64)	2013	Germany	Cross-sectional	A total of 22,050 adults 18 years and older were surveyed in the German National Health Telephone Interview Survey (GEDA) 2010	Aimed to assess the prevalence of these major comorbidities among adults with asthma and examine their	Out of 1,136 adults with asthma, 49.6% had GERS and 42.3% had AR within the past 12 months; 14.0% met the criteria of AERD, and 75.7% had at least one out of the three conditions. Overall, the prevalence of at least one exacerbation requiring emergency room or hospital admission within the past year was

				using a highly standardized computer-assisted interview technique.	impact on asthma exacerbations requiring hospital care.	9.0%. Exacerbation prevalence was higher among participants with comorbidities than among those without (9.8% vs. 8.2% for GERS; 11.2% vs. 7.6% for AR, and 22.2% vs. 7.0% for AERD), but only differences in association with AERD were statistically significant
Iribarren et al. (62)	2012	USA	Retrospective cohort	The authors ascertained the association of asthma with CVD and the roles that sex, concurrent allergy, and asthma medications may play in this association. They assembled a cohort of 203,595 Northern California adults with asthma and a parallel asthma-free referent cohort (matched 1:1 on age, sex, and race/ethnicity); both cohorts were followed for incident nonfatal or fatal CVD and all-cause mortality from January 1, 1996, through December 31, 2008. Each	The aims of the study were to investigate the association between asthma and major CVD incidence (including CHD, cerebrovascular disease and its subtypes, and heart failure) and to assess whether pre-specified subgroups (women, persons with concomitant allergy diagnoses, and persons using asthma medication—particularly combination therapy	Each cohort was 66% female and 47% white. After adjustment for age, sex, race/ethnicity, cardiac risk factors, and comorbid allergy, asthma was associated with a 1.40-fold (95% confidence interval (CI): 1.35, 1.45) increased hazard of coronary heart disease, a 1.20-fold (95% CI: 1.15, 1.25) hazard of cerebrovascular disease, a 2.14- fold (95% CI: 2.06, 2.22) hazard of heart failure, and a 3.28-fold (95% CI: 3.15, 3.41) hazard of all-cause mortality. Stronger associations were noted among women. Comorbid allergy predicted CVD but did not synergistically increase the CVD risk associated with asthma. Only asthma patients using asthma medications (particularly those on oral corticosteroids alone or in combination) were at enhanced risk of CVD. In conclusion, asthma was prospectively associated with increased risk of major CVD. Modifying effects were noted for sex and asthma medication use but not for comorbid allergy.

			including systemic corticosteroids) may be at particularly elevated or reduced risk of CVD.

ER: emergency department

1.5.3 COPD

1.5.3.1 Global Burden

COPD is one of the most debilitating diseases in the middle-aged and the elderly. In 2010 COPD was named the third leading cause of death in the world (65). More than 3 million people died of COPD in 2012, which is equal to 6% of all deaths globally (8) and is projected to be the fourth leading cause of mortality in 2030 (26,66) and the third leading cause of death as projected by the American Thoracic Society and WHO (2,8). More than 90% of all deaths occur in low-income and middle-income countries (8). It was estimated that 23 million people in Europe are living with COPD stage II-IV and that 17 million have stage I disease (67). In the United Kingdom (UK) alone an estimated 3 million people have COPD and about 900,000 have been diagnosed with COPD while an estimated 2 million people are living with COPD which remains undiagnosed (68). The primary cause of COPD is cigarette smoke (active or passive use) and now affects both men and women almost equally as over the years the use of cigarettes has increased among women in first world countries (8). However, there is a wide variation in the prevalence of COPD across countries. This variation is due somewhat to the different methods of diagnosis and classification. It has been proven that the prevalence estimate is higher when the patients were diagnosed with spirometry PFTs compared to other methods (69).

COPD is a more costly disease than asthma, with the majority of the cost relating to services associated with exacerbation (2,21,22). Frequent exacerbation and increased

severity of the disease, is however very common, especially in poorly controlled or elderly patients with a history of low medication adherence. This is associated with frequent emergency room visits, significant healthcare cost, and lower quality of life and satisfaction (34,35).

In high-income countries, COPD exacerbations leading to hospitalizations account for a large portion of the cost of disease. For example, the annual cost of COPD in Europe, including health care costs, has been estimated to be 141 billion Euros (67). In the European Union, the total direct costs of respiratory diseases are estimated to be 6% of the total health care budget, with COPD accounting for 56% (€38.6 billion) of the total (65).

1.5.3.2 United States

Approximately 12 million Americans have been diagnosed with COPD, but at least another 12 million Americans may be undiagnosed (36). COPD is the fourth leading cause of death in the United States. Over the last 20 years in the USA alone the death toll in females rose from 20.1/100,000 in 1980 to 56.7/100,000 in 2000 compared to males, 73.0/100,000 in 1980 to 82.6/100,000 in 2000 (72) a devastating increase. In 2002, for example, the direct costs of COPD were $18 billion, and the indirect costs totaled $14.1 billion. By 2010, the cost estimate for direct medical costs attributable to COPD was estimated to be 32.1 billion, although the cost could potentially be much higher. People in the US with a COPD diagnosis in 2010 incurred total costs of about $9,800 per person, more than twice the amount incurred by people without a COPD diagnosis ($3,770). Even

after adjusting for demographics, this difference remained large ($4,040), but did decrease after adjusting for multiple comorbid diseases ($3,120).

In 2011 the CDC using the NCHS data reported that between 2007 and 2009, 5.1% (11.8 million) of adults aged 18 and over had COPD. Approximately 6% of women (7.4 million) had COPD compared with 4.1% of men (4.4 million) (73). The prevalence of COPD was higher in older age groups, in women compared to men throughout their lifetime, and it was highest among women aged 65–74 years, and 75–84 years and among men aged 75–84 years.

1.5.3.3 Canada

In Canada, COPD is a major cause of disability and death (74). A recent study reported that 1.5 million Canadians self-reported having COPD, and another 1.6 million reported having symptoms but are undiagnosed (75). The PHAC (2011) reported that in 2009-2010, 772,200 (4%) Canadians, aged 35 years and older, were diagnosed with COPD. COPD has significantly impacted the lives of Canadians concerning overall health, mental health, and limitations to mobility, activities of daily living, work, volunteer participation, and social and recreational activities (74,76). COPD is one of the leading causes of morbidity and mortality in Canada and is said to be the fourth leading cause of death (69).

In 2009 an estimated 4.2% of Canadians aged 35 and older were diagnosed with COPD. This estimation was based on self-reporting conducted by the CCHS, a 0.4% difference than 2008. There was no statistically significant difference between the self-reported diagnosis of COPD among males and female (35,77). In 2011, the estimated

prevalence of COPD in Canada based on self-reporting was 4%. Statistics Canada reported that between the year 2009 to 2011, 4% of Canadian aged 35 -79 reported having COPD. However, when direct measurement of lung function was done by the *Canadian Health Measures Survey* (CHMS) based on a study conducted to estimate the prevalence of COPD in Canada by comparing self-reporting of diagnosis to pre-bronchodilator spirometry 13% was found to have measurements indicating COPD. Among the 4% that reported being diagnosed by a physician, women were 5% more likely to report their diagnosis than men, a statistically significant difference according to the 2009 reports. This inconsistency reflects under-reporting and under-diagnosis, which cause difficulties in knowing the true prevalence (4,69).

1.5.3.4 Risk factors for COPD

Many factors contribute to the development of COPD and its progression as well as the morbidity and mortality rate. Tobacco smoke is the main risk factor for COPD (2,4,8,73,74,78,79). Studies indicate that approximately 75% (some sources say) (80) of COPD cases are attributed to tobacco smoke, and about 15% of all cases of COPD is work-related exposures. This leaves approximately 25% of those that never smoked who developed COPD indicating that other factors are linked to COPD (81). Additionally, age, sex/gender, socioeconomic status, genetic factors/family history, asthma, respiratory infections, indoor and outdoor exposures to air pollutants, and comorbidities all play a role in the development and degeneration of COPD (4) account for an estimated 75% of all cases. However, only 15% to 30% of people who smoked develop COPD (79). In 2000, an estimated 20% of all adults in Canada aged 15 years and over (4.7 million)

smoked cigarettes on a daily basis (2.5 million men and 2.2 million women), with an additional 5% (1.2 million) occasional smokers (0.6 million men and 0.6 million women) (82). Passive smoking exposure is also associated with an increased risk of COPD. In a study conducted by Hagstad et al. using pooled data from three cross-sectional studies of obstructive lung disease in Northern Sweden that examined the association between environmental tobacco smoke and COPD, passive smoking was found to be strongly associated with COPD when exposed in multiple settings, that is, in the home, work and in public (78). In another study looking at the impact of passive and active smoking, the authors found that exposure to passive smoke of either cigarettes or narghiles (a middle eastern tobacco pipe in which the smoke is drawn through water before reaching the lips) was associated with airway obstruction ($FEV_1/FVC<70\%$) (83,84). **Table 1.5** summarizes characteristics that are associated with COPD (78,80,84–100)**.**

Table 1.5: a Summary review of characteristics associated with the risk of COPD

	Author	Year	country	Study design	Study Population and Methods	Study objectives	Results
Socio-economic status	Hagstad et al (38)	2014	Sweden	Cross-sectional	3 cohorts derived from the general population. 1996, a 10 year follow up performed in 2	Passive Smoking Exposure Is Associated With Increased Risk of COPD in Never Smokers	passive smoking was found to be strongly associated with COPD when exposed in multiple settings, that is, in the home, work and in public (OR:3.80; 95%CI:1.29-11.2)
	Mohammad et al. (84)	2013	Syria	Cross-sectional	This study administered the questionnaire to 788 randomly selected females seen during 1 week in the fiscal year 2009–2010 in 22 primary care centers in six different regions of Syria	Impact of active and passive smoking as risk factors for asthma and COPD in women presenting to primary care in Syria: first report by the WHO-GARD survey group	Exposure to active cigarette smoke but not narghile smoke was associated with doctor-diagnosed chronic obstructive pulmonary disease (COPD). However, neither cigarette nor narghile active smoking was associated with an increased incidence of spirometrically diagnosed COPD.
	Daldoul et al.	2013	Tunisia	Cross-sectional	The study surveyed 807 adults aged 40+ years and have collected information on respiratory history and symptoms, risk factors for COPD and quality of life. Post-bronchodilator spirometry was performed and COPD and its stages were defined according to the Global Initiative for Chronic Obstructive Lung Disease		The prevalence of GOLD Stage I and II or higher COPD were 7.8% and 4.2%, respectively (Lower Limit of Normal modified stage I and II or higher COPD prevalence were 5.3% and 3.8%, respectively). COPD was more common in subjects aged 70+ years and in those with a BMI < 20 kg/m2. Prevalence of stage I+ COPD

				(GOLD) guidelines. Six hundred and sixty-one (661) subjects were included in the final analysis		was 2.3% in <10 pack-years smoked and 16.1% in 20+ pack-years smoked. Only 3.5% of participants reported doctor-diagnosed COPD.
Smith et al. (85)	2014	China	Cross-sectional	The study analyzed data on 287 000 female and 30 000 male never-smokers aged 30-79 years from 10 regions in China, who participated in the China Kadoorie Biobank baseline survey (2004-2008)	Prevalence and correlates of airflow obstruction in approximately 317,000 never-smokers in China	In females, odds ratios of AFO were positively associated with lower household income (1.63, 95% CI 1.55-1.72 for lowest versus highest income groups), prior tuberculosis (2.36, 95% CI 2.06-2.71), less education (1.17, 95% CI 1.12-1.23 for no schooling versus college education), rural region and lower body mass index. AFO was positively associated with cooking with coal but not with other sources of household air pollution.
Yin et al. (86)	2011	China	Cross-sectional	The study used data from the 2007 China Chronic Disease Risk Factor Surveillance of 49,363 Chinese men and women aged 15-69 years	To examine the association between the prevalence of self-reported physician diagnosed COPD and socioeconomic status defined by both educational	Both low educational attainment and low household income were independently associated with higher risk of physician-diagnosed COPD. Compared to subjects with high educational level, subjects with low educational level had a significantly increased risk of COPD (OR 1.67, 95%CI 1.32-2.13, p for

					level and annual household income.	trend< 0.001 for urban, OR 1.76, 95%CI 1.34-2.30, p for trend < 0.001 for rural) after adjusting for age, sex, smoking status, passive smoking and geographic regions. Similarly increased risk was observed for household income and COPD in urban (OR 1.64, 95%CI 1.28-2.09, P for trend< 0.001) but not rural areas. Among never smokers, low educational level, and household income were still associated with a significantly higher prevalence of COPD (OR 1.77, 95%CI 1.40-2.25, OR 1.31, 95%CI 1.05-1.62).
Pleasants et al. (87)	2013	USA	Cross-sectional	Of the 13,277 adults in North Carolina who were interviewed during the 2009 BRFSS survey, 12,165 respondents provided complete data.	Describing the prevalence, characteristics, and impact of COPD in North Carolina using data from the 2009 North Carolina Behavioral Risk Factor Surveillance	Rates of self-reported COPD were highest among elderly individuals, smokers, individuals with less education, and those with lower incomes. Mental and physical impairment were significantly worse in those with COPD, two-thirds of whom reported that dyspnea affected their quality of life. Prednisone use was reported by 27.4% of persons with COPD, 11.4% of respondents

					System (BRFSS) survey.	with COPD had been hospitalized for this condition within the preceding year, and COPD admissions accounted for 1.44% of all hospital charges. Asthma, heart disease, stroke, and diabetes mellitus were significantly more common in persons with COPD. In terms of mortality, COPD was the fourth leading cause of death (n = 4,324); 77% of COPD deaths were among persons who had no education beyond high school, and 53% of those who died were women
Kainu et al. (88)	2013	Finland	Cross-sectional	A general population sample of 628 adults (368 women) completed flow-volume spirometry with bronchodilation test and a structured interview. Post-bronchodilation spirometry was assessed both using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria and relative to the fifth percentile of the reference value (lower limit of normal, LLN)	The aims of this study were to assess the prevalence of COPD in Helsinki, Finland, with international diagnostic criteria and to analyze risk factors including socioeconomic status, and disease severity	According to GOLD criteria, 37 (5.9%), and by using the LLN criteria, 43 subjects (6.8%) had airway obstruction consistent with COPD. Using the GOLD criteria, four subjects or 0.6% of the population had severe, 3.0% moderate, and 2.2% mild COPD. Of those with post-bronchodilator obstruction, 49% had no previous diagnosis of obstructive airways disease and did not use medication for any respiratory disease.

family history	Hersh et al (89)	2011	USA		The study compared 821 patients with COPD to 776 control smokers from the Genetic Epidemiology of COPD (COPDGene) Study.	To identify the effects of family history of smoking and family history of COPD on COPD susceptibility.	Parental history of smoking (85.5% case-patients, 82.9% control subjects) was more common than parental history of COPD (43.0% case-patients, 30.8% control subjects). In a logistic regression model, parental history of COPD (OR, 1.73; P, .0001) and educational level (OR, 0.48 for some college vs no college; P, .0001) were significant predictors of COPD, but the parental history of smoking and childhood ETS exposure were not significant.
	Zhou et al. (90)	2014	China	Cross-sectional	Based on a cross-sectional survey in seven provinces/cities in China (Beijing, Shanghai, Guangdong, Liaoning, Tianjin, Chongqing, and Shaanxi) from 2002 to 2004.	To investigate the familial aggregation in chronic obstructive pulmonary disease (COPD).	FEV_1 was lower in the subjects with a family history of COPD-related diseases than in those without (2.24 +/- 0.70) L vs (2.28 +/- 0.73) L]. The prevalence of COPD in the population with a history of COPD-related diseases was 12.1% (540/4 481), which was significantly higher than that without 7.2% (1 128/15 764), chi (2) = 110.599, P < 0.001]. After adjusted for potential confounder, the population with a family history of COPD-related diseases still had a much higher incidence

							of COPD OR = 2.18 (95%CI 1.94-2.46)].
	Patel et al. (91)	2008	The United Kingdom and the USA	Cohort	A total of 3,096 individuals were recruited to the study. Index cases with COPD and their smoking siblings underwent spirometry and were offered high-resolution computed tomography scans of the thorax to assess the severity of airway wall thickening and emphysema.	To determine whether airway wall thickening and emphysema (1) make independent contributions to the severity of COPD and (2) show independent aggregation in families of individuals with COPD	Of the 3,096 individual recruited 1,159 (519 probands and 640 siblings) had technically adequate high-resolution computed tomography scans without the significant non-COPD-related thoracic disease. Airway wall thickness correlated with pack-years smoked (P < or = 0.001) and symptoms of chronic bronchitis (P < 0.001). FEV_1 (expressed as % predicted) was independently associated with airway wall thickness at a lumen perimeter of 10 mm (P = 0.0001) and 20 mm (P = 0.0013) and emphysema at -950 Hounsfield units (P < 0.0001). There was independent familial aggregation of both the emphysema (adjusted odds ratio, 2.1; 95% confidence interval, 1.1-4.0; P < or = 0.02) and airway disease phenotypes (P < 0.0001) of COPD.
Occupational/Environmental	Würtz et al. (92)	2015	Denmark	a population-based cohort	The study population (N=1575) was aged 45–84, COPD was defined by lung function measurements and	We analyzed this association and the population	More than a threefold increased risk (LLN OR=3.69 (95% CI 1.36 to 10.04) was found for occupational

					the method of the lower limit of normal (LLN), and occupational exposure was assessed by questionnaire and expert judgement.	attributable fraction.	exposure to vapour, gas, dust, and fumes (predominantly organic dust) in this never-smoking population, with a corresponding 48% (95% CI 30% to 65%) population attributable fraction among never-smokers.
	Bang et al. (101)	2013	USA	Cross-sectional	The 1997 to 2004 National Health Interview Survey data for working adults aged 25 years or more were used to estimate the COPD prevalence and to examine change in COPD prevalence between 1997 to 2000 and 2001 to 2004 by occupational groups.	To examine the prevalence of chronic obstructive pulmonary disease (COPD) among non-smokers by occupation in the United States.	During 1997 to 2004, the COPD prevalence among non-smoking working adults aged 25 years or more was 2.8% (95% CI = 2.7 to 3.0). The prevalence was significantly higher in females than in males, in both whites and blacks compared with other races. Between 1997 to 2000 and 2001 to 2004, the overall average annual COPD prevalence and prevalence by age, sex, and race did not change significantly. The COPD prevalence was highest in financial records processing (4.6%) occupations. There was a slight increase in COPD prevalence during the two survey periods from 2.8% during 1997 to 2000 compared with 2.9% from 2001 to 2004.

Zhou et al. (93)	2014	China	A 9-y prospective cohort	996 participants aged at least 40 y were offered cooking interventions (i.e., the opportunity to use clean fuels [biogas] and to have improved kitchen ventilation) with the support of local village committees beginning in November 2002. Participants adopted the interventions according to their preference. The participants underwent spirometry tests and questionnaire interviews once every 3 y to assess the association of the adoption of these non-randomized interventions with the subsequent rate of lung function decline and the incidence of COPD.	The purpose of this study was to determine whether improved cooking fuels and ventilation have effects on pulmonary function and the incidence of COPD.	A total of 72 new cases of COPD occurred over the follow-up period among 604 participants without COPD at baseline. Compared with participants without improved ventilation for cooking, those with improvements for 5–9 y had a lower risk of COPD, with an adjusted OR of 0.39 (95% CI, 0.15 to 0.99). The use of both improvements had the greatest benefit for the reduction of COPD incidence, with an adjusted OR of 0.28 (95% CI, 0.11 to 0.73). Those who had a clean fuels index of more than 9 year-hours appeared to show a benefit over those had never used clean fuels, with an adjusted OR of 0.33 (95% CI, 0.10 to 1.03, $p=0.06$), although the difference was not statistically significant. Use of clean fuels and improved ventilation were associated with a reduced decline in forced expiratory volume in 1 s (FEV_1): decline in FEV_1 was reduced by 12 ml/y (95% CI, 4 to 20 ml/y) and 13 ml/y (95% CI, 4 to 23 ml/y) in those who used clean fuels and improved ventilation, respectively,

						compared to those who took up neither intervention, after adjustment for confounders. The combined improvements of use of clean fuels and improved ventilation had the greatest favorable effects on the decline in FEV_1, with a slowing of 16 ml/y (95% CI, 9 to 23 ml/y).
Koh et al. (94)	2014	Korea	cohort	The study involved 306 male welders working at two shipyards who underwent an annual health examination in 2010. Subjects completed a questionnaire about smoking habits and occupational history and a pulmonary function test (PFT) was carried out with strict quality control measures. Welding fume exposure concentrations were estimated using 884 measurements taken between 2002 and 2009 in one of the shipyards.	To examine the relationship between welding fume exposure and COPD in Korean shipyard welders.	Two hundred and forty subjects participated, with a mean age of 48 and mean work duration of 15 years. The mean cumulative fume exposure was 7.7 mg/m3. The prevalence of COPD was 15%. FEV1 and FVC showed non-significant negative correlations with cumulative fume exposure. Odds ratios of COPD were significantly elevated for the middle (3.9; 95% CI 1.4–13.3) and high exposure groups (3.8; 95% CI 1.03–16.2) compared with the low fume exposure group.

	Mehta et al. (95)	2012	Switzerland	cohort	Pre-bronchodilator ratio of forced expiratory volume in 1 second over forced vital capacity (FEV1/FVC) was measured in 4,267 non-asthmatic SAPALDIA participants ages 18–62 at baseline in 1991 and at follow-up in 2001–2003. COPD was defined by the GOLD criterion gases, dust, or fumes (VGDF) (high, low, or unexposed as reference).	We evaluated the association between occupational exposures and incidence of COPD in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA).	Statistically significant (P,0.05) IRRs of stage II1GOLD and LLN- COPD, indicating risks between two- and fivefold, were observed for all occupational exposures at high levels. Occupational exposure- the associated risk of stage II1 COPD was observed mainly in males and ages >40 years and remained elevated when restricted to non-smokers.
Comorbidities	Ekstro¨m et al. (96)	2013	The Netherlands		National prospective study of patients aged 50 years or older, starting long-term oxygen therapy (LTOT) for COPD in Sweden between 1992 and 2008	The study evaluated the differences in comorbidity between men and women and tests the hypothesis that comorbidity contributes to sex-related differences in mortality in oxygen-dependent COPD.	Compared with women, men had significantly more arrhythmia, cancer, ischemic heart disease and renal failure, and less hypertension, mental disorders, osteoporosis and rheumatoid arthritis (P<0.05 for all odds ratios). Comorbidity was an independent predictor of mortality, and the effect was similar for the sexes. Women had lower mortality, which remained unchanged even after adjusting for comorbidity; hazard ratio 0.73 (95% confidence interval, 0.68-0.77; P<0.001).

Joo et al. (97)	2012	Korea	Cross-sectional	Data were derived from the fourth Korean Health and Nutrition Examination Survey in 2008.	To evaluate the nationwide incidence of COPD comorbidities, after controlling for sex, age, smoking, and other factors, using data from the fourth Korean Health and Nutrition Examination Survey (4th KNHANES).	The prevalence of COPD ($FEV_1/FVC < 0.7$) in subjects ≥ 40yr of age was 14.1%. Multivariate analysis showed that underweight (odds ratio [OR] 3.07, 95% confidence interval [CI] 1.05-8.98), coronary heart disease (OR, 0.43; 95% CI, 0.20-0.93) and dyslipidemia (OR, 0.61; 95% CI, 0.45- 0.82) were significantly associated with COPD, whereas allergic rhinitis, anemia, arthritis, chronic renal failure, depression, diabetes mellitus, hypertension, gastrointestinal ulcer, and osteoporosis were not.
Negro et al. (98)	2015	Italy	Cross-sectional	The study was a non-interventional, cross-sectional investigation carried out via automatic and anonymous selection from the institutional database over the period 2012-2015. Inclusion criteria were: subjects of both sex aged >/=40 years; diagnosis of COPD according to GOLD guidelines 2014).	The aim of the study was to assess the prevalence of main comorbidities by gender and disease severity in a cohort of COPD patients referring for the first time to a specialist institution	At least one comorbidity of clinical relevance was found in 78.6 % of patients, but at least two in 68.8 % and three or more were found in 47.9 % of subjects. Mean CCI was 3.4 +/- 1.6sd. The overall prevalence was 2.6 comorbidities per patient, but 2.5 in males, and 3.0 in females, respectively ($p < 0.05$). Cardio-vascular disorders were the most frequent, but significantly more frequent in males (44.7 vs 30.7 %,

						respectively), while the metabolic, the digestive and the osteoarticular disorders were prevailing in females (12.4 vs 9.2; 14.2 vs 4.8, and 6.0 vs 3.8, respectively). In particular, chronic corpumonale and arrhythmias mainly prevailed in men and congestive heart failure in females, while arterial hypertension resulted equally distributed. Anaemia, gallbladder stones, and osteoporosis mostly prevailed in females, while gastric disorders of inflammatory origin were more frequent in males. Cognition disorders, dementia, and signs of degenerative brain disorders were more frequently found in men, while depression in females. Finally, lung cancer was at the first place in men, but at the second in females
Garcia-Olmos (99)	2013	Spain	Observational, Descriptive, Cross-sectional	The practice population totaled 198,670 persons attended by 129 Family Physicians (FPs), and the study population was made up of persons over the age of 40 years drawn from the practice population. Patients were deemed to have COPD if this diagnosis	The aim of the study was to quantify the prevalence of COPD and related chronic comorbidity among patients aged over 40 years visiting family practices	Prevalence of COPD in family medicine was 3.2% (95% CI 3.0–3.3) overall, 5.3% among men and 1.4% among women; 90% of patients presented with comorbidity, with a mean of 4 ± 2.04 chronic diseases per patient, with the most prevalent related diseases being arterial hypertension (52%), disorders of lipid

					in an area of Madrid.	metabolism (34%), obesity (25%), diabetes (20%) and arrhythmia (15%).
Fumagalli et al. (100)	2013	Italy	Observational (INDACO project: Pilot study)	169 patients (124 males, mean age 74±8 years). For each patient, we recorded anthropometric and anamnestic data, smoking habits, respiratory function, GOLD (Global initiative for chronic Obstructive Lung Disease) severity stage, Body Mass Index (BMI), number of acute COPD exacerbations in previous years, presence and type of comorbidities, and the CCI.	INDACO observational pilot study was planned to evaluate the impact of comorbidities in patients referred to the outpatient wards of four major hospitals in Rome.	The prevalence of patients with comorbidities was 94.1% (25.2% of cases presented only one comorbidity, 28.3% two, 46.5% three or more). There was a high prevalence of arterial hypertension (52.1%), metabolic syndrome (20.7%), cancers (13.6%) and diabetes (11.2%) in the whole study group, and of anxiety-depression syndrome in females (13%). Exacerbation frequency was positively correlated with dyspnea score and negatively with BMI. Use of a combination of bronchodilators and inhaled corticosteroids was more frequent in younger patients with more severe airways obstruction and lower CCI.

CCI: Charlson Comorbidity Index, COPD: chronic obstructive pulmonary disease, AFO: Airflow Obstruction

1.5.4 Epidemiology of ACOS

1.5.4.1 Prevalence

The true prevalence of ACOS in any population is unknown. The prevalence varies across countries and groups based on the criteria being used to define ACOS. However, the prevalence has been shown to increase with age (102). In a longitudinal study by de Marco et al. using the European Community Respiratory Health Survey II (ECRHS II) data on young adults (ages 20-44) of the general population collected between 1991-1993 and follow-up data from 1999-2001 found the prevalence of ACOS to be 3.12% (218 out of 6984 participants), asthma was 13.47% and COPD 2.37%. Interestingly, subjects with COPD were older (60.4 years of age) compared to those with ACOS and asthma (50.5 and 44.2 years, respectively). The authors also found that among the young adults ACOS was seen more of a form of severe asthma "*characterized by more frequent hospitalizations, and to be the result of early-onset asthma that has progressed to fixed airflow obstruction*"(103). In a more recent Finnish cross-sectional study by Kiljander et al. investigating the prevalence of ACOS among 190 primary care asthmatics with a smoking history 27.4% of the patients had ACOS. These newly determined ACOS patients also had an average age of 60 and older. The authors concluded the main predictors of ACOS is age ≥60 with a >20 pack years smoking history (102). A literature review was conducted by Wurst et al. with the aim of characterizing the "the prevalence of ACOS and the effect of different disease definitions on these estimates." The authors found that ACOS prevalence varied widely (12–61%)

among patients with COPD or asthma and that the variability is linked to the differences in COPD and asthma diagnostic criteria as well as age, gender and the population being studied. Specifically, the authors reported that after analyzing the literature published in English from 2000 to 2014 the prevalence of ACOS was estimated to range from 12.1% to 55.2% among patients with COPD and 13.3% to 61.0% among patients with asthma alone (104). A study published in 2014 by Hardin et al., reported the prevalence of ACOS in a study population of 10,000 subjects to be 4.5% and that 13% of the COPD patients in the study reported a history of doctor-diagnosed asthma. They found that subjects with an overlap were significantly younger ($p<0.001$) compared to subjects with COPD only. Overlap subjects also had a higher BMI and were predominantly women and African American (p-value <0.001 and 0.006, respectively). Besides ACOS subjects had more exacerbation and greater wall thickness compared to subjects with COPD only. They identified a unique gene that was present in the ACOS subjects only (105).

Similarly, a Canadian systematic review involving 19 studies evaluated the prevalence of ACOS in COPD patients and the association between ACOS and exacerbation, hospitalization, health care utilization and HRQoL and found the pooled prevalence of ACOS among the COPD patients to be 27% in population-based studies and 28% in hospital-based studies. ACOS patients were found to be younger than those with COPD alone but older than those with asthma alone, confirming previous studies. They found that the prevalence of ACOS among male and female COPD patients was statistically insignificant. Additionally, subjects with ACOS compared to COPD only were found to have higher BMI, health care utilization due to frequent and more severe exacerbation, and lower health-related QoL (106).

1.5.4.1 Risk Factors

The epidemiological risk factors for ACOS are still under investigation, and current research is urgently required to understand these factors. However, the literature is in consensus that ACOS comprises of two diseases overlapping, that is, asthmatic patients with COPD symptoms or features; and COPD patients having asthmatic symptoms or features (4,15,107–112). The literature also shows that asthma predominantly occurs in patients younger than 40 years, while COPD patients are generally older (≥60 years). Additionally, approximately 75% (101,113,114) of COPD developed are attributed to tobacco smoke. ACOS however, are diagnosed in patients 40 years and older (30). Therefore tobacco smoke, age, and asthma/atopy may be important risk factors for ACOS (115). A study by Lee et al. compared patients asthma only patients with ACOS patients (115). They found that there was a significantly higher percentage of smokers among the ACOS patients compared to asthma only patients. Also, the percentage of patients with ACOS increased with age (115). Patients with ACOS are believed to have an increase in reversibility of airflow. Nonetheless, smoking increases the rate of lung function decline in asthma hence developing features of COPD resulting in overlapping. Therefore, identifying patients with ACOS is increasingly relevant for the management.

1.6 Thesis rationale

Over, under and misdiagnosis of the two main obstructive airway diseases (that is, COPD and asthma) in the SOB population are common presentations in family practice (FPs) due to underutilization of pulmonary function testing (PFT) (116).

Although SOB may be caused by a plethora of conditions, many patients presenting to their FPs are often treated with inhaled medications and sometimes without proper diagnostic workup. PFTs along with physical examination and patient history are recommended by the *Canadian Thoracic Society* (CTS), *American Thoracic Society* (ATS), *European Respiratory Society* (ETS), and other International guidelines including the GOLD (4) and GINA (15) to objectively assist in the diagnosis, differentiation and categorization of those with obstructive airway diseases (OADs) for proper management. Nonetheless, few family physicians use it routinely because of difficulty in interpreting laboratory PFT output and the significant overlap in the characteristics associated with asthma and COPD in a patient with SOB (117).

Care gaps exist in understanding the similarities and differences in characteristics of OADs patients for appropriate management. Studies designed to assess differences in patient characteristics among patients with different OADs are needed for appropriate disease management. Elucidating individual and clinical characteristics of different OADs in SOB symptomatic patients will help communications among the key players (physicians, pharmacists, nurses, government, etc.) to identify where existing care gaps need improvement for appropriate diagnosis, treatment, and management of patients with SOB symptoms.

1.6.1 Aim and objectives

The overall aim of this thesis project is to examine the epidemiology of spirometrically-derived or specialist diagnosis of obstructive airway diseases in SOB patients and to describe the similarities and differences in factors associated with

physician-diagnosed asthma and COPD in community patients with SOB symptoms recruited from in Edmonton and Saskatchewan in Canada. The specific objectives addressed in the two studies presented in this thesis are:

1.6.2 Objectives of Study 1 – Chapter 3

1) To determine the prevalence of spirometrically-derived or specialist diagnosis of COPD and asthma;

2) The prevalence of PFT usage among family physician (FPs) to perform diagnosis of OADs in community patients;

3) To examine the agreement of family physician diagnosis with that of spirometrically-derived or specialist diagnosis of asthma and COPD.

1.6.3 Objectives of Study 2 – Chapter 4

1) To examine the similarities and differences in the patient factors predicting a spirometrically-derived or specialist diagnosis of asthma, COPD and asthma-COPD overlap syndrome (ACOS),

2) To delineate factors associated with increased risk of in ACOS among patients with SOB symptoms.

Data analyzed for this thesis was collected from the *Epidemiology of Shortness of Breath* (EpiSOB) study, a research program coordinated and conducted in 2007 through 2013 at the *Epidemiology Coordinating and Research* (EPICORE) center at the

University of Alberta in Edmonton. In Chapter 2, we detailed the methodology employed to collect data in the EpiSOB study.

1.6.4 The primary aim of the EpiSOB study program

The primary objective of the EpiSOB program was to examine the diagnosis, treatment and management outcomes of community patients; and compared patients' diagnosis obtained from FPs to that of spirometrically-derived diagnosis based on standard guideline as approved by expert respiratory physicians. The ethics committees at the University of Alberta and the University of Saskatchewan approved the EpiSOB program and the protocol and all patients provided written informed consent. The Health Research Ethics committee at the Memorial University of Newfoundland approves the thesis proposal used to conduct the analysis of the studies presented in chapters three and four.

1.7 References

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CHAPTER 2

Methods of the EpiSOB study program

2.1 EpiSOB Study Overview

The ***Epidemiology of Shortness of Breath*** (EpiSOB) study program was conducted in Saskatoon and Edmonton using community patients with SOB presenting to the pharmacy center for a new prescription or refill of inhaler medication. Data analyzed for this thesis was part of the information collected from the EpiSOB research program conducted in 2007 through 2013 by the *Epidemiology Coordinating and Research* (EPICORE) center at the University of Alberta in Edmonton; and the University of Saskatchewan in Saskatoon, Canada. Information was collected on patients' demographic factors (Appendix H), baseline spirometry (Appendix J), pre-existing comorbidity factors (Appendix H), and history of medication-use (Appendix D). Patients were invited to have their PFTs done to determine their diagnosis of obstructive airway disease based on spirometrically-derived algorithms using standard guidelines for PFTs diagnosis set out by GOLD, 2006 and GINA, 2006 (1,2). Three expert physicians involved in the study approved the spirometrically-derived algorithm used to diagnose the patients for asthma or COPD or both, respectively.

2.1.1 The EpiSOB study program

The EpiSOB program is a study to investigate the diagnostic outcomes of community-dwelling patients with prescribes inhalers for SOB symptoms. Of primary interest is to collect patient data to determine a spirometrically-derived diagnosis of obstructive airway diseases (OADs), mainly asthma, and COPD and others using information based on PFTs recommended by the guideline (1). The methods and materials for the EpiSOB research program are described in full detail in the program manual, which may be obtained upon request at wmidodzi@ualberta.ca.

In brief, the baseline sample of the study subject was a cross-sectional survey of community patients who reported they had been prescribed an inhaler medication for relief or treatment of SOB symptoms by their family physicians. Community pharmacists recruited all patients with new inhaler prescriptions within the past six month or refills.

Eligible respondents were enrolled after obtaining informed consent. Subjects are eligible if they were: *18 years and older with active or recent prescription (within the past six months) for a short-acting beta-2-agonist (SABA), short-acting anticholinergic (SAAC), long-acting beta-2-agonist (LABA), and/or long-acting anticholinergic (LAAC) including combination products and inhaled steroids prescribed by their family physicians for relieve of their SOB symptoms.*

Patients were excluded from the study if they were: *unable to communicate in English, unable or refused to take a physical exam and pulmonary function tests (PFTs), pregnant, and did not provide signed an informed consent form.* All patient included in the study gave informed consent for participation.

For each patient initially recruited, the participating pharmacy centers used an approved script in Edmonton (no. of pts recruited=384) and Saskatoon (no. of pts. recruited=91) to obtain the consent after which an appointment was made to perform a full PFT to obtain the official diagnosis for SOB symptoms. The script used by the pharmacist to recruit patients specifically requested that patient indicate the prescribed inhaler was meant for SOB, and not for viral or bacterial infections, or a cough. However, the patient must indicate that the inhaler prescribed were for SOB from obstructive airway origins. On rear occasions where the recruiting pharmacist is not satisfied with the reasons for the inhaler prescription, a check is made with the patient-physician to ascertain the reason for the prescription. Next section is an excerpt from the recruitment script used by each pharmacy center.

***Pharmacist Recruitment Script**	Hi Mr/Mrs/Ms _____ I see you are prescribed _____. Were you given this medication for shortness of breath?.
	OR
	Hi Mr/Mrs/Ms _____, this is _____ from _____Pharmacy. I noticed that you filled / refilled a prescription for _____. Do you remember why you were given this medication?
	(it needs to be SHORTNESS OF BREATH not for viral or bacterial infections, or a cough).
***If the answer is yes*:**	Are you interested in finding out more about your condition? A research program conducted at the U of S/ or U of A is interested in patients who are given this medication for SHORTNESS OF BREATH, and to look into the cause of shortness of breath.
If yes:	Can I provide your name and phone number to the program office at the University of Saskatoon/ or Alberta?
If patient consents:	Complete Patient Screening/Eligibility Form.
If the patient is eligible:	Someone from the Project Office will be contacting you in the next week to explain the study and set up a time that is good for you.

To standardize the recruitment process of patients, each recruiting pharmacist receives a two day (4 hours per each session) workshop to familiarize with the Pharmacy Manual of Operation developed by the study three physicians at the University of Alberta and the University of Saskatchewan.

Subjects taking bronchodilators were asked to withhold these before visiting the PFT laboratory for pre- and post-bronchodilator spirometry evaluation. A separate consent was provided for bronchodilator withholding before the patients were booked in (Forms in Appendix E). Patients were also asked to complete a questionnaire that included socio-demographic factors, smoking history, comorbidities, family history, current medication, respiratory symptoms, occupational and environmental history,

awareness of diagnosis, and previous tests procedures performed for diagnostic evaluation for SOB (Form in Appendix I). Additionally, patients were asked to complete an asthma control questionnaire (ACQ, Form in Appendix F), and a COPD assessment test (CAT, in Appendix G survey. At the PFT laboratory, a physical examination was conducted on each patient as well as the collection of blood and urine to determine *brain natriuretic peptide* (BNP) (test for heart failure and other biomarkers). The Canadian Thoracic Society (CTS) has recommended a BNP <100pg/ml as the threshold to differentiate obstructive airway diseases as the possible cause of SOB.

2.1.1.1 *Pulmonary function testing in the EpiSOB program*

Pre and post-bronchodilator spirometry and methacholine challenge testing was performed identically at both Edmonton and Saskatoon according to procedures recommended by the standard manual of the American Thoracic Society (ATS). Spirometers were calibrated at the beginning of each workday. After the initial procedure, 2.5 mg salbutamol/albuterol was administered using a nebulizer mask over 5 to 10 minutes to all subjects. After an additional 15 minutes, post-bronchodilator spirometry was performed. All spirometry loops were blinded and reviewed by both PFT technician and a site pulmonologist for adequacy of effort. The pulmonologist who was not associated with the study reviewed all loops and made a recommendation of possible diseases of the patient to the principal investigators.

2.2 Definition of diagnostic outcomes

After patient complete full PFT (pre- and post-bronchodilator), determination of a definite diagnosis of asthma or COPD based on spirometrically-defined PFT using standard international guidelines (GINA and GOLD) was determined. **Table 2.1** (See Form in Appendix L) presents the algorithm used for the spirometrically-derived diagnostic labels used for each patient in the sample. Where a definite diagnosis of asthma or COPD is not clear, patients history of current respiratory symptoms and pre-existing medical record were evaluated by a three expert specialist physician for two-third consensus in cases, where PFT data did not provide the clear indication of asthma or COPD diagnosis. BNP assessment was performed for all patient recruited to rule out heart failure or other heart conditions as the cause of SOB. All patient provide consent to obtain their previous test results for a specialist physician in this study to determine their diagnosis. Previous test results were determined from patient medical records obtained from the Alberta Health Netcare system (http://www.albertanetcare.ca/).

Table 2.1: Study diagnosis of OADs in SOB patients

Diseases	Study diagnosis	Criteria
Asthma (by GINA guideline CTS)	Definite Asthma (spirometrically-defined)	Guideline diagnosis: an increase in FEV_1 >200ml and >12% above pre-bronchodilator FEV_1 OR: Diagnosis by the response to methacholine provocation test: an airway hyperresponsiveness as defined by use of PC_{20} by ATS recommendation
	Probable Asthma (specialist diagnosis)	Diagnosis by 2/3 physician consensus from the review of examination, current respiratory symptoms, and prior medical records.
COPD per GOLD guideline	Definite COPD (spirometrically-defined)	Guideline diagnosis: post-bronchodilator FEV_1 <80% predicted together with an FEV_1/FVC <0.70
	Probable COPD (specialist-diagnosis)	Diagnosis by 2/3 physician consensus from a review of examination, current respiratory symptoms, and prior medical records.
Non-OADs	Probably normal (specialist assessment)	Does not fulfill the criteria for definite or probable asthma and COPD diagnosis.

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1second; FVC, forced vital capacity. (See Appendix A to R for complete diagnostic forms)

2.2.1 Asthma

Definite or spirometrically-defined asthma diagnosis was determined as an increase in FEV_1 >200ml and >12% above pre-bronchodilator FEV_1. If a patient did not meet these criteria, a full methacholine test was performed to determine the presence of positive bronchoprovocation in the diagnosis of asthma. Again, if the patient did not meet the above-specified criteria, a complete review of patient medical record was performed and based on current symptoms history. A specialist-diagnosis is made by three specialist physicians to determine probable asthma diagnosis when two-third consensus agreement is achieved.

2.2.2 COPD

Definite or spirometrically-defined COPD diagnosis is determined based on post-bronchodilator FEV_1 <80% predicted together with an FEV_1/FVC <0.70. If a patient has no history of asthma or COPD diagnosis, a complete review of patients' symptoms history for COPD was performed by the three specialist physicians and a two-thirds consensus achieved constitute a specialist-diagnosis as probable COPD.

2.2.3 ACOS

ACOS was defined based on recent guidelines that specified that when a patient has a similar number of features attributed-to both asthma and COPD, the diagnosis of ACOS should be considered (3). In this study, ACOS was defined based on recent reviews of epidemiological definitions (4).

Table 2.2 presents some of the various definitions of ACOS that have been used in epidemiologic literature and presented recently in a systematic review (5). In this thesis, ACOS was operationalized as follows:

Major Criteria:

1) Physician diagnosis of asthma and COPD in the same patient as per the definition in 2.2.1 (for asthma) and 2.2.2 (for COPD)

OR

2) *Post-Bronchodilator FEV_1 < 80 % predicted and COPD per GOLD*

AND with one minor criterion below:

a. ≥15 % increase in post-bronchodilator FEV_1 or

b. ≥12 % and ≥200 ml in post-bronchodilator FEV_1.

The derivation of ACOS employed was consistent with the recent GINA/GOLD ACOS Consensus Statement: *"ACOS is characterized by persistent airflow limitation*

with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified by the features that it shares with both asthma and COPD"

Table 2.2: Review of epidemiologic definitions of ACOS

	ACOS Criteria or Definitions Utilized in the Literature
Marsh et al. (2008)	COPD per GOLD and any of the following: 1. BDT $FEV_1 \geq 15$ % 2. Peak flow variability ≥20 % during 1 week 3. Physician diagnosis of asthma and either symptom (wheeze or nocturnal SOB and wheeze or nocturnal chest tightness in **the** last 12 months) or use of an inhaler in the last 12 months
Louie et al. (2013)	Major criteria: 1. **Physician diagnosis of asthma and COPD in the same patient** **2.Post-Bronchodilator FEV_1 < 80 % predicted and COPD per GOLD** 3. >40 years old 4. Smoking >10 pack years Minor criteria (AND one of the following): 1**. ≥15 % increase in post-bronchodilator FEV_1** or 2. **≥12 % and ≥200 ml in post-bronchodilator FEV_1**
Soler-Caralunaet al. GesEPOC/SEPAR Consensus Guideline (2012)	**COPD per GOLD** and either 2 major criteria or 1 major and 2 minor criteria are met: Major criteria: 1. **Very positive BDT (increase in FEV_1 > 15 % and >400ml)** 2. Eosinophilia in sputum 3. Personal history of asthma Minor criteria: 1. High total IgE 2. Personal history of atopy 3. **Positive BDT (increase in FEV_1 > 12 % and >200 ml) on two or more occasions**
GINA/GOLD ACOS Consensus Statement	**Characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified by the features that it shares with both asthma and COPD**

The asthma-COPD overlap syndrome (ACOS), Bujarski et al., 2015. The bolded items were employed in this study FEV_1: Forced Expiratory Volume in one second, COPD: Chronic Obstructive Pulmonary Disease, GINA: Global Initiative for Asthma, GOLD: Global Initiative for Chronic Lung Disease.

2.3. Description of the baseline characteristics of patients in the study

Baseline patients' factors that were pre-specified for examination with the three diagnostic outcomes included *socio-demographic factors*, *patient-reported comorbidities*, *family history*, *current medication history*, *current symptoms* based on New York Heart Association Functional Classification (NYHAFC) (6), modified medical research council (mMRC) dyspnea scale (7), ACQ (8), CAT (9), occupational/environmental history, and previous test/procedure.

2.3.1 Socio-demographics factors

This included age, marital status, education level, ethnicity, drug insurance coverage, and smoking history (including second-hand exposure and number of cigarettes/day). Drug insurance was recorded from private/government/other (specify)/none into drug insurance: yes/no; and a number of cigarettes per day were calculated for 10 pack years.

2.3.2 Comorbidities

Patient-reported comorbidities factors comprised of 17 disease conditions namely; allergies, asthma, COPD, chronic bronchitis, sinusitis or nasal polyps, diabetes type I/II, coronary artery diseases (ischemia, history of myocardial infarction, angina, etc.), hypertension, high cholesterol, heart failure, arrhythmias, malignancy, osteoporosis, depression, anxiety, GERD/heartburn, anaemia, or none of the above. These conditions were coded simply yes/no. The conditions were then summed to delineate the number/percentage of patients with one or more conditions. This sum was then grouped

and coded into 1 ‘no comorbidities,' 2 ‘1-2 comorbidities', 3 ‘3-4 comorbidities' and 4 ‘greater than 4 comorbidities'. Family disease history examined included COPD, heart disease, asthma, cystic fibrosis and none of the above. These factors were coded yes/no. Cystic fibrosis was removed from the analysis as no one answered yes to a first-degree family member having it.

2.3.3 Medication History

Patients were asked to respond from a list of 19 medications or specify if the medication name was not identifiable from the list provided the medication they were using within the last six months. For accuracy/comparison, the pharmacists also presented a list of medications each patient was using for the past six months. These individual medications were the factors examined under medication. The medication included, angiotensin-converting enzyme inhibitor (ACE inhibitor), Angiotensin II Receptor Blocker (ARB), beta blockers, calcium channel blocker, diuretics, antidepressant, antipsychotic, antihistamine, LAAC, SAAB, SABA, LABA, inhaled corticosteroids, oral steroids, combination/Symbicort, combination/Advair, theophylline, and Leuko-Triene Receptor Antagonist (LRTA). These factors were coded yes/no. The medications that are used to treat obstructive air diseases (OADs) were then summed into the number/percentage of patients that were using one or more than one medication. This newly created variable was coded as a number of inhaler medications: 1 ‘one,' 2 ‘two,' and 3 ‘three or more.'

2.3.4 Functionality and symptoms scales

Factors examined were New York Association Functional Classification (NYAFC), mMRC dyspnea scale, ACQ, and CAT. The NYHAFC was recoded from a 4 level tier of symptoms into 1 ‘No to mild symptoms (1+2)' 2 ‘marked to the severe limitation (bed bound) (3+)'. The mMRC dyspnea scale was also recoded from a five-level tier of symptoms into 1 ‘No trouble breathing to SOB walking up a slight hill (1+2)' and 2 ‘Walks slower on level ground to too breathless to leave the house (3+)'. Asthma control was measured using the ACQ. The ACQ was a seven questions questionnaire which asked the patients to recall their asthma symptoms over the past week. The score was then averaged, this score tells how well or badly the patient's asthma was being controlled (10). A score of 1 is termed well control while a score above 1 is not well controlled. The mean score computed from this questionnaire was used in the analysis. The CAT questionnaire was used to assess the patients with COPD. This questionnaire consists of 8 questions that were compiled for easy understanding by any patient without assistance. The CAT has a scoring range of 0-40. Total CAT Score is used to help in assessing the severity of the individual condition. However, it was advised by GOLD to used CAT in conjunction with the SGRQ and not on its own (9,11). The total CAT score was computed and analyzed as such.

2.3.5 Occupational or environmental history

Occupational and environmental factors examined were exposure to wood/cotton dust, asbestos (including silica, coal, and talc), stone/glass/clay manufacture, welder/pottery-making, plastic/rubber manufacturer, grains, hooved farm animals (sheep,

goat, cattle, horses, pigs etc.), non-hooved farm animals (chickens, turkeys), hooved wild animals (moose/deer), animal hide or wool processing, gases from formaldehyde (including ammonia, chlorine), paint/lacquer/hairspray/pesticide/acid/solvent, latex gloves, cigarette smoke, and landscaping/gardening soil, or none. These factors were coded as yes to exposure/no exposure.

2.3.6 Prior diagnostic information from physician

Previous tests and procedures done by patients' data based on their responses to the question, "*have you ever had any of the following tests for your SOB symptoms?*" PFT, chest x-ray, echo, ECG or methacholine were coded yes or no. Also, this information confirmed from the patient record on Alberta Netcare (http://www.albertanetcare.ca/).

2.3.7 Physical exam performed and laboratory variables

Also, physical examination was performed for each patient. Variables include weight (kg), height (cm), heart rate (bpm), the respiratory rate per minute, systolic and diastolic blood pressure (mmHg) and oxygen saturation (%). Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. All data cleaning, manipulation, and storage for the EpiSOB program were performed using SPSS version 20 (12).

2.4 Study sample flowchart

The flow chart for the evaluation of diagnostic outcome in the study participants is outlined in Figure 2-1. Of the 475 eligible patients initially screened and agreed to participate for inclusion, 328 provided full PFTs and baseline information for diagnostic

evaluation. The 147 patients that dropped out were mainly due to not showing up at the PFT laboratory after providing initial consent to participate at the recruiting pharmacy centers. There were no baseline characteristics for these patients to evaluate the difference between those patients (n=328) that attended the laboratory for PFTs and were included in this study. The patient recruitment was stopped when the targeted sample size of 323 was attained.

2.5 Ethics approval

The EpiSOB study program was approved by the Research Ethics Office at the University of Saskatchewan (Bio-REB # 09-132, Approved: 29 August 2009), and the Health Research Ethics Board at the University Board at the University of Alberta (# 7530, Approved: October 7, 2008).

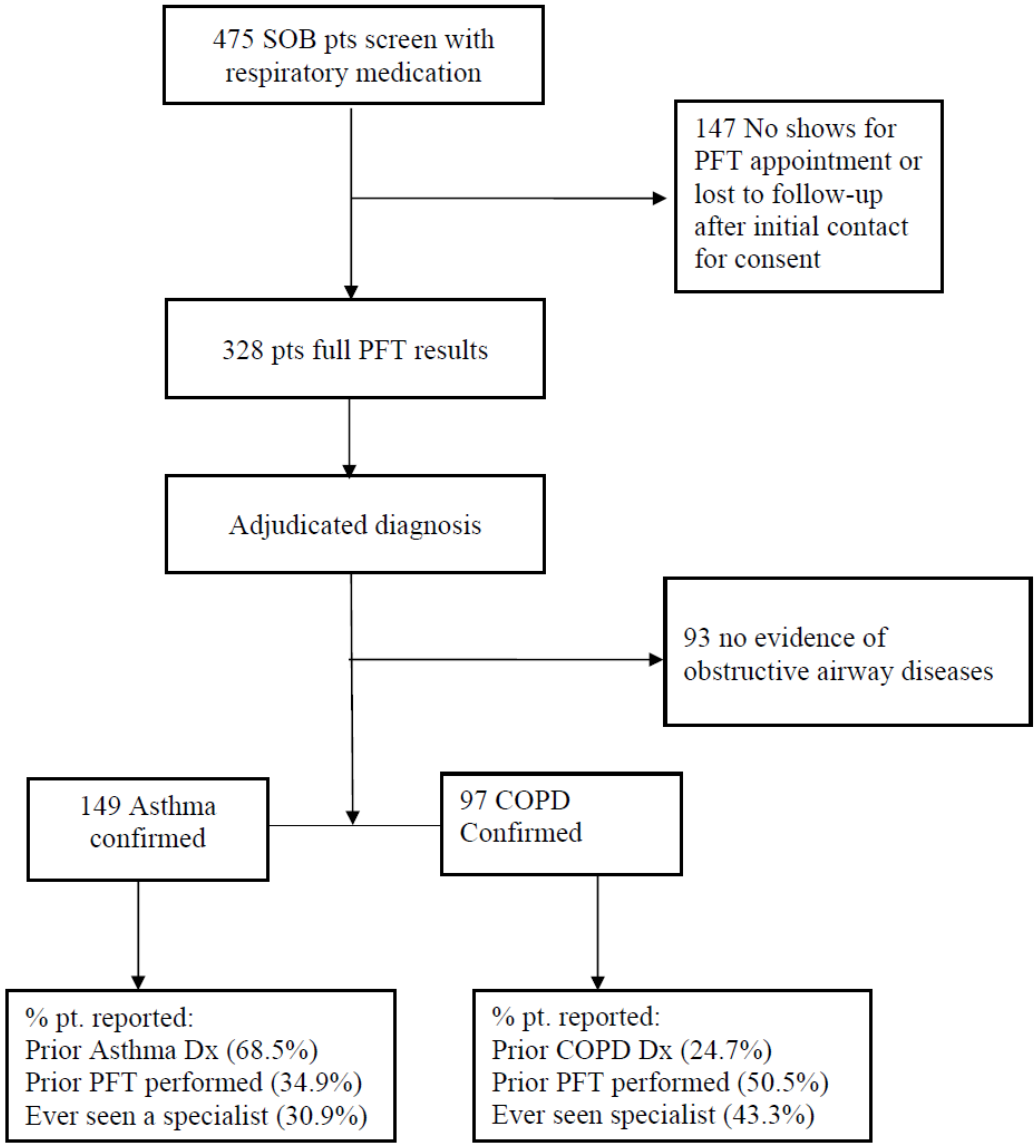

Figure 2.1 Study flow diagram

2.6 Sample size

The EpiSOB study sample size was estimated to be 323 based on 80% power to determine the prevalence of 70% OADs and with a precision of +/- 5%. This was inflated to 350 to account for information that may be missing in some patients. In the final study, 328 patients were achieved to perform their PFTs for diagnostic evaluation for asthma and COPD.

2.6 References

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CHAPTER 3:

Research Study #1: Assessing Misdiagnosis of OADs in community patients with inhaled prescription medication for shortness of breath

A version of this chapter will be submitted for publication

3.1 Abstract

Background: *Obstructive airway diseases* (OADs) mainly asthma and *chronic obstructive pulmonary disease* (COPD) are the two common diseases associated with *shortness of breath* (SOB) symptoms.

Objective: To compare family- physicians (FPs) diagnosis of asthma and COPD among community patients with prescribed inhalers for SOB symptoms to *spirometrically-derived diagnosis* or expert consensus based on ATS/ERS standard guidelines.

Method: Number of 328 eligible SOB patients were identified through community pharmacies in Edmonton and Saskatoon, in Canada. Full pre and post-bronchodilator PFT were performed for each patient and diagnosis was subsequently determined based on guideline-derived criteria approved by three expert physicians (adjudicated by 2/3 consensus).

Result: Forty-five percent (45.4%) of patients had a diagnosis of asthma and 29.6% COPD. Patient subjects were mainly Caucasian (86%), female (57%), and had a postsecondary education (49%) and with a median age of 50 years. Only 41% of patients had prior PFT performed to provide a diagnosis from an FPs. Self-reported medications

for management included SABA (74.1%), inhaled corticosteroids (28.0%), and combination inhaler products (35%). Measures of agreement (that is, sensitivity (Sens) and specificity (Spec)) of physician-diagnosis with guideline-derived diagnosis were: asthma (Sens=71%, Spec=51%, Kappa=0.22, p=0.001), and COPD (Sens=28%.; Spec=95%, Kappa=0.28, p=0.001).

Conclusion: Significant disagreement exists between FPs diagnosis and spirometrically-derived diagnosis among community patients with SOB symptoms. Most community patients have prescribed inhaler medications without a PFT diagnostic workup. This may be in part due to the inadequate understanding of PFT interpretation and usage by family-care physicians.

3.2 Introduction

Asthma and *chronic obstructive pulmonary diseases* (COPD) are the two most frequent diagnoses for OADs in patients with SOB symptoms. OADs are common in Canada (1) and are associated with significant morbidity and mortality. In Alberta, acute exacerbation due to OADs accounts for the most emergency department visits in the province, about 1 in every 37 minutes (2,3). In Ontario, the burden of asthma alone is projected as 1 in 8 individuals by the year 2022, suggesting that OADs will continue to be a major burden on individuals and the health care system in Canada (1). All major guidelines including the GOLD (4) and GINA (5) sponsored by international association such as the *American Thoracic Society* (ATS), *European Respiratory Society* (ERS), the Canadian Thoracic Society (CTS), and the *National Institute for Heart, Lung and Blood* (NIHLB) have recommended the use of full PFT for diagnostic workup for patients with suspected OADs. Despite this recommendation, there is evidence PFTs are underutilized, especially in the primary care setting (6,7).

Recent studies have discussed concern over the accuracy of diagnosis of OADs, including both under- and over-diagnosis of both asthma and COPD (8,9). Among asthma patients in a primary care setting, underdiagnoses were reported despite the widespread use of the *Global Initiative for Asthma* (GINA) guidelines for nearly over 20 years (5). Bellia et al reported COPD had been improperly diagnosed in 19.5% asthmatics, whereas 27.3% of asthma patients were over-diagnosed (9). Misdiagnosis was mainly reportedly to be associated with older age and presence of comorbidities. In addition, it was reported that, among patients on the emergency department treatment of heart failure, 38% were

improperly treated with inhaled beta agonists (10). Furthermore, the above studies used a starting point of a "physician diagnosis" of OAD in their determination of diagnostic accuracy. However, some patients are not specifically given their diagnosis (i.e., are prescribed a trial of the beta agonist or other inhaled therapy) – such patients would be excluded from these studies. The implications of poor diagnostic accuracy are that asthmatics with severe disease may not have optimal management for their condition; COPD patients may be misclassified as asthmatics and vice versa, increasing the risk of OADs hospitalization and subsequent acute exacerbations of the condition leading to death. Taken together, these studies give rise to concerns about the diagnostic workup for desirable management of patients with OADs.

3.2.1 Study objectives

The primary objective of this study is to compare *family-care physician* (FPs) diagnosis of asthma and COPD among community patients with prescribed inhalers to *spirometrically-derived diagnosis* or expert consensus based on ATS/ERS standard guidelines.

The specific objectives are:

1) To determine the prevalence of *spirometrically-derived* or specialist diagnosis of asthma, COPD, and other respiratory diseases in community patients presenting SOB symptoms;
2) To determine the prevalence of FPs usage of PFT for the diagnosis of asthma and COPD, in community-dwelling patients prescribed inhalers for symptoms of SOB;

3) To compare the accuracy of FPs diagnoses of asthma and COPD to *spirometrically-derived* PFT-based diagnosed,
4) To assess patient characteristics predicting misdiagnosis of asthma and COPD from family-care practice.

The ethics committees at the University of Alberta and the University of Saskatchewan approved the EpiSOB program and the protocol. The protocol for the analysis presented in this study was approved by the Health Research Ethics committees at the Memorial University of Newfoundland and Labrador (# 2016.054).

3.3 Methods

3.3.1 Study Setting

The data were gathered as part of a cross-sectional study design in the EpiSOB program to investigate the treatment and management of community patients with an SOB. The design of the EpiSOB program has been described in Chapter 2. In brief, pharmacists recruited patients who had an active prescription (refilled within the past 6 months) for an inhaled medication for shortness of breath symptoms. This included beta agonists (long and short-acting), anticholinergics (long and short-acting), and steroids and combination products. Patients were identified by either a review of a medication list generated by each pharmacy or when patients present themselves to their pharmacist for a refill of their inhaled medications. Patients were excluded if they were prescribed inhaled medications for symptoms other than shortness of breath (e.g., for cough only without

shortness of breath), or if they were not available for follow-up (due to plans to move away from either city or if they could not be contacted).

3.3.2 Study setting, variables, and outcomes

The EpiSOB program collected data from consenting patients who were invited to receive full PFT. At the testing session, a questionnaire was used to collect patient information on baseline *socio-demographic characteristic, smoking, medical and comorbidity, and allergy history, respiratory symptoms, and prior history of diagnosis obtained from family physicians.* Again, the research coordinator (or designated laboratory technician) collected patient information including baseline symptoms such as *COPD assessment test* (CAT) and *Asthma Control Questionnaire* (ACQs), functional capacity using the *Medical Research Council* (MRC) dyspnea scale and *New York Heart Association Functional Classification Scale* (if applicable). Patients were also asked for their knowledge of their diagnosis of asthma and COPD from their family-care physician or specialist.

Standard full PFT laboratory testing, as per recommendations from the American Thoracic Society (ATS) and European Thoracic Society (ETS) was employed to collect data for diagnosis. This included pre-post bronchodilator testing. Bronchi-hyperresponsive was later performed with further methacholine challenge testing for all asymptomatic patients that did not show any evidence of OADs from the initial pre- and post-bronchodilator PFT results. Further, BNP assessment was performed for all patients to rule out heart failure or other heart conditions as the causes of SOB. The *Canadian Thoracic Society* (CTS) has recommended a BNP <100pg/ml as the threshold to

differentiate OADs as the possible cause of SOB. All patients consented to obtain previous diagnostic test results of PFT, Chest X-rays, Echocardiogram (ECG), and methacholine from a specialist physician for the determination of other diagnoses. The patient medical and diagnostic records were retrieved from health record archived and obtained from the Alberta Health Net care system (http://www.albertanetcare.ca/).

3.3.3 Spirometry PFT-based or specialist adjudicated OADs outcomes

After data cleaning, subjects were placed into diagnostic categories based on PFT-based diagnostic criteria drawn from the guidelines developed by the GOLD. The algorithm for the diagnostic criteria is well described in Chapter 2. In brief, Asthma diagnosis was determined by an increase in forced expiratory volume in the first second, FEV_1 >200ml and >12% above pre-bronchodilator FEV_1. If a patient did not meet this criterion, a full methacholine test was performed to determine the presence of positive bronchoprovocation in the diagnosis of asthma. Further, if the patient did not meet the above-specified criteria, a complete patient medical record review is performed for adjudication by our physician panel. A diagnosis of asthma was defined as, two of three agreements from our 3-physician panel. COPD diagnosis is determined based on post-bronchodilator FEV1 <80% predicted together with an FEV1/FVC <0.70. If the patient did not meet these criteria, then they were reviewed by our physician panel. Again, a consensus of two of the three physicians on our adjudication panel was required to confirm a diagnosis of COPD. *Adjudicated diagnosis for other diagnoses of non-OAD origin* (that is; where PFTs and current symptom review data did not provide a clear indication of asthma or COPD diagnosis), a further review of the pre-existing medical

record from Alberta Net CARE, and history of current symptoms are evaluated by our physician panel. As outlined above, agreement by two of the three physician adjudication panel constituted a diagnosis for the patient. In patients with a BNP >100pg/ml, a cardiologist consultation was performed to evaluate the patient for heart failure.

3.3.4 Statistical analysis

The main analyses presented in this chapter included: (1) assessment of the incidence of PFT based adjudicated diagnosis for asthma, COPD, and other pulmonary diseases in SOB patients as approved by expert physicians ; (2) prevalence of patients' reported baseline characteristics, (3) examination of patients' reported prior health status, comorbidity outcomes, laboratory diagnostic factors, and medications prescribed from FP as compared by PFT-based adjudicated diagnosis of asthma and COPD; (4); assessment of agreement of FP diagnosis with a PFT-based derived diagnosis of asthma and COPD; and (5), multivariate analysis of patient factors predicting family-physician misdiagnosis of asthma and COPD.

Baseline univariate analyses were performed using SPSS Version 20.0 (IBM Corporation, USA). Percentage of baseline characteristics and patient final diagnostic outcomes were presented for categorical variables and median and quartiles for continuous variables. After identifying univariate patient factors predicting PFT based adjudicated diagnosis of asthma and COPD in a bivariate analysis, multiple logistic regression analysis was performed using purposeful selection and including clinically relevant baseline factors that were significant in the univariate analysis at $p<0.05$.

Using the spirometrically-derived PFT-based or three panels of expert adjudicated diagnosis of asthma and COPD as the Gold Standard, we conducted sensitivity, and specificity analysis to determine the validity and accuracy of a prior family-care physician (FP)-based diagnoses. Agreement of FP diagnosis compared with PFT-based guideline-derived diagnosis (as determined by 2/3 consensus by respiratory specialist) was assessed by the following measures: sensitivity (%), specificity (%), positive predicted values, PPV (%), negative predicted values, NPV (%), the Kappa statistics, and p-value for significance

Outcomes for FP misdiagnosis of obstructive airway diseases were defined as 'false positive' or 'false negative' asthma, and 'false positive' or 'false negative' COPD. These false outcomes were employed separately in asthma diagnosed (yes and no) and COPD diagnosed (yes or no) samples to assess patient characteristics associated with the family physician misdiagnosis (false positive and false negative) of asthma and COPD.

Individual patient factors associated with family physician misdiagnosis of OADs in a univariate model were entered in a final multivariate logistic model. The Odds ratios (ORs) and the 95% confidence interval (95%) for each multivariate factor predicting family-physician misdiagnosis of asthma and COPD together with the classification index (c-index) for each male of false positive or negative diagnosis of asthma and COPD from family physician were presented. Effect modification was assessed for all factors that were retained in the final multivariate model at $p<0.01$ using the interaction term.

3.4 Results

The subjects included in the analysis and presented in this chapter comprised of the 328 patients that had performed full pre and post-bronchodilator PFT diagnostic workout of obstructive airway diseases (that is, asthma and COPD), and diagnostic workout for other pulmonary diseases as adjudicated by a panel consensus from three specialist physicians. **Table 3.1** present the incidence of diagnostic workout for the sample.

3.4.1 PFT-based adjudicated outcomes from specialist physicians

The PFT-based or specialist adjudicated diagnoses from our study physician panel are shown in **Table 3.1**. Asthma was confirmed in 149 patients (45%), COPD was confirmed in 97 patients post-bronchodilator (30%), and 93 patients (28%) had no evidence of obstructive airway diseases either by PFT data or with further methacholine challenge testing. Of patients diagnosed with asthma or COPD, 11 had both diseases. Heart failure (3%) and restrictive lung disease such as pulmonary atrial hypertension were the main other diagnosis determined for the patient with no evidence of obstructive airway disease. Diagnoses could not be determined by our expert physician panel for 71 (22%) of the patients with no evidence of OADs after pulmonary function testing and expert evaluation of information available in patients' medical log on Netcare.

Table 3.1: PFT based adjudicated diagnosis for shortness of breath approved by expert physicians

Diagnostic outcome	n (% of N=328)
*Asthma diagnosis	149 (45.4)
*COPD diagnosis	97 (29.6)
#Others diagnosis	20 (6.1)
Heart failure	9 (2.7)
Bronchitis	2(0.61)
Obesity	1(0.3)
Restrictive lung diseases/Pulmonary hypertension	8(2.4)
Unknown origin (indeterminate cause for SOB)	71 (21.6)

*11 patients may have both asthma and COPD diagnosis; N: number; COPD: Chronic Obstructive Pulmonary Disease, %: Percentage. #Numbers may include multiple diagnoses.

3.4.2 Baseline characteristics

Major characteristics of patients at baseline are summarized in **Table 3.2**. The study sample comprised of 42.7% male, 86% Caucasian race, 49.1% had completed post-secondary education, and 58% were married and median smoking pack-year for current smokers was 7.5. The median age was 50 years, and 97% had at least one comorbid condition reported with an average of 4.3 ± 2.3 per patient. The most frequently reported comorbid conditions were allergies (78%), hypertension (26%), depression (32%), anxiety (27%), heartburn (13%), bronchitis (25.0%) and existing or prior history of asthma (68.8%) and COPD (11.9%).

The median for the ACQ score was 7.0 and CAT scores 12.0 with a lower score representing the absence of airway disease symptoms and a higher score representing frequent respiratory symptoms for OADs. Twenty-two percent (22%) of patients reported moderate (three) to severe (five) scores on the modified Medical Research Council dyspnea scale and 26% with reported NYHA-FC III or IV symptoms. Current symptoms mostly reported were the day-time or a night-time cough (36%), sputum production

(47%), chest tightness (52%), wheezing (60%), and fatigue (50%). A total of 216 (66 %) out of 328 patients reported ever receiving a diagnosis for their shortness of breath symptoms provided by their family physician. Thirty-nine percent of patients reported seeing a specialist for diagnosis, and 41% had previous PFTs conducted. Medications prescribed included short-acting beta-agonists in 74%, inhaled corticosteroids in 28%, and combinations products in 59% of the study participants.

Table 3.2: Patient characteristics (N=328)

Baseline characteristics	**Median (Q1, Q2)**	**No. (%)**
Edmonton subjects recruited		274 (83.5)
Age, years	50.0 (32, 64)	
Male, sex		140 (42.7)
Caucasian ethnicity		283 (86.3)
Completed post-secondary education		161 (49.1)
Married or common-law status		190 (57.9)
Weight, kg	80.8 (68.0, 95.7)	
Height, cm	167 (160, 173)	
Current Smoker		65 (19.8)
Pack-years	7.5 (5.0, 10.0)	
Comorbidity History		
Allergies		255(77.7)
Prior asthma		225 (68.6)
Chronic Bronchitis		82 (25.0)
Prior COPD		30 (11.9)
Diabetes		29 (8.8)
CAD		28 (8.5)
Hypertension		85(25.9)
High Cholesterol		58 (17.7)
Prior Heart Failure		6 (1.8)
Depression		104 (31.7)
Heart Burn		142 (43.3)
Current respiratory symptoms		
MRC Dyspnea Scale (3-5)		73(22.3)
Nocturnal cough		119 (36.3)
Sputum production		153 (46.7)
Chest tightness		171 (52.1)
Wheeze		197 (60.1)
Other symptoms		
Edema		57 (17.4)
Fatigue		163 (49.7)
Bilateral ankle edema		76 (23.2)

Recently absent from work		50 (15.2)
Fever or Flu symptoms present		54 (16.4)
Median total ACQ	7.0 (3.0, 12.0)	
Mean total CAT	12.0 (8.0, 19.0)	
Current inhaler medication used for SOB		
Anticholinergic		
Long-acting		25 (7.6)
Short-acting		14 (4.3)
Beta 2 agonist		
Long-acting		18 (5.5)
Short-acting		243 (74.1)
Steroid		
Inhaled corticosteroids		92 (28.0)
Oral steroids		16 (4.9)
Combination		
Symbicort		113 (34.5)
Advair		85 (25.9)
Theophylline		5 (1.5)
LTRA (singular)		26 (7.9)
Patient-reported outcomes		
Ever had a diagnosis for SOB		216 (65.9)
Ever diagnosed with asthma		181 (55.2)
Ever diagnosed with COPD		34 (10.4)
Ever seen a specialist		128 (39.0)

CAD: Cardiac Artery Diseases. COPD: Chronic Obstructive Pulmonary Disease, SD: Standard Deviation, N: number; ECG: %: Percentage Electrocardiogram; mMRC: modified Medical Research Council; SOB: Shortness of Breath; ACQ: Asthma control Questionnaire; CAT: COPD Assessment Test; LTRA: Leukotriene Receptor Antagonist

3.4.3 Comparative analysis of FPs-based to PFT- based diagnostic outcomes

Of the total of 328 patients who received full PFT diagnostic workup, only 41% of patients had reported ever had prior PFT performed for diagnostic workup from FP for their SOB symptoms. **Table 3.3** present the patient's prior diagnosis and treatment outcomes from their FPs compared to PFT-based adjudicated diagnosis. Based upon adjudicated results by the specialist physicians in our study, only 69% and 25% were diagnosed accurately with asthma and COPD respectively, in their prior history. Of the 149 patients diagnosed with asthma, only 35% reported ever had PFT performed, while for the 97 patients with confirmed COPD, only 51 % ever had PFT performed (**Table**

3.3). Prior use of methacholine was only 1% and 2% respectively for asthma and COPD patients.

Table 3.3: Patients' prior outcome reported, laboratory diagnostic factors, medications prescribed from FP compared by PFT based adjudicated diagnosis

FP based diagnosis/treatment outcome	PFT based adjudicated diagnosis of SOB		
	Asthma (n=149)	**COPD (n= 97)**	**Neither (n=93)**
Ever diagnosed by Family physician	110 (73.8)	65 (67.0)	49 (52.7)
Asthma	102 (68.5)	45 (46.4)	41 (44.1)
COPD	9 (6.0)	24 (24.7)	2 (2.2)
Ever referred to specialist by family physician	40 (26.8)	45 (46.4)	33 (35.5)
Ever seen or specialist	46 (30.9)	51 (52.6)	36 (38.7)
Ever diagnosed by specialist	38 (25.5)	42 (43.3)	21 (22.6)
Asthma	29 (19.5)	24 (24.7)	16 (17.2)
COPD	3 (2.0)	15 (15.5)	2 (2.2)
Prior Test/procedure			
Ever had a diagnostic test perform for SOB	92 (65.10)	85 (87.6)	73 (79.5)
PFT	52 (34.9)	49 (50.5)	39 (41.9)
Chest X-ray	58 (38.9)	67 (69.1)	56 (60.2)
Echo	7 (4.7)	24 (24.7)	18 (19.4)
ECG	55 (36.9)	57 (58.8)	44 (47.3)
Methacholine test	1 (0.7)	2 (2.1)	1 (1.1)
Respiratory medication (inhalers)			
Anticholinergic			
Long acting	4 (2.7)	20 (20.6)	1 (1.1)
Short acting	120 (80.5)	9 (9.6)	1 (1.1)
Beta 2 agonist			
Long acting	7 (4.7)	5 (0.5)	6 (6.5)
Short acting	120 (80.5)	68 (70.1)	65 (69.9)
Steroid			
Inhaled corticosteroids	42 (28.2)	24 (24.7)	29 (31.2)
Oral steroids	8 (5.4)	3 (3.1)	5 (5.4)
Combination			
Symbicort	54 (36.2)	37 (38.1)	27 (29.0)
Advair	36 (24.2)	33 (34.0)	21 (22.6)
Theophylline	1 (0.7)	4 (4.1)	None
LTRA (singular)	12 (8.1)	7 (7.2)	9 (9.7)

COPD: Chronic Obstructive Pulmonary Disease, N: number, ECG: Electrocardiogram; SOB: Shortness of Breath; ACQ: Asthma control Questionnaire; CAT: COPD Assessment Test, LTRA: Leukotriene Receptor Antagonist

Table 3.4 presents the sensitivity and specificity analysis for asthma and COPD for the assessment of agreement of FP diagnosis compared with the PFT-based diagnosis which was used as the reference based on the standard guideline. Agreement of FP diagnosis compared with PFT-based guideline-derived diagnosis (as determined by respiratory specialist) was minimal for asthma (Sens=71.1%, Spec=51.4%, Kappa=0.22, p=0.001) and COPD (Sens=27.8%; Spec=97.2%, Kappa=0.28, p=0.001) but statistically significant.

Table 3.4: Agreement of FP diagnosis with a PFT-based derived diagnosis of asthma and COPD

		PFT-based adjudicated diagnosis					
		Asthma			COPD		
		Yes	No	Total	Yes	No	Total
Family physician diagnosis for OADs	Yes	106	87	**193**	27	11	**38**
	No	43	92	**135**	70	220	**290**
	Total	**149**	**179**	**328**	**97**	**231**	**328**
	Sensitivity (%)			71.1			27.8
	Specificity (%)			51.4			95.2
	PPV (%)			54.9			71.1
	NPV (%)			68.1			75.9
	Kappa			0.22			0.28
	p-value			<0.001			<0.001

OADs: Obstructive Airway Diseases, COPD: Chronic Obstructive Pulmonary Disease, %: Percentage

Table 3.5 presents patient factors associated with family physician misdiagnosis of OADs in SOB patients. In the multivariate models, factors associated with a false-positive asthma diagnosis were: age, years, history of allergies and current sputum production, and factors for false positive COPD were: increased pack-year of smoking, lower oxygen saturation and lower FEV ratio of percent predicted at baseline. All interaction term examined showed no significant association. The classification index (c-index) for the false positive COPD was 95.6% including increased pack-year of smoking, low oxygen saturation and low FEV_1/FVC ratio as the most significant predictors.

Table 3.5: Multivariate analysis of patient factors predicting family-physician misdiagnosis of asthma and COPD

	Asthma OR (95%CI)		COPD (n=97) OR (95%CI)	
Patient predictors	False Negatives (43/149)	False Positives (87/179)	False Negatives (70/97)	False Positives (11/231)
Age, years		.97 (.95-.99)	.95(.91-.99)	
Female sex	2.8(1.2-6.8)			
No allergic history	5.2(1.7-15.5)	0.4(0.2-0.7)		
Pack-years of smoking				1.2(1.1-1.3)
No Fatigue	3.1 (1.3-1.0)		4.2 (1.5-12.0)	
History of hypertension	6.8 (2.4-19.1)			
Sputum production		2.0 (1.1-3.7)		
*Oxygen saturation				0.7 (0.5-9.0)
No 1st degree Family has a history of COPD			3.7 (1.2-11.2)	
FEV1/FVC ratio % predicted				.94(.86-.98)
C-index (%)	**78.5**	**65.9**	**71.1**	**95.6**

Patient with true spirometry PFT-based or adjudicated diagnosis of SOB, %: Percentage

3.5 Discussion

3.5.1 Summary results from this study

Very few studies have yet been conducted to assess PFT use in community patient with shortness of breath and suspected to have OADs. This study has shown that many community-dwelling patients treated for presumed OADs with inhalers and shortness of breath symptoms do not have asthma or COPD. This coupled with the fact that only 41% of patients had ever had PFT performed, highlights the need to avoid empiric treatment with beta agonists and steroids and increase the use of objective lung function tests such as spirometry or full PFT.

Our results are comparable to other study conducted in Quebec and Ontario to evaluate primary care practice in patients with COPD compared to recommended care (11). In this reported study, participating physicians recruited 1090 patients of which 320 were from Quebec and 770 in Ontario. Spirometric confirmation of diagnosis, based on recommended guidelines was reported in 56% of the patients recruited (11). Also, in a multicenter study conducted in Italy involving 24 pulmonary or geriatric institutions, 128 asthmatic patients, mostly elderly women (98 women, aged 73 ± 6.4 years) were recruited for this study (9). The study reported that under-diagnosis was associated with better functional conditions, expressed by spirometry, even when wheezing or a proportional response to a bronchodilator test was performed. Of 123 asthmatics, COPD had been improperly diagnosed in 19.5%, whereas 27.3% of asthmatics did not report any previous diagnosis of asthma (insert reference). A recent study conducted in Italy by Magnoni et

al. (2015) using GP database of patients with at least three prescriptions of inhaled or nebulized corticosteroids found out that there was vast under/misdiagnosis of asthma in the Italian primary care setting despite the over 20 years use of the GINA guidelines before the study was conducted (8). In a survey conducted by Chapman et al (2001), of 96 American and 96 Canadian primary-care physicians, using a hypothetical case presentation and a structured interview, the likelihood of COPD diagnosis rates increased for both men and women at 74% vs 66% (p = not significant) with spirometry after initial diagnosis without spirometry (12). The study revealed that only 22% of physicians would have requested spirometry after initial presentation by COPD patients. Currently, there is a consensus proposal for the need to increase the use of PFT in family care practice for better diagnosis, treatment, and management of obstructive airway disease. This will also improve the differential diagnosis and to rule-out restrictive lung diseases that might be the potential causes of SOB symptoms.

Strength and study limitations

The main strength of this study is the used of well-accepted diagnostic criteria from the ETS/ATS guideline that have been approved by three Respirologist on adjudication panel. Also, the use of community-dwelling patients recruited through their community pharmacist removes selection bias by physician diagnosis in previous studies, although may have reflected the recruitment of patients with a pharmacist's clinical suspicion for the need for confirmation of the diagnosis. The main limitation is those subjects were only recruited from Edmonton and Saskatoon which may not be reflective of Canada as a whole.

Taken together with other studies such as Tinkleman DG, 2006 (13), this study suggests that many community-dwelling patients receiving inhaled medications may be incorrectly diagnosed with obstructive airways disease. This may lead to exposure to unnecessary treatments (and their expense), and be forgoing more definitive therapies for other conditions such as heart failure or primary pulmonary hypertension. Our study and others highlight the need for all patients suspected of obstructive pulmonary disease to have objective measures of lung function (spirometry and/or pulmonary function testing) performed to make the diagnosis. Another implication of our study relates to pharmacoepidemiologic studies which often use inhaler prescriptions as a proxy for asthma. Based on our findings, up to half of such cases may not have asthma. Future work should evaluate the barriers to using PFT, as well as efforts to empower patients and other primary care providers such as pharmacists (14) to advocate or request such testing.

3.5.2 Conclusions

This study found that in a group of community-dwelling patients being treated with inhaled medications for presumed obstructive airways disease and shortness of breath, fewer than half had asthma, about a quarter had COPD, and another quarter had no demonstrable obstructive airways disease. Modest but significant agreement exists between family physician diagnosis and PFT-based guideline-derived diagnosis for SOB patients. Most patients with SOB symptoms are prescribed inhalers without a PFT diagnostic workup. This may be, in part, due to the inadequate understanding of PFT interpretation and usage by family-care physicians. Further reasons why family physicians would rationally "underuse" PFTs maybe cost, non-adherence, time off work,

the trial of therapeutics etc. Access to timely testing may also play a role. This highlights the need to increase the use of PFT or spirometry to prevent the misdiagnosis and overtreatment of patients with symptoms of shortness of breath.

3.6 References

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CHAPTER 4:

Research Study 2: Examining the determinants of Asthma, COPD and the Overlap Syndrome in patients with shortness of breath

A version of this chapter will be submitted for publication

4.1 Abstract

Background: Recently acknowledged, physician-diagnosed outcomes of asthma and COPD have several overlapping symptoms, and approximately 10% of COPD patients may have concurrent features of asthma. This has been termed the ***asthma-COPD overlap syndrome*** (or ACOS) and has its first international guideline diagnosis, treatment, and management in 2015.

Objective: This study primarily aimed at examining the similarities and difference in patients' characteristics associated with spirometrically-derived asthma, COPD, and the ACOS.

Methods: The three diagnostic outcomes for comparative analysis in patients with shortness of breath were spirometrically-derived diagnosis for *asthma only*, (with no indication of COPD), COPD only (with no evidence of asthma) using a definition based on the standard guideline and ACOS using epidemiological studies as defined in Chapter 2(***see*** **Table 2.1**). All patients with no diagnosis of asthma and COPD were classified as non-obstructive airway diseases (NOADs) and used as the comparator for the multinomial analysis of the three outcomes presented in the study.

Results: Age was an important variable associated with the diagnosis of *asthma only*, *COPD only*, and *ACOS*. ACOS patients were ten times more likely to have a previous history of asthma (OR: 10.60, 95% CI: 3.53 – 31.83) compared to *COPD only* which were less likely to have a previous history of asthma (OR: 0.57, 95% CI: 0.35 - 0.94). In a multivariate analysis, patients diagnosed with *asthma only* were more likely to have allergies; and patients with a spirometrically-derived diagnosis for *COPD only* were significantly less likely to have anaemia as a comorbidity (p=0.015) and are significantly less likely to have had a history for asthma.

Conclusion: This study shows that patient with ACOS are usually older than 40 years, have a previous history of asthma as well a history of cigarette smoking, and are more likely to be prescribed a combination therapy as a treatment for their SOB symptom.

4.1 Introduction

A new phenotype of obstructive airway diseases (OAD) termed Asthma-COPD overlap syndrome (ACOS) has recently been identified (1). The current review of the literature suggested patients diagnosed with ACOS, when compared with COPD or asthma alone are associated with low health-related quality of life, increased hospitalization, more frequent exacerbation, higher mortality rates, and higher health care cost (2–6). Very few epidemiological studies have been conducted to understand patient physiological characteristics, comorbidities, and quality of life (QoL) associated with ACOS. Especially, the similarities and differences in a patient's characteristics related to ACOS are not apparent. There is an urgent need for epidemiological studies to understand and guide better recognition of risk factors for ACOS and appropriate treatment options for patients(4,7).

Asthma and chronic obstructive pulmonary disease (COPD) are the two most chronic obstructive airway diseases and account for over 70% of patients presenting to family physician requiring relief for shortness of breath (SOB) symptoms (8). Both conditions involved airflow obstruction and have been associated with many genetic and environmental factors and gene-environment interactions (9,10). While airway obstruction is usually reversible in asthma, airflow limitation in COPD is not completely reversible in most patients (11,12). COPD is a progressive respiratory disease and is characterized by airflow obstruction over time and increased inflammation (13). A daily morning cough that produces phlegm is a characteristic of chronic bronchitis, a type of COPD. Treatment with bronchodilators, and inhaled corticosteroids or combination

products reduces the risk of exacerbation of both diseases; although only one-third of COPD patients show improvement in airflow obstruction with bronchodilators. During COPD exacerbation, the airways are usually narrowed with increased resistance to exhaling air from the lung, resulting in air entrapment in the lung with a worsened SOB (14,15). Pharmacologically, COPD is treated based on its severity and phenotype (16). The aim of COPD pharmacological therapy as set out by the GOLD and Finnish guidelines are to control symptoms and improve QoL, reduce and prevent future risk for exacerbation, slow disease progression, increase exercise tolerance and reduce mortality (10,17). These therapies include bronchodilators, the combination of Inhale corticosteroids (ICS) and long-acting bronchodilators, phosphodiesterase 4 (PDE4) inhibitors or theophylline, and influenza and pneumococcal vaccination (17). In COPD patients with frequent exacerbation, a triple therapy is usually recommended for COPD exacerbation, this usually includes a long-acting muscarinic antagonist (LAMA), long-acting inhaled beta-agonists (LABA), and an ICS (7,16)

Although asthma and COPD are two distinct disorders (18), family physicians often find it difficult to differentiate between the two and make an accurate diagnosis and initiate medical therapy (2,19). Wheezing associated with chest tightness is more familiar with asthma, and patients are more likely to have allergies such as allergic rhinitis or atopic dermatitis in the presence of an increased level of circulating immunoglobulin E (IgE) in the blood(18). Thus, a clinical diagnosis of asthma includes a history of allergies, the presence of wheezing symptoms and reduced spirometry forced expiratory volume in one second (FEV_1). A sputum producing chronic cough, with a significant reduction in spirometry FEV_1/FVC ratio, is more indicative of COPD (7).

Recently acknowledged, asthma and COPD have several overlapping symptoms, and approximately 10% of COPD patients may have concurrent features of asthma. This has been termed the asthma-*COPD overlap syndrome* (or ACOS) and has its first international guideline diagnosis, treatment, and management in 2015 (19). GOLD and GINA has collectively defined ACOS as "*persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD*" (19). The features, therefore, identify ACOS that it shared with both asthma and COPD (20).

Most commonly, this phenotype is thought of as a diagnosis of COPD in previously diagnosed asthma patients or as incomplete reversibility of the airway obstruction in asthma patients. In recent studies, 13% and 17% of COPD patients reported that they have previously been diagnosed with asthma (3,21). History of asthma that has become unresponsive to treatment may lead to chronic irreversible airflow obstruction with reduced lung function resulting in clinical ACOS (22,23).

4.1.1 Study objectives

This study aimed at examining the similarities and difference in patient's characteristics associated with asthma, COPD, and the ACOS.

The specific objectives are:

1) To examine the similarities and differences in the patient factors predicting a spirometrically-derived or specialist diagnosis of asthma, COPD and asthma-COPD overlap syndrome (ACOS),

2) To delineate patient factors that differentiate ACOS from the diagnosis of asthma alone and COPD alone among patients with SOB symptoms.

To the best of our knowledge, there is no epidemiological study yet conducted in the population to understand the similarity and difference in patient characteristics associated with these phenotypes of OADs. To understand the delicate nuances between these seemingly similar OADs it is important to identify individual and clinically relevant patient factors differentiating between them. This could help differentiate the proper diagnosis of these three OADs phenotypes in community patients with SOB symptoms. Understanding the distinct patient factors distinguishing these diseases will assist the family physician to guide appropriate treatment and management of SOB patients.

The ethics committees at the University of Alberta and the University of Saskatchewan approved the EpiSOB program and the protocol. The proposal for the study was approved by the Health Research Ethics Board at the Memorial University of Newfoundland (# 2016.054).

4.2 Methods

4.2.1 Study Objective

In this study, the primary goals are: (I) to examine the similarities and differences in risk factors associated with specialist-physician diagnosed asthma and COPD using standard guidelines; and (II) to delineate risk factors for ACOS compared to those diagnosed with asthma only or COPD only; in SOB patients with prescription of inhaled medication.

4.2.2 Study Setting

This study analyzed secondary data from The *Investigation of the Epidemiology of Shortness of Breath (EpiSOB)* study, which was conducted in Edmonton and Saskatoon, Canada. The proposal for this study was approved by the Health Research Ethics Board (HREB) at the Memorial University in St. John's, Newfoundland and Labrador. The EpiSOB study and variables collected for analysis has been described extensively in **Chapter 2** for review. All patients' data were collected and stored for analysis on an encrypted computer accessible only to the student and the primary supervisor at the Clinical Epidemiology Unit at the Memorial University Faculty of Medicine.

4.2.3 Study variable and outcomes

The description of the factors included in the analysis of this study has been described in **Chapter 2**. These include socio-demographic characteristic *(age sex, race, marital status, education, smoking history),*comorbidities including previous history of asthma and/or COPD, medications, respiratory symptoms (measured by NYHA-FC, and mMRC dyspnea scale), occupation/environmental history, physical exam, and previous

test procedures for SOB symptoms (*PFT, chest X-ray, echocardiogram, electrocardiogram (ECG), and methacholine*). Additional information was also collected on patients' symptoms management using the *COPD assessment test* (CAT) and the *Asthma Control Questionnaire* (ACQs).

The three outcomes variables examined in this study were patients diagnosed with *asthma only, COPD only*, and defined ACOS. The specialist physicians used patients' laboratory results (Chapter 2) as well as patient medical records obtained from the Alberta Health Net care system (http://www.albertanetcare.ca/).

4.2.4 Statistical analysis

The three primary diagnostic outcomes for comparative analysis were *asthma only*, (with no indication of COPD), COPD only (with no evidence of asthma) and ACOS with a definition based on based on the standard guideline and epidemiological studies (see **Table 2.1**). All patients with no diagnosis of asthma and COPD were classified as non-obstructive airway diseases (NOADs) and used as a comparator for the analysis. Pearson's chi-squared tests and t-test or ANOVA was used when appropriate to describe the categorical and continuous data. Simple proportions or means were examined across demographic categories, and comparisons were made using the t-test and Pearson's chi-squared test, respectively. Significant differences using p-Values were determined at the 0.05 threshold. In a bivariate analysis, binary logistic regression was employed to identify individual and important variables predicting outcome across the three major diagnostic groups. Binary logistic regression was performed individually on each interested outcome variables (asthma only, COPD only, and ACOS), comparing each one to all the others.

First, a univariate analysis was done on each independent variables (comparing asthma to other patients with no asthma, and similarly COPD to other patients with no diagnosis of COPD, and similarly ACOS to others). All independent variables at $p<0.20$ level in the bivariate analysis were then entered into the multivariate selection model. Multivariate backward forward and stepwise regression was then performed on the significant independent variables controlling for the variables that were a known cause or associated with COPD and asthma or ACOS. All variables that were then significant at the $p<0.20$ level were then *forced entered* into a final multivariate model.

A multinomial regression analysis was performed to simultaneously evaluate the similarities and differences between asthma and COPD and to examine the factors that are associated with ACOS. The multinomial analysis is more appropriate than the logistic regression. The reason is that multinomial analysis allows you to compare all the outcomes simultaneously. The multinomial logistic regression approach performs the analysis in a single model with a global p-Value which is conservative than the binary logistic regression which performs the analysis in a pairwise fashion for each outcome with separate p-value obtain for each model. In this multinomial analysis, all the variables which have been identified in the multivariate logistic analysis of each of the three outcomes were included in the multinomial regression analysis. A backward variable selection was employed to build the model.

4.3 Results

4.3.1 Prevalence of AODs diagnostic outcomes in shortness of breath

The sample in this analysis included a total of 328 SOB patients, 83.5% of which were recruited from Edmonton. Of these, the prevalence of the three diagnostic outcomes was: 42% of patients were diagnosed with asthma only, 13% with only COPD and 17% had ACOS. The remaining 28% were determined as having no evidence of obstructive airway diseases (NOAD) as determined by the specialist physicians.

4.3.2 Description of patient baseline characteristics by diagnostic groups.

In column 1 of **Table 4.1**, the characteristics at baseline for all 328 patients in the sample are shown. Of the total sample (328) 83.5% were recruited from Edmonton with a median age of 49 years and 42.7% being males. Eighty-six percent (86.3%) of this study population were Caucasians, 88.4% had drug insurance, and 19.8% were current cigarette smokers. 77.7% of all patients had allergies with 68.6% being told previously by their family physician they have asthma. Short-Acting Beta-2 agonists were the currently prescribed inhaler medication for 74.1% of the study population.

Table 4.1: Baseline patient characteristics by diagnostic outcomes

Socio-demographics variables	**All (N=328)**	**Asthma only (n=136)**	**COPD only (n=44)**	**ACOS (n=55)**	**NAD (n=93)**	**p-Value**
Edmonton recruits, %	83.5	89.7	72.7	78.2	82.8	**0.034**
Median age, years (SD)	49 (18)	42 (17)	67 (14)	59 (14)	47 (16)	**<0.001**
Age at interview, Category						
Age > 60 years %	31.1	19.1	72.7	47.3	19.4	**<0.001**
Age 40- 60 years, %	32.9	25.7	25.0	41.8	41.9	
Age < 40 years %	36.0	55.1	2.3	10.9	38.7	
Male, sex, %	42.7	39.7	52.3	52.7	36.6	0.120
Drug insurance %	88.4	91.9	77.3	87.3	89.2	0.069
Ever married %	42.1	36.8	43.2	49.1	45.2	0.381
Caucasian ethnicity, %	86.3	89.0	86.4	87.3	81.7	0.473
Post-secondary education, %	49.1	49.3	27.3	54.5	55.9	**0.013**
Smoking History						
Current Smoker, %	19.8	18.4	38.6	18.2	14.0	**<0.001**
Median 10 Pack-years(SD)	7 (5)	7(4)	8(4)	11 (8)	6 (4)	0.08
History of Second hand smoke exposure %	90.9	91.9	97.7	89.1	87.1	0.215
Physical Examination						
Median Weight, kg (SD)	81(21)	80 (19)	77 (22)	84 (21)	81 (21)	0.227
Median Height, cm (SD)	167(10)	167 (9)	164 (10)	167 (10)	166 (9)	0.308
Median Heart rate, (SD)	75 (12)	76 (12)	71 (15)	75 (10)	75 (11)	0.869
Median respiratory rate,(SD)	20(3)	19 (2)	20 (3)	20 (4)	19 (2)	**0.018**
Median SO_2 (SD)	96(2)	96 (2)	95 (2)	95 (2)	96 (2)	**<0.001**
Median SBP, mmHg (SD)	121(18)	118 (16)	133 (18)	124 (19)	119 (20)	**0.004**
Median DBP, mmHg (SD)	77((11)	77 (11)	74 (12)	80 (9)	75 (11)	0.335
Median Baseline FEV_1 -% (SD)	89 (20)	91 (13)	64 (19)	66 (19)	97 (15)	**<0.001**
Median baseline FVC – predicted % (SD)	100 (17)	103 (15)	92 (20)	93 (15)	103 (17)	**<0.001**
Median baseline FEV_1/FVC ratio, % predicted(SD)	88 (14)	90 (12)	75 (13)	74 (14)	95 (7)	**<0.001**
Median PEF, -% predicted (SD)	102 (26)	108 (23)	79 (22)	84 (25)	115 (20)	**<0.001**
Previous Test Procedure						
Prior PFT, %	40.9	33.1	52.3	49.1	41.9	0.061
Prior Chest X-ray, %	53.4	37.5	77.3	61.8	60.2	**<0.001**
Echo, %	14.9	5.1	34.1	16.4	19.4	**<0.001**
ECG, %	45.1	33.8	63.6	54.5	47.3	**0.002**
Methacholine, %	1.2	0.7	0.0	3.6	1.1	0.322
Medical history comorbidities						
Prior Allergies. %	77.7	86.8	59.1	83.6	69.9	**<0.001**

Prior Asthma, %	68.6	79.4	25.0	87.3	62.4	**<0.001**
Prior COPD, %	11.9	4.4	36.4	23.6	4.3	**<0.001**
Sinusitis or Nasal polyps, %	31.4	25.7	31.8	38.2	35.5	0.270
Diabetes, %	8.8	5.9	15.9	10.9	8.6	0.212
CAD, %	8.5	1.5	31.8	9.1	7.5	**<0.001**
Heart failure, %	1.8	0.0	6.8	0.0	3.2	**0.014***
Hypertension, %	25.9	15.4	47.7	34.5	25.8	**<0.001**
High cholesterol, %	17.7	8.8	34.1	18.2	22.6	**0.001**
Osteoporosis, %	11.6	5.1	20.5	25.5	8.6	**<0.001**
Malignancy, %	6.7	2.9	15.9	10.9	5.4	**0.013***
Depression, %	31.7	24.3	29.5	36.4	40.9	**0.052**
Arrhythmia, %	13.4	8.1	22.7	14.5	16.1	**0.064**
Anxiety, %	26.8	24.3	20.5	27.3	33.3	0.337
Anemia,%	12.8	14.7	9.1	7.3	15.1	0.405
GERD/Heart burn, %	43.3	37.5	36.4	52.7	49.5	0.104
Asthma in 1st degree relative, %	39.3	45.6	31.8	38.2	34.4	0.236
COPD in 1st degree relative, %	16.5	14.0	25.0	21.8	12.9	0.176
Heart disease in 1st degree , %	44.8	39.0	54.5	47.3	47.3	0.269
Current respiratory symptoms						
Mean, total ACQ, (SD)	8 (6)	7 (5)	9 (6)	9 (6)	7 (6)	0.15
Mean, total CAT, (SD)	14(8)	12 (7)	43 (163)	14 (8)	14 (8)	**0.03**
NYHAFC scale (1-2)	26.2	80.9	31.8	41.8	24.7	**0.010**
MRC Dyspnea Scale (1-2)	22.3	86.8	27.3	34.5	25.8	**0.006**
Nocturnal cough ,%	36.3	33.8	34.1	32.7	43.0	0.463
Sputum production,%	46.6	40.4	40.9	58.2	51.6	0.088
Chest tightness,%	52.1	58.8	29.5	49.1	54.8	**0.008**
Wheeze,%	60.1	62.5	47.7	76.4	52.7	**0.010**
Other symptoms						
Edema,%	17.4	14.0	15.9	20.0	21.5	0.469
Fatigue,%	49.7	46.3	43.2	50.9	57.0	0.337
Bilateral ankle edema,%	23.2	16.2	40.9	27.3	22.6	0.007
Recently absent from work,%	15.2	12.5	9.1	18.2	20.4	0.223
Fever or Flu symptoms present,%	6.7	5.9	4.5	3.6	10.8	0.291
Current inhaler medications						
Anticholinergic, Long acting,%	7.6	2.2	29.5	14.5	1.1	**<0.001**
Anticholinergic, Short acting,%	4.3	2.9	13.6	5.5	1.1	**0.006**

Beta-2 agonist, Long acting,%	5.5	5.1	6.8	3.6	6.5	0.871
Beta-2 agonist, Short acting,%	74.1	80.1	56.8	80.0	69.9	**0.010**
Inhaled corticosteroid,%	28.0	28.7	22.7	25.5	31.2	0.734
Oral steroid,%	4.9	5.9	4.5	1.8	5.4	0.690
Combo(Symbicort or Advair),%						
Symbicort, %	34.5	35.3	29.5	45.5	29.0	0.198
Advair, %	25.9	22.8	31.8	34.5	22.6	0.245
Theophylline,%	1.5	0.7	0.0	7.3	0.0	**0.002***
LTRA (Singulair) ,%	7.9	7.4	0.0	12.7	9.7	0.113
Other concomitant medication						
ACE inhibitor,%	13.7	10.3	18.2	18.2	14.0	0.389
ARB,%	7.6	4.4	20.5	10.9	4.3	**0.002**
Beta Blocker,%	7.9	3.7	15.9	10.9	8.6	**0.047**
Calcium Channel Blockers,%	7.9	5.1	11.4	10.9	8.6	0.410
Diuretics,%	13.4	9.6	25.0	14.5	12.9	0.075
Antidepressants,%	20.4	16.9	13.6	23.6	26.9	0.171
Antipsychotics,%	2.7	2.2	0.0	5.5	3.2	0.394
Antihistamine,%	6.1	6.6	0.0	3.6	9.7	0.134
Environmental and occupational exposures						
Wood or cotton dust,%	35.4	37.5	29.5	30.9	37.6	0.657
Asbestos, silica, coal, talc,%	22.0	19.9	29.5	23.6	20.4	0.563
Manufacture of stone, glass, clay,%	9.1	8.8	9.1	5.5	11.8	0.632
Welding or pottery-making,%	18.3	17.6	20.5	18.2	18.3	0.981
Manufacture of plastic or rubber,%	9.8	8.8	2.3	9.1	15.1	0.115
Grains,%	29.9	25.7	36.4	34.5	30.1	0.462
Hooved farm animals,%	32.3	27.2	36.4	32.7	37.6	0.368
Non-hooved farm animals,%	25.9	20.6	36.4	32.7	24.7	0.116
Hooved wild animals ,%	18.0	17.6	22.7	14.5	18.3	0.770
Animal hide or wool processing,%	9.8	11.0	6.8	5.5	11.8	0.514
Gases from formaldehyde, ammonia, chlorine,%	28.7	28.7	25.0	27.3	31.2	0.890
Paint, lacquer, hair spray, pesticide, acid, solvent,%	51.8	55.9	54.5	38.2	52.7	0.161
Latex gloves,%	34.8	40.4	25.0	27.3	35.5	0.160
Landscaping or gardening soil,%	39.3	44.9	31.8	32.7	38.7	0.284

Abbreviations and symbols: COPD: Chronic Obstructive Pulmonary Disease, SD: Standard Deviation, N: number; Y: Yes; N: No; OR: Odds Ratio; CI: Confidence Interval ACOS: Asthma-COPD Overlap Syndrome, ECG: Electrocardiogram; FEV1: % predicted Forced expiratory volume in one second; FVC: % Predicted Forced vital capacity; CAD: Coronary Artery Disease; GERD: Gastroesophageal Reflux Disease; NYHAFC: New York Heart Association Functional Classification; mMRC: modified Medical Research Council; SOB: Shortness of Breath; ACE: Angiotensin-converting Enzyme, ARB: Angiotensin II Receptor Blocker ACQ: Asthma control Questionnaire; CAT: COPD Assessment Test; LTRA: LeukoTriene Receptor Antagonist, mmHg: millimeters of mercury, SaO2: Oxygen Saturation, %: Percentage

4.3.2.1 Baseline factors associated with diagnosed with Asthma only, COPD only, and ACOS

Asthma only: Of the patients diagnosed with *asthma only*, 55.1% were less than 40 years old, 39.7% were male, and 91.9% were exposed to second-hand smoke. The percentages of asthma patients with previous PFT, chest X-ray, and ECG were 33.1%, 37.5%, and 33.8% respectively. 45.6% had a family history of asthma, and 86.8% had allergies. 25.7% had sinusitis/nasal polyps, 24.3% had depression, and 37.5% had GERD/heartburn as comorbidity. The New York Heart Association Functional Classification (NYHAFC) assessment scale showed more patients having none to mild symptoms (80.9%), and the mMRC dyspnea scale revealed that 86.8% had no symptoms to SOB while walking a slight hill. The median ACQ score for asthma only patients were 7, while 80.1% were on short-acting beta antagonist (SABA), and 55.9%, 40.4%, and 44.9% were exposed to paint (lacquer, hairspray, pesticide, acid, and solvent) latex and soil respectively.

COPD only: Of the 44 patients diagnosed with COPD only, 72.7% were older than 60 years, and 52.3% males. A total of 34 of the COPD patients had drug insurance (77.3%). 38.6% of the patients were current smokers, 40.9% were ex-smokers, and the remaining 20.5% had never smoked. Additionally, 61.4% were exposed to second-hand smoke at work. The median predicted baseline FEV_1, FVC, and FEV_1/FVC ratio were 66, 93, and 74 respectively. 77.3% of the patients had had previous chest X-ray, 63.6% had ECG done, 52.3% had PFT, and 34.1% had also had an echo done prior to the EpiSOB study. The majority of the patients had a family history of heart disease (54.5%), and

25.0% had a family history of COPD, while 31.8% a family history of asthma. Also, 25% of the 44 COPD only patients were previously told by their family physician they have asthma, while only 36.4% were told they have COPD. Also, as a comorbidity, 34.1% had high cholesterol, 47.7% had hypertension, and 31.8% had CAD. 22.7% and 45.5% were taking LAAC and SABA respectively as their prescribed inhaler medication.

ACOS only: **Table 4.1** also shows the baseline characteristics of the 55 patients with ACOS diagnosis. Of these 55 ACOS patients, 41.8% were between ages 40 to 60, and 47.3% were older than 60 years respectively, and 52.7% were males. The majority of the ACOS patients were ex-smokers (50.9%), while 83.6% were exposed to second-hand smoke. The median oxygen saturation was 96 ± 2 (normal SaO2: 95-98%). 87.3% and 23.6% of the ACOS patients were previously told by their family physician they had asthma and COPD respectively, while 25.5% has osteoporosis as a comorbidity. 45.5% and 34.5% were combination therapy for treatment of their SOB symptoms (combination/Symbicort and combination/Advair respectively).

4.3.2.2 Logistic Regression Analysis of factors associated with patients diagnosed with Asthma only

Table 4.2 presents univariate and multivariate patient factors associated with an asthma diagnosis. **Figure 4.1** shows 25.7% of asthma diagnosed patients to have one or two comorbidities, a high of 47.8% reported three or four and another 25.7% reported having more than four. In a univariate analysis, using the dyspnea scale as an assessment, patient diagnosed with *asthma only* were found to be less likely to be limited by their SOB symptom (MRC dyspnea scale, p=0.006), but had significantly increased chest

tightness (OR: 1.59, 95%CI: 1.02 – 2.46, p=0.039). These patients were also found to be significantly more likely on SABA (OR: 1.88, 95%CI: 1.13 – 3.15, p=0.015).

Figure 4.2 shows 58.8% of asthma used two or more inhaler medications. Patients exposed to latex and soil were 56% and 39% more likely to be diagnosed with asthma respectively (although not statistically significant at p= 0.05). Conversely, patients were less likely to be diagnosed with *asthma only* when they exposed to hooved farm animals, p=0.030.

In the multivariate analysis, controlling for sex and center of recruitment city, patients who were older than 40 years old were significantly less likely to be diagnosed with asthma. Patients older than 60 years were 63% less likely and those that were between 40 and 60 years were 58% less likely to be diagnosed with asthma. Allergies were two times more likely to be associated with a diagnosis for asthma only (OR: 2.32, 95% CI: 1.19 – 4.50) compared to the other groups (COPD, ACOS). However, being exposed to hooved farm animal was less likely to be linked to asthma diagnosis, p=0.030. Also, having a prior history of chest X-ray and echo were less likely to be used as tools aiding the diagnosis of asthma.

Table 4.2: Univariate and multivariate patient factors associated with Asthma diagnosis

Variables associated with asthma diagnosis	Univariate factors				Multivariate factors		
	OR	**95%CI**	**P-value**		**OR**	**95%CI**	**P-value**
Socio-demographics variables							
Edmonton patients	2.78	1.44 – 5.33	0.002		0.29	0.14 – 0.62	0.001
Age at interview, Category							
Age > 60 years	0.22	0.13 – 0.39	<0.0001		0.37	0.19 – 0.71	0.003
Age 40- 60 years	0.34	0.20 – 0.58	<0.0001		0.42	0.23 – 0.76	0.005
Age < 40 years	Ref						
Male sex	0.92	0.59 – 1.43	0.72		0.81	0.48 – 1.35	0.416
Drug insurance	2.23	1.07 – 4.66	0.030				
Ever married	1.56	0.98 – 2.43	0.051		2.09	1.23 – 3.54	0.006
SaO_2 %	1.19	1.06 – 1.33	0.004				
SBP, mmHg	0.98	0.97 – 0.99	0.003				
Baseline FEV_1	1.01	1.00 – 10.2	0.033				
baseline FVC	1.02	1.00 – 1.03	0.021				
PEF	1.01	1.00 – 1.02	0.114				
Previous Test Procedure							
Prior PFT	0.63	0.41 – 0.99	0.045				
Prior Chest X-ray	0.34	0.22 – 0.53	<0.0001		0.36	0.21 – 0.62	<0.0001
Echo	0.16	0.07 – 0.37	<0.0001		0.30	0.12 – 0.75	0.009
ECG	0.54	0.45 – 0.84	0.006				
Medical history comorbidities							
Prior Allergies	2.96	1.66 – 5.27	<0.0001		2.32	1.19 – 4.50	0.013
Prior Asthma	2.40	1.47 – 3.93	<0.0001				
Prior COPD	0.37	0.18 – 0.79	0.008				
Sinusitis or Nasal polyps	0.68	0.42 – 1.09	0.105				
CAD	0.13	0.04 – 0.43	<0.0001				
Heart failure	1.86	1.68 – 2.06	0.024				
Hypertension	0.43	0.25 – 0.73	0.001				
High cholesterol	0.39	0.21 – 0.73	0.003				

Osteoporosis	0.28	0.13 – 0.64	0.001				
Malignancy	0.25	0.08 – 0.75	0.008				
Depression	0.59	0.36 – 0.95	0.028				
Arrythmia	0.46	0.23 – 0.91	0.23				
GERD/Heart burn	0.65	0.42 – 1.01	0.057				
Asthma in 1st degree relative	1.54	0.99 – 1.59	0.057				
COPD in 1st degree relative	0.66	0.36 – 1.21	0.175				
Heart disease in 1st degree	0.68	0.44 – 1.05	0.083				
Current respiratory symptoms							
Mean, total ACQ	0.98	0.94 – 1.02	0.354				
Mean, total CAT	0.97	0.94 -1.00	0.051				
NYHAFC scale (1-2)	0.68	0.41 – 1.12	0.126				
MRC Dyspnea Scale (1-2)	0.44	0.25 – 0.76	0.003				
Chest tightness,(Y/N)	1.59	1.02 – 2.46	0.039				
Wheeze	1.47	0.94 – 2.31	0.089				
Other symptoms							
Bilateral ankle edema	0.51	0.30 – 0.87	0.012				
Current inhaler medications							
Anticholinergic, Long acting	0.21	0.07 – 0.62	0.002				
Anticholinergic, Short acting	0.47	0.14 – 1.52	0.195				
Beta-2 agonist, Short acting	1.88	1.13 – 3.15	0.015				
Other concomitant medication							
ARB	0.4	0.18 – 1.09	0.069				
Beta Blocker	0.33	0.13 – 0.85	0.017				
Calcium Channel Blockers	0.42	0.17 – 1.02	0.048				
Diuretics	0.58	0.30 – 1.13	0.105				
Environmental and occupational exposures							
Grains	0.72	0.45 – 1.17	0.181				
Hooved farm animals	0.59	0.37 – 0.95	0.030		0.54	0.31 – 0.94	0.030
Non-hooved farm animals	0.65	0.39 – 1.08	0.094				
Paint, lacquer, hair spray, pesticide, acid, solvent	1.47	0.95 – 2.28	0.084				

Latex gloves	1.56	0.99 – 2.47	0.056				
Landscaping or gardening soil	1.39	0.89 – 2.17	0.146				

Univariate results include all significant at p=0.200 level. Controlling for sex and recruitment centers (Edmonton + Saskatoon). COPD: Chronic Obstructive Pulmonary Disease, SD: Standard Deviation, N: number; Y: Yes; N: No, OR: Odds Ratio; CI: Confidence Interval ACOS: Asthma-COPD Overlap Syndrome, ECG: Electrocardiogram; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; CAD: Coronary Artery Disease; GERD: Gastroesophageal Reflux Disease; NYHAFC: New York Heart Association Functional Classification; mMRC: modified Medical Research Council; SOB: Shortness of Breath; ACE: Angiotensin-converting Enzyme, ARB: Angiotensin II Receptor Blocker ACQ: Asthma control Questionnaire; CAT: COPD Assessment Test; LTRA: LeukoTriene Receptor Antagonist, mmHg: millimeters of mercury, SaO_2: Oxygen Saturation, %: Percentage

4.3.2.3 Logistic regression analysis of factors associated with patients diagnosed with COPD only

Table 4.3 presents both the univariate and multivariate factors associated with patients diagnosed with *COPD only*. Patients diagnosed with COPD only were 82% more likely to have a family history of COPD but were less likely to have been told previously by their primary care physician they have asthma. However, patients diagnosed with *COPD only* were more likely to be told by their primary care physician they have COPD. Also, *COPD only* patients were more likely to have CAD, hypertension, high cholesterol, osteoporosis, and malignancy as comorbidities ($p<0.0001$, $p<0.0001$, $p=0.030$, $p<0.0001$, and $p=0.002$ respectively). In addition, **Figure 4.1** shows that 38.6% of the COPD only patients had three to four comorbidities and 45.5% had more than four comorbidities. The NYHAFC scale and mMRC dyspnea scale indicated that patients are limited in their physical activities due to severe SOB symptoms ($p=0.008$, and $p=0.031$ respectively). COPD patients were more likely to be on LAAC, SAAC, combination Advair as their current inhaler medications, as well as ARB, beta-blockers, and diuretics ($p<0.0001$, $p=0.004$, $p=0.030$, and $p=0.001$, $p=0.017$ and $p=0.034$ respectively); and, were less likely to be on an antihistamine, $p=0.048$. **Figure 4.2** also shows that 38.6% of the *COPD only* patients were on one, 34.1% on two, and 27.3% on three or more inhaler medications.

Controlling for the center of recruitment or city and sex, patients diagnosed with *COPD only* were found to be more likely to be older than 60 years of age with a less than normal oxygen saturation level as well as below normal, $p=0.008$ and the FEV_1/FVC ratio at baseline, $p<0.0001$. The diagnosis for *COPD only* patients was twice as likely to have a prior chest x-ray and three times as likely to have had an echo done aiding in their previous diagnosis. In addition, they were 57% less likely to have experienced chest tightness as a symptom.

Table 4.3: Univariate and multivariate patient factors associated with COPD diagnosis

Variables associated with COPD diagnosis	Univariate factors				Multivariate factors		
	OR	**95%CI**	**P-value**		**OR**	**95%CI**	**P-value**
Socio-demographics variables							
Edmonton recruits, (Y/N)	0.45	0.25 – 0.83	0.009		0.12	0.04 – 0.32	<0.0001
Age, years	1.07	1.05 – 1.09	<0.0001				
Age at Interview, Category							
Age > 60 years	20.09	8.52 – 47.37	<0.0001		8.17	2.68 – 24.86	<0.0001
Age 40- 60 years,	6.98	2.93 – 16.60	<0.0001		3.69	1.20 – 11.38	0.023
Age < 40 years	ref						
Male, sex, (Y/N)	1.77	1.10 – 2.86	0.019				
Drug insurance (Y/N)	0.47	0.24 – 0.94	0.029				
Post-secondary education, (Y/N)	0.68	0.42 – 1.09	0.110				
Ever Smoked, (Y/N)	2.95	1.76 – 4.96	<0.0001				
10 Pack-years	1.10	1.04 – 1.17	0.001				
Physical Examination							
respiratory rate,	1.17	1.05 – 1.31	0.005				
SBP, mmHg	1.02	1.01 – 1.04	0.001				
DBP, mmHg	1.02	0.99 – 1.04	0.157				
SaO_2 %	0.62	0.54 – 0.72	<0.0001		0.75	0.57 – 0.91	0.008
Baseline FEV_1 %	0.92	0.90 – 0.93	<0.0001				
Baseline FVC %	0.96	0.94 – 0.97	<0.0001				
Baseline FEV_1/FVC ratio %	0.89	0.87 – 0.92	<0.0001		0.88	0.85 – 0.91	<0.0001
PEF	0.95	0.93 – 0.96	<0.0001				
Previous Test Procedure							
Prior PFT, (Y/N)	1.75	1.09 – 2.83	0.021				
Prior Chest X-ray, (Y/N)	2.54	1.54 – 4.20	<0.0001		2.48	1.11 – 5.53	0.027
Echo, (Y/N)	2.71	1.46 – 5.04	0.001		3.31	1.30 – 8.46	0.012
ECG, (Y/N)	2.19	1.35 – 3.55	0.001				
Medical history comorbidities							
Allergies. (Y/N)	0.65	0.37 – 1.12	0.115				

Asthma, (Y/N)	0.57	0.35 – 0.94	0.026				
COPD, (Y/N)	7.04	3.39 – 14.63	<0.0001				
Diabetes, (Y/N)	2.08	0.96 – 4.51	0.059				
CAD, (Y/N)	5.04	2.23 – 11.37	<0.0001				
Hypertension, (Y/N)	2.70	1.61 – 4.54	<0.0001				
High cholesterol, (Y/N)	1.91	1.06 – 3.43	0.030				
Osteoporosis, (Y/N)	4.48	2.22 – 9.03	<0.0001				
Malignancy, (Y/N)	3.82	1.57 – 9.26	0.002				
Arrhythmia, (Y/N)	1.80	0.93 – 3.46	0.077				
Anemia,(Y/N)	0.52	0.23 – 1.17	0.109		0.17	0.04 – 0.71	0.015
COPD in 1st degree relative, (Y/N)	1.82	1.00 – 3.34	0.049				
Heart disease in 1st degree , (Y/N)	1.39	0.86 – 2.23	0.179				
Current respiratory symptoms							
Mean, total ACQ	1.04	1.00 – 1.09	0.069				
Mean, total CAT	1.03	0.99 – 1.06	0.088				
NYHAFC scale (3-4)	1.99	1.19 – 3.35	0.008				
mMRC Dyspnea Scale (3-5)	1.81	1.05 – 3.13	0.031				
Chest tightness,(Y/N)	0.50	0.31 – 0.82	0.005		0.43	0.19 – 0.97	0.043
Other symptoms							
Bilateral ankle edema,(Y/N)	2.09	1.23 – 3.58	0.006				
Current inhaler medications							
Anticholinergic, Long acting,(Y/N)	11.74	4.26 – 32.35	<0.0001				
Anticholinergic, Short acting,(Y/N)	4.62	1.51 – 14.18	0.004				
Combination Advair,(Y/N)	1.76	1.05 – 2.99	0.030				
Theophylline,(Y/N)	9.89	1.09 – 89.68*	0.013				
Other concomitant medication							
ACE inhibitor,(Y/N)	1.54	0.80 – 2.97	0.194				
ARB,(Y/N)	4.04	1.75 – 9.36	0.001				
Beta Blocker,(Y/N)	2.60	1.57 – 5.83	0.017				
Calcium Channel Blockers,(Y/N)	1.842	0.81 – 4.17	0138				
Diuretics,(Y/N)	2.01	1.05 – 3.85	0.034				
Antihistamine,(Y/N)	0.25	0.06 – 1.10	0.048				

Environmental and occupational exposures							
Wood or cotton dust,(Y/N)	0.71	0.42 – 1.18	0.179				
Manufacture of plastic or rubber,(Y/N)	0.52	0.21 – 1.31	0.158				
Non-hooved farm animals,(Y/N)	1.65	0.98 – 2.79	0.058				
Hooved wild animals, (Y/N)							
Animal hide or wool processing,(Y/N)	0.41	0.15 – 1.10	0.069				
Paint, lacquer, hair spray, pesticide, acid, solvent,(Y/N)	0.69	0.43 – 1.11	0.129				
Latex gloves,(Y/N)	0.60	0.35 – 1.00	0.050				
Landscaping or gardening soil,(Y/N)	0.64	0.39 – 1.05	0.077				

Univariate results include all significant at p=0.200 level. Controlling for sex and recruitment city (Edmonton + Saskatoon). COPD: Chronic Obstructive Pulmonary Disease, SD: Standard Deviation, N: number; Y: Yes; N: No, OR: Odds Ratio; CI: Confidence Interval ACOS: Asthma-COPD Overlap Syndrome, ECG: Electrocardiogram; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; CAD: Coronary Artery Disease; GERD: Gastroesophageal Reflux Disease; NYHAFC: New York Heart Association Functional Classification; mMRC: modified Medical Research Council; SOB: Shortness of Breath; ACE: Angiotensin-converting Enzyme, ARB: Angiotensin II Receptor Blocker ACQ: Asthma control Questionnaire; CAT: COPD Assessment Test; LTRA: LeukoTriene Receptor Antagon, mmHg: millimeters of mercury, SaO_2: Oxygen Saturation, %: Percentage

4.3.2.4 Logistic regression analysis of factors associated with patients diagnosed with ACOS

Table 4.4 present the data for univariate and multivariate factors associated with patients diagnosed with ACOS. In the univariate analysis, ACOS patients were more likely to have had a prior history of asthma (OR: 3.71; 95% CI: 1.62 – 8.54; p=0.001), and more likely to have had a history COPD (OR: 2.94, 95% CI: 1.40 – 6.17, p=0.003). ACOS patients were also four times more likely to have osteoporosis as comorbidity. Compared to the other patients, 38.6% of ACOS patients had three to four comorbidities, and 54.0% had more than four (**see Figure 4.1**). Using NYHAFC and the MRC dyspnea scale to assess patients SOB symptom, the ACOS patients were found to be more likely to have marked to severe limitation of physical activities (OR: 2.40, 95%CI: 1.31 – 4.39, p<0.004), and more likely to have to walk slower on level ground, stop for breath after walking short distance and or too breathless to leave the house, or getting dress or undress (OR: 2.14, 95%CI: 1.14 – 4.02, p<0.015). ACOS patients were also likely to be on LAAC and 75% more likely to be on combination medications. Figure 4.2 shows that 58.0% of ACOS patients were on two medications and 27.3% on three or more.

In the multivariate analysis, the ACOS patients were significantly older than 40 years (40 to 60 years; OR: 4.19, 95%CI: 1.35 – 12.98, and >60 years; 3.97, 95%CI: 1.20 – 13.45) and 7% more likely to have 10 pack-years smoked. *Prior asthma history was significantly associated with ACOS diagnosis (p<0.0001) and two* times more likely to have GERD/heartburn as a comorbidity compared to other, p=0.047. ACOS patients were

also significantly more likely to be on a combination drug therapy compared to other (Symbicort combination; p=0.036).

Table 4.4: Univariate and Multivariate factors associated with ACOS diagnosis

Variables associated with ACOS diagnosis	Univariate factors				Multivariate factors		
	OR	**95%CI**	**P-value**		**OR**	**95%CI**	**P-value**
Socio-demographics variables							
Edmonton recruits, (Y/N)	0.65	0.32 – 1.34	0.240		1.88	0.70 – 5.06	0.213
Age, years	1.04	1.02 – 1.06	<0.0001				
Age at interview, Category							
Age > 60 years	0.16	0.06 – 0.40	<0.0001		3.97	1.20 – 13.45	0.027
Age 40- 60 years	0.20	0.08 - 0.40	0.001		4.19	1.35 – 12.98	0.013
Age < 40 years	ref						
Male Sex	1.63	0.91 – 2.91	0.099		1.02	0.47 – 2.22	0.967
Ever Smoked	2.00	1.08 – 3.72	0.026				
Pack-years	1.11	1.05 – 1.18	0.001		1.07	1.01 – 1.14	0.026
Physical Examination							
SaO2,	0.77	0.67 – 0.88	<0.0001				
SBP, mmHg	1.01	1.00 – 1.03	0.069				
DBP, mmHg	1.02	1.00 – 1.05	0.075				
Baseline FEV_1	0.95	0.93 – 0.96	<0.0001		0.91	0.88 – 0.94	<0.0001
Baseline FVC	0.98	0.96 – 0.99	0.007		1.06	1.03 – 1.10	<0.0001
% Baseline FEV_1/FVC ratio %	0.93	0.91 – 0.95	<0.0001				
PEF	0.97	0.96 – 0.98	<0.0001				
Previous Test Procedure							
Prior PFT	1.50	0.34 – 2.68	0.173				
Prior Chest X-ray	1.52	0.84 – 2.74	0.168				
Echo							
ECG	1.58	0.88 – 2.82	0.124				
Methacholine	5.11	0.71 – 37.12*	0.073				
Medical history comorbidities							
Prior Asthma	3.71	1.62 – 8.54	0.001		10.60	3.53 – 31.83	<0.0001
Prior COPD	2.94	1.40 – 6.17	0.003				

Hypertension	1.66	0.89 – 3.08	0.109				
Osteoporosis, (	3.54	1.70 – 7.41	<0.0001				
Malignancy	1.97	0.73 – 5.28	0.172				
GERD/Heart burn	1.58	0.88 – 2.83	0.122		2.27	1.01 – 5.08	0.047
Current respiratory symptoms							
NYHAFC scale (3-4)	2.40	1.31 – 4.39	0.004				
mMRC Dyspnea Scale (3-5)	2.14	1.14 – 4.02	0.015				
Sputum production	1.75	0.97 – 3.14	0.060				
Wheeze	2.46	1.26 – 4.79	0.007				
Current inhaler medications							
Anticholinergic, Long acting	2.56	1.05 – 6.28	0.034				
Combo Symbicort,	1.75	0.97 – 3.16	0.060		2.35	1.06 - 5.25	0.036
Combo Advair	1.66	0.89 – 3.08	0.109				
LTRA (Singulair)	1.95	0.78 – 4.89	0.149				
Other concomitant medication							
Antipsychotics	2.57	0.62 – 10.59	0.177				
Environmental and occupational exposures							
Exposure to paint, lacquer, hair spray, pesticide, acid, solvent	0.51	0.28 – 0.93	0.026		0.39	0.17 – 0.88	0.024

Univariate results include all significant at p=0.200 level. Controlling for sex and recruitment city (Edmonton + Saskatoon). COPD: Chronic Obstructive Pulmonary Disease, SD: Standard Deviation, N: number; Y: Yes; N: No; OR: Odds Ratio; CI: Confidence Interval ACOS: Asthma-COPD Overlap Syndrome, ECG: Electrocardiogram; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; CAD: Coronary Artery Disease; GERD: Gastroesophageal Reflux Disease; NYHAFC: New York Heart Association Functional Classification; mMRC: modified Medical Research Council; SOB: Shortness of Breath; ACE: Angiotensin-converting Enzyme, ARB: Angiotensin II Receptor Blocker ACQ: Asthma control Questionnaire; CAT: COPD Assessment Test; LTRA: LeukoTriene Receptor Antagonist, mmHg: millimeters of mercury, SaO_2: Oxygen Saturation, %: Percentage

3.3.3 Multinomial analysis comparing factors associated with a diagnosis of asthma, COPD, and ACOS

A multinomial logistic regression analysis was performed to examine the characteristics which were similar or different between asthma only, COPD only and ACOS simultaneously. As shown in **Table 4.5**, the global p-value showed that age, ever married, baseline FEV1, baseline % FEV1/FVC ratio, 10 pack-years of smoking, prior history of chest- X-ray, ECHO, allergies, and exposure to paint, lacquer, hair spray, pesticide or acid solvent were important factors associated with differential diagnosis for asthma, COPD, and ACOS. Across all diagnostic groups, the increase % baseline FEV_1/FVC ratio was significantly associated with less likelihood of being diagnosed with outcomes. A history of smoking greater than ten pack-years was significantly associated increase likelihood of being diagnosed with any of the three groups. Allergies history was a risk factor for the diagnosis of both asthma, and ACOS. *Asthma only* patients were the only patient who was significantly less likely to have had their chest x-rayed to facilitate diagnosis. There was no association between being exposed to paint (lacquer, hairspray, pesticide, and solvents) and asthma, or COPD. However, there was significantly less association between ACOS diagnosis and history of exposure to paint (lacquer, hairspray, pesticide), OR: 0.29; 95% CI: 0.10 – 0.80.

Table 4.5: Final multinomial logistic regression analysis of different factors associated with diagnostic outcomes

Variables	Asthma only				COPD only				ACOS				Global
	OR	**95%CI**	**P-value**		**OR**	**95%CI**	**P-value**		**OR**	**95%CI**	**P-value**		**p-value**
Edmonton Vs Saskatoon	1.28	0.49 – 3.31	0.529		**0.20**	**0.05 – 0.85**	**0.029**		0.32	0.08 – 1.27	0.104		0.045
Age, years	**0.98**	**0.96 - 1.00**	**0.053**		**1.06**	**1.02 – 1.11**	**0.003**		1.02	0.99 – 1.06	0.186		<0.001
Male sex, (Y/N)	**0.50**	**0.23 – 1.00**	**0.048**		0.67	0.22 – 2.06	0.484		0.72	0.25 – 2.08	0.547		0.236
Ever married	1.92	1.00 – 3.71	0.051		1.17	0.40 – 3.52	0.779		0.67	0.24 – 1.76	0.394		0.041
Baseline FEV_1	0.98	0.95 – 1.00	0.081		**0.92**	**0.88 – 0.99**	**<0.0001**		0.94	0.91 – 0.98	**0.002**		<0.001
% Baseline FEV_1/FVC	**0.78**	**0.67 – 0.91**	**<0.0001**		**0.84**	**0.79 – 0.90**	**<0.0001**		**0.81**	**0.76 - 0.87**	**<0.0001**		<0.001
10 Pack years	**1.10**	**1.02 – 1.20**	**0.016**		**1.17**	**1.06 – 1.29**	**0.002**		**1.19**	**1.08 – 1.31**	**0.001**		0.004
Prior Chest X-ray	**0.41**	**0.21 – 0.80**	**0.009***		1.95	0.59 – 6.47	0.278		0.97	0.33 – 2.84	0.956		0.005
Prior Echo	**0.28**	**0.09 – 0.84**	**0.024**		3.02	0.83 –10.92	0.093		1.56	0.42 - 5.76	0.502		0.003
Prior Allergies	**3.06**	**1.40 – 7.00**	**0.007**		2.33	0.68 – 8.00	0.178		**5.69**	**1.59 - 20.41**	**0.008**		0.010
Exposure to taint, lacquer, hair spray, pesticide, acid, solvent	0.77	0.40 – 1.50	0.445		0.92	0.31 – 2.74	0.880		**0.29**	**0.10 – 0.80**	**0.018**		0.033

Controlling for sex and recruitment city (Edmonton + Saskatoon). COPD: Chronic Obstructive Pulmonary Disease; OR: Odds Ratio; CI: Confidence Interval ACOS: Asthma-COPD Overlap Syndrome, ECG: Electrocardiogram; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; Y: Yes; N: No

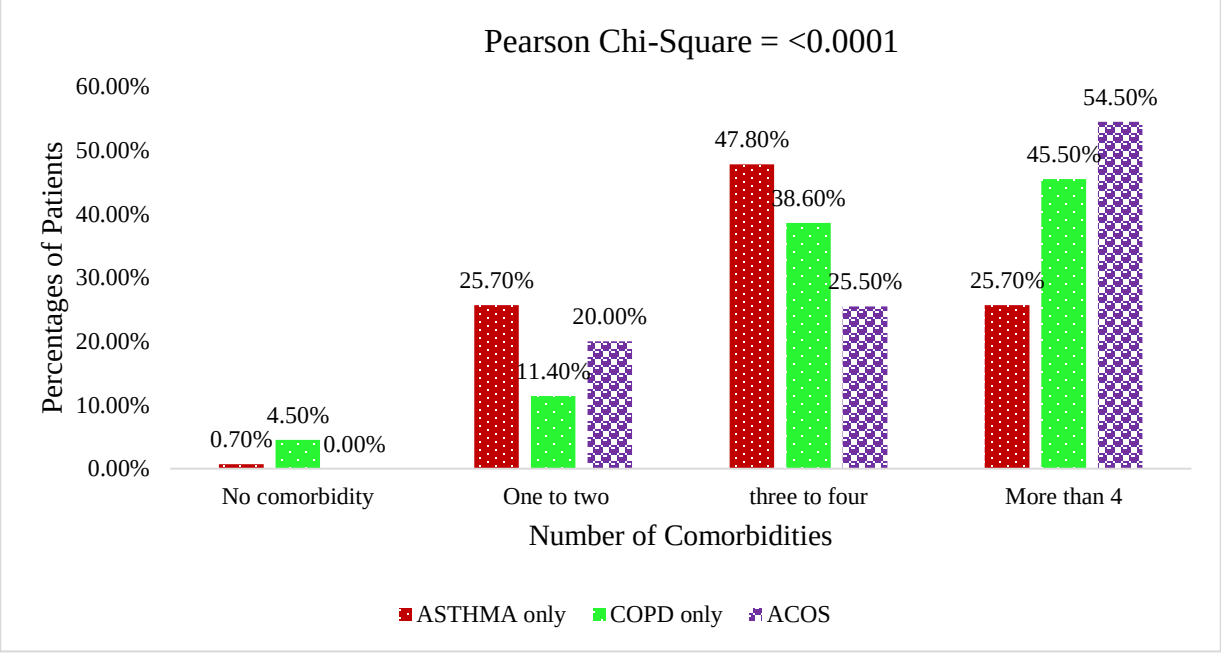

Figure 4.1: Number of comorbidities by diagnostic groups

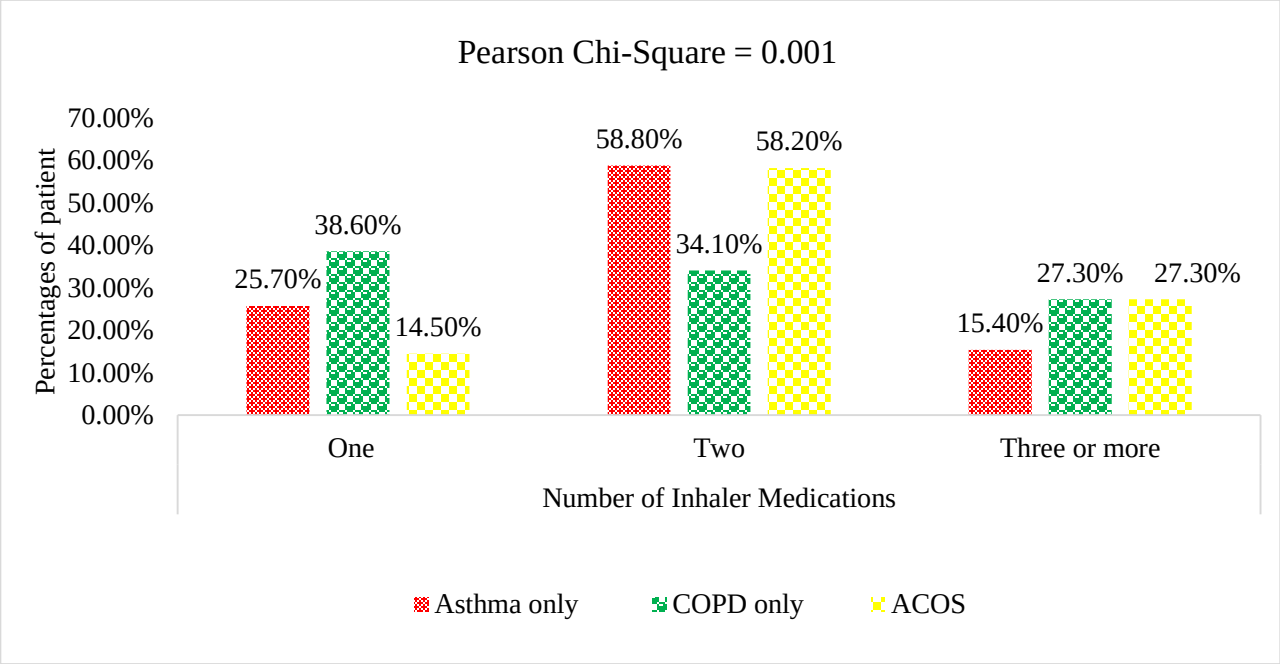

Figure 4.2: Number of inhaler medication used by the diagnostic group

4.4 Discussion

4.4.1 Summary results from this study

This study analyzed differential factors associated with the diagnostic outcomes for 328 patients visiting pharmacies in Edmonton and Saskatoon to fill their prescribed inhaler medication for their SOB symptom. It was found that 41.5% had a diagnosis for *asthma only*, 13.4% had a diagnosis for *COPD only*, and 16.8% have an element of asthma-COPD overlap syndrome or ACOS. The remaining 28.3% were determined as having no evidence of airway diseases (NOAD) determined by the specialist physicians.

In this study, asthma diagnosis was significantly associated with SAAB prescriptions. In this study, 58.8% of asthma only patients were on two inhaler medication with 15.4% on three or more. This is in keeping with the guidelines outlining the proper course of treatment for adult asthma patients. As the guidelines stated (9,30) adult asthma patients should be on a SAAB as well as a controller. In addition, patients are generally treated based on their symptoms and therefore those with the worst disease would have been given the most therapies, that is, 15.4% of the patients reported taking three or more inhaler medications. This combination therapy may have been due to the age or severity of the disease, as GINA recommends that the patient asthma is managed with one or two controller medications as well as an as-needed reliever medication (9).

This study found that patients who are current and ex-smokers, and also above age 60 were at an increased risk of developing COPD versus asthma. Since 20.5% of non-smokers were diagnosed with COPD, work-related second-hand smoke alone may

significantly increase the risk for COPD. Hagstad et al. reported that passive smoking was found to be strongly associated with COPD diagnosis when exposed in multiple settings, that is, in the home, work and in public (31). There was a significant (p=0.019) difference between a male and female patient in the diagnosis of *COPD only*. Conversely, studies have shown that in light of an increased rate of tobacco smoking among women in recent years as well as the high risk of exposure to indoor pollutant such as cooking and heating fuel (14,32). A report published by the CDC in 2002 over the span of two decades reported that the prevalence of COPD in women had exceeded that of men (33).

In this study, education and drug insurance were used to mark socio-economic status (SES). Also, SES may be characterized by other factors such as income and occupation. Patients who were diagnosed with COPD were less likely to have had post-secondary education and drug insurance. SES is said to be substantially related to the severity of COPD in patients (10,34). This may be the reality for those of lower socio-economic status as these patients are less likely to afford medication due to lack of drug insurance. One study reported that childhood socioeconomic status contributed to their association with health risk factors in adulthood such as smoking leading to health problem as they get older (35). In another study investigating the relationship between education and lifetime smoking patterns, the authors found that the number of pack-years smoked was higher among individuals with less than a high school education (36). These studies show similar results in that patient who are diagnosed with COPD are therefore less likely to be college educated. However, not having drug insurance could have been a result of the lack of insurance due to loss of work because of disability (s) developed from COPD.

COPD patients in this study were more likely to have a prior history of PFTs done. We can somewhat delineate that family physician was indeed using PFTs in their diagnosis as recommend by the GOLD guidelines (10,37,38). Spirometry is the most commonly used lung function screening test in detecting airflow limitation and is crucial in diagnosing COPD and asthma (39). In addition, GOLD and the WHO stated that PFT is the most reproducible and objective measurement of airflow limitation available (10,14,40). Additionally, COPD patients were significantly more likely to have had ECG, echo, and chest X-ray. In the evaluation of patients with COPD, a chest x-ray is used to exclude alternative diagnoses, evaluate for comorbidities such as lung cancer with airway obstruction, heart failure, and interstitial lung diseases, or assess a change in symptoms that suggest a complication of COPD (10,38).

There was a significant association between family history of COPD and COPD diagnosis at the univariate level in this study. A study by Hersh et al. reported that family history is a risk factor for COPD (34). He linked a family history of smoking to COPD (possibly due to learned behavior), however, that a family history of COPD increases the risk for developing COPD (34).

Symptoms of COPD diagnosed patients were significantly more likely to be managed with SAAC, LAAC and combination Advair. These results are in agreement with GOLD 2014, which stated that anticholinergic has the most important effect on COPD management (10). GOLD stated that the effect of SAAC lasts longer (up to 8 hours) than SABA which wears off within 6 hours, while, LAAC reduces exacerbation and related hospitalization as well as improving symptoms and health status.

Although not statistically significant patients exposed to non-hooved farm animals were at a higher risk of developing COPD. This result is in accordance with previous studies. One such study was conducted in Denmark. The Danish population-based study looking at occupational COPD in never-smokers and reported that non-smokers that were exposed to particles occupationally were three times more likely to have COPD compared to those not being exposed to their jobs. Organic dust exposure from farm, crops, and animals; carpenters, etc. was at a higher at 86% risk for developing COPD. However, no specific occupational exposure was significantly associated with COPD (41). Comorbid conditions are strongly related to COPD. This study showed that CAD, Hypertension, High cholesterol, Osteoporosis, and Malignancy were significantly related to COPD diagnosis. As shown in Figure 4.1, 38.6% of COPD only patients had three to four comorbid conditions, while 45.5% had more than four. These findings correlate with GOLD as well as multiples studies which reported COPD patients as having multiple comorbidities (38,42–47).

In this thesis, the ACOS outcome was defined based on a review published by Bujarski et al. 2015. Patients were labeled ACOS when diagnosed with asthma and had clinical features of COPD or have a diagnosis of COPD and have clinical features of asthma. In this population of SOB patients, the prevalence of ACOS was 16.8% compared to previous studies which reported that the range of ACOS was between 13% and 38% in obstructive lung diseases, with the percentage of ACOS in asthma patients higher and COPD lower (20,48–50).

The findings suggested ACOS tend to affect patients in the mid-age range of 40-60 year compared to asthma and COPD (40 and above vs. <40 (asthma) vs. <60 years (COPD). These study findings are similar to a study done by de Marco et al reported that subjects with COPD were older (60.4) compared to those with ACOS and asthma (50.5 and 44.2 respectively), a significant difference (50).

Comorbid factors which showed significance includes osteoporosis at the univariate level and GERD (Gastroesophageal Reflux Disease) at the multivariate level. A study by van Boven et al. found that osteoporosis and GERD were more frequent in ACOS than COPD (51). There were no environmental/occupational factors linked with ACOS. Specifically, exposure to environmental/occupational factors such as paint, lacquer, hairspray, pesticides, and solvents was of no significant risk to ACOS in our study (OR: 0.47, 95%CI: 0.23 – 0.98, p=0.040).

The difference in results in this study and the previous body of work referenced in this study may be due to the snapshot/broad spectrum of the data collection. The literature shows that the comorbid conditions along with the environment/occupational exposure to irritants or risk factors listed in this study were significantly associated with asthma and or COPD. Previous studies looked at specific risk factors, for example, the environment or comorbid conditions, and therefore had more detailed data collected on the topic. The EpiSOB study has questions in these areas that were yes/no answers. It is possible that if more details were collected on each risk factor (for example, the number of years worked in the area, and/or where were you exposed work/hobby/home etc.?) the results obtained may have been different.

4.4.2 Summary of finding comparing similarity and differences for asthma, COPD, and ACOS

The major findings of this study suggest that there more differences between asthma and COPD than there are similarities. Packed years smoked was the only factor common to the diagnosis of asthma, COPD, and ACOS diagnosis. Whereas there were more similarities between asthma only patients and ACOS patients, the main common elements shared between asthma, and ACOS patients were pack-years smoked, and allergies. Factors similar to COPD only and ACOS patients were packed years smoked. There were no factors identified as distinct to patients labeled as ACOS.

Study strength and limitations

The present study has strengths and potential limitations that should be noted, as occurs in many studies. A strength of this study is that established guidelines (9,10) were used to accurately diagnosed asthma only and COPD only patients as well as to delineate ACOS patients (52). Limitation of this study is that results may not be generalized due to the study sample. Recall bias, selection bias, as well as attrition bias may all be a factor in this study. Based on the design of this study the patients had to fill out questionnaires which would require them to recall information. There may be attrition bias due to the fact that only patients that showed for their full PFTs by the specialist physician provided full data which made up the study sample. In addition to this, all patients who did their PFTs did so voluntarily. Due to the nature of this study, it is impossible to know to what extent biases have affected the results of the study and therefore may not be generalized.

4.4.3 Conclusion

In this study, among patient diagnosed with asthma in the community setting of patients SOB symptoms tend to be younger than 40 years while, while COPD patients are older than 40 years. Also, ACOS patients are older than 40 years and seem to represent a form of severe asthma with similar features of prior asthma and COPD. There was no association between asthma diagnosis and history of depression. Contrary to the literature, asthma patients were less likely to have addition comorbidities than the others. COPD patients, however, were more likely to have a wide range of comorbidities. Asthma patients were also less likely to be on anticholinergic and more likely to be on beta-antagonists and vice versa. The final results show a prior history of asthma may be the strongest determinant of ACOS diagnosis later in life. Also, patients above age 40 were significantly associated with ACOS diagnosis, that is, when they are more likely to be diagnosed with COPD.

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CHAPTER 5

Overall summary, discussions, and conclusions

5.1 General overview of findings

OADs are common, but recent concerns of over (or under) diagnosis of asthma and chronic obstructive pulmonary disease (COPD) has been voiced. The study presented in Chapter 3 was conducted to determine the prevalence of pulmonary function testing (PFT) for the diagnosis of asthma, COPD and other conditions in patients treated with inhaled medications for shortness of breath (SOB) in a community setting. It was a secondary analysis of the EpiSOB to determine the epidemiology of asthma and COPD in inhaled drug users for SOB and compare family-care physician diagnosis to ATS/ERS standard guidelines for the diagnosis of OADs. Agreement of PFT diagnosed outcomes with the FPs diagnosis was tested by the kappa statistic. Simple proportions were reported for outcomes (i.e., the proportion of patients aware of their diagnosis, proportion of patients who received an appropriate diagnostic workup for their condition before entry into the current program). A total of 328 patients received full diagnostic workup, including PFT (median age 50 years, 43% male). Based upon adjudicated results, 136 (42%) were diagnosed with asthma only, 44 (13%) with COPD only, 11 (3%) with both, 22% with no demonstrable lung disease and 6% with other conditions which cause SOB symptoms such as heart failure and pulmonary atrial hypertension.

Among the patients prescribed with an inhaler, and mainly from a family-care physician; only 40% had PFT performed to provide a diagnosis for their condition. Inhaler medications commonly prescribed for SOB symptom management included

SABA (74.1%), inhaled corticosteroids (28.0%), and combination inhaler products (35%). First-time prescribers were mainly family-care physician (75%). Agreement of family-care physician diagnosis with guideline-derived diagnosis (as determined by respiratory specialist) was minimal for asthma (Sens=0.71, Spec=0.51, Kappa=0.22, p=0.001) and COPD (Sens=0.51; Spec=0.38, Kappa=0.28, p=0.001) but statistically significant. In this study, a modest but significant agreement exists between family-care diagnosis and expert guideline-derived diagnosis for SOB patients. Most patients with SOB symptoms are prescribed inhalers without a PFT diagnostic workup. This may, in part, be due to the inadequate understanding of PFT interpretation and usage by family-care physicians. Access to appropriate testing may also play a role.

Chapter 4 present the second paper which examined the determinants of diagnosis for asthma, COPD and ACOS in patients with SOB. Patients diagnosed with asthma were less likely to be over the age of 40 years. Asthma patients were more likely to have allergies, and hooved farm animals exposure was not linked to asthma (OR: 0.54; 95% CI: 0.31 – 0.94). COPD patients were over the age of 40 years and have a history of smoking. Patients with COPD were significantly less likely to have anaemia as a comorbidity (p=0.015) and are significantly less likely to have had asthma previously. This study shows that ACOS patients are usually older than 40 years, have a previous diagnosis of asthma as well a history of cigarette smoking, and are more likely to be prescribed a combination therapy as a treatment for their SOB symptom.

5.2 Comparison of current findings with previous literature

Asthma diagnosis

Asthma is a major public health concern affecting nearly 8.5% of Canadians (1). A variety of demographic factors are said to be associated with asthma. The most common factors include age, gender/sex, and race/ethnicity, however, other factors may be associated such as the order of birth, the season of birth, region, and country (2).

Age and sex are two non-modifiable risk factors that are linked with the development of asthma (3). Although not statistically significant in this study (p=0.359), epidemiologic studies have shown significant differences in asthma prevalence as it relates to sex (4). The American Lung Association reported in 2012 that the likelihood of developing asthma in a lifetime is about 10.5% greater in women than men. The National Centre for Health Statistics reported (NCHS) in 2010 reported the prevalence of asthma in persons <15 years of age to be 11.9% in boys and 7.7% in girls while in young adults aged 15–34 years, the numbers shifted, with a prevalence of 6.3% in men and 9.6% in women. The difference continued to broadening in adults >35 years with a prevalence of 5.6 versus 10.1% in men and women, respectively (5). In a study by Zharan et al using the CDC's 2009-2010 Behavioral Risk Surveillance system data, the authors reported that 10.5% (10.3–10.7) of the asthma cases were women a significant value at a p-Value <0.0001. In addition, a systematic review and meta-analysis looking at the prevalence of asthma and COPD in Aboriginal and non-Aboriginal populations, the authors reported that in Australian Aboriginals 15.2% women have asthma compared to 8.5% of males. In a Canadian Aboriginals, 17% of females have asthma while 11% of males and in Native Americans, 14.1% females compared to 6.7% males (6).

In addition to sex, race/ethnicity has been reported to be of great significance to asthma development and prevalence. This study showed no association of race/ethnicity

with asthma, this may have been due to a lack of diversity within the study sample as 86.3% of the sample was Caucasians. Nonetheless, Blacks/African Americans and other minority racial groups have been reported to have the highest prevalence of asthma compared to whites (7–9). However, it is unclear if this difference is due to genetics and or cultural and environmental factors. Studies have reported that this difference may due to socioeconomic status across the racial/ethnic groups. A study published in 2003 reported that Blacks and Hispanics had a history of more hospitalization and a higher rate of hospitalization in the last years compared to Whites, significant differences at a $p < 0.001$. They also reported that after controlling for confounding variable Blacks and Hispanics were two times more likely to be admitted to hospital. They further concluded that SES appeared to have accounted for most of the observed acute asthma differences, although hospital admission rates were higher among Black and Hispanic patients after adjustment for confounding factors (10).

Socioeconomic status (SES), measured on the basis of occupation and educational level. Has been labeled an important risk factor for acute asthma as low-SES have been significantly associated with hospitalization (10). A 2004 study by Basagaña et al, the authors reported that the prevalence of asthma was higher in the lower socioeconomic groups, whether defined by educational level or social class regardless of atopic status (11). An Australian study looking at SES and self-reported asthma in Indigenous and non-Indigenous adults aged 18-64 years reported that asthma prevalence was higher for Indigenous than non-Indigenous people in every age group. SES (education, income and employment status) were shown to be significantly associated with asthma in the non-Indigenous but not the Indigenous population. However, the authors made a claim for this

result in that it may be due to the episodic nature of asthma as well of lack of access to healthcare by Indigenous Australians due to racism (12). Additionally, a 2010 study by Ekerljung et al found low SES to be significantly associated with an increased risk for prevalence and incidence of asthma and respiratory symptoms (13).

This study reports some association between family history of asthma and asthma (OR: 1.56; 95%CI: 1.00 - 2.45). However, the genetics of asthma continue to be investigated. The role of genetic predisposition in adult-onset asthma is less clear than atopy in childhood-onset asthma (14). An international population-based cohort conducted by Anto et al reported that participant with maternal asthma was 1.91 times more likely to develop asthma in adulthood (95% CI 1.13 -3.21) and that atopy was attributed for 12% to 21% new onset asthma (15).

Numerous epidemiologic studies have identified occupations and/or workplaces along with environmental particles that are at high risk for asthma development and asthma exacerbation (16–22). In a study evaluating the occupation held at the time of asthma onset, the researchers found that 37.1% of the working adults developed asthma while in employment (21). In a Northern Europe population-based study, the authors reported that men who were exposed to epoxy, diisocyanates, and acrylates were at a higher risk of new-onset asthma. In addition, both males and females were at higher risk for individuals working cleaners, spray painters, plumbers, and hairdressers (20). In another Northern Europe study, the authors reported that exposure to irritant gases and fumes (a previously thought low-risk exposure) posed a higher risk for asthma. An increased risk was also shown for men who were exposed to plant-associated irritants (19). In a US study, the authors found that 5.1% of farm operators had asthma. Of the

5.1%, 15.4% had farm work-related asthma, and among those, 33.3% had an attack that occurred while doing farm work. 65% of the reported asthma attack were associated with plant or tree materials (23). In a most recent (2015) cohort study aimed at investigating the association between air pollution and adult-onset asthma, after evaluating 23,704 participants there was no significant association between asthma and nitrogen dioxide and or particulate matter (24).

Comorbidities increase the likelihood of poorly controlled asthma as individuals may not respond to treatment which may aid in asthma misdiagnosis (25), as well as poor quality of life (26). Common comorbidities of asthma are anxiety, depression, behavioral disorders, Gastroesophageal reflux (GERD) and other gastrointestinal disease, metabolic disorders (Diabetes), allergic rhinitis, Rhinitis and rhinosinusitis, obesity, COPD, Respiratory infection, Neurologic disorders, Atherosclerotic cardiac disease and circulatory disorders, Bronchitis and bronchopneumonia, Connective tissue diseases, Dermatologic conditions (eczema), Immunologic and hematologic diseases, and vocal cord dysfunction (VCD) (25). This study, however, reported no comorbidities directly associated with asthma. In fact, patients were less likely to have comorbidity (**Table 4.2**). Numerous studies have reported an association between at least one of the aforementioned disease/condition to asthma (27–35). For example, a prospective study of two matched cohorts found that patients with asthma were at higher risk for coronary artery disease by 40%. Asthma patients were also at a 20% increased risk for cerebrovascular disease. Additionally, asthma patients were 3.2 times more like to have heart failure (32).

COPD diagnosis

Tobacco smoke (primary exposure) has been the number one risk factor linked to COPD, accounting for an estimated 75% of all cases (36). In addition, Passive smoking exposure has also been associated with an increased risk for COPD (37,38).

Age is a major risk factor for developing COPD, as COPD generally presents itself mainly in people of older age (39–42). Though it is unclear as to whether age itself has a causal effect on the development of the disease or whether it is due to the years that the individual is exposed to the pathogens/other factors contributed to the developmental process (40). This study reports that COPD patients were found to be significantly more likely to be 60 years and older ($p<0.0001$).

Although of no statistical significance in this study (OR: 1.56; 95%CI: 0.83 – 2.96; p= 0.169) other studies have reported sex as a significant factor in COPD diagnosis. Moreover, there has been a significant increase in the incidence of COPD among women compared to men has changed over the past two decades (43). The CDC published in 2002 a report on data collected from 1980 to 2000, which showed an increase in the prevalence of COPD in women (43). It is now believed that this change in prevalence is due to the increase in women smoking and well as the high risk of exposure to indoor pollutant such as cooking and heating fuel (44,45) as well as a difference in the lung function between both men and women (46).

Race/Ethnicity is of no statistical significance in this study, however, race/ethnic has been linked to COPD prevalence (46–50)**.** As smoking among the minority groups (especially African Americans) increase rapidly so does the prevalence of COPD. African Americans are said to have "smaller trunk/leg" ratios than whites and therefore lower lung function" (46–48); and therefore more susceptible to the harmful effects of tobacco

smoke. In a study by Dransfield et al, looking at susceptibility index of African American compared with Caucasian to tobacco smoke as the primary outcome, defined as loss of lung function per pack-year smoked, the authors found that African-American smoked less and was younger than Caucasian though their lung function was similar (FEV_1 51% predicted in both groups) (49,51).

SES, conditioned mainly by education, income, professional activity, and actual profession with education level often being the main socioeconomic status indicator; (12) has also been linked to COPD and its severity (26). This study reports that COPD patients were significantly less likely to have had a post-secondary education (p=0.003). It is believed that individuals who grew up in unfavorable socioeconomic conditions are more prone to develop unhealthy behaviors in adulthood (52). In a study investigating the association between education and lifetime smoking patterns, the authors found that the number of pack-years smoked was higher among individuals with less than a high school education (53). A Korean study looking at the risk factors for COPD in non-smokers the authors found that subjects with low education status were two times more likely to develop COPD (OR: 2.0; 95%CI: 1.2-3.2) (54). Subsequently, a study conducted in China found similar results. The authors reported that subjects that have less education were 17% more likely to have airflow obstruction (OR: 1.17; 95% CI: 1.12 - 1.23) for no schooling versus college education) (55). Additionally, a study by Pleasants et al found that the rates of self-reported COPD were highest among those who had less education (56). In the Helsinki COPD study, it was reported that socioeconomic status was significantly associated with airflow obstruction. Also, they reported that the risk

associated with smoking increased significantly and in manual and non-manual workers compared to professionals (57).

Various occupational, as well as environmental exposures, have been associated with COPD often in combination with tobacco smoking. These exposure includes organic and inorganic dust and chemical agents and fumes (40) and accounts for about 26% to 43% of COPD cases in never-smokers (58). The occupational and environmental factors associated with COPD are: NO2, Ozone, dust gas, minerals (coal, oil mist, and silica), fibers, chemicals (vanadium, cadmium, isocyanate, vinyl chloride, and polycyclic aromatic hydrocarbons), wood, animal dung, crop residues, cooking fuels, and welding fumes (40,59). In the United States (US) the prevalence of COPD among non-smoking working adults aged 25 and older was found to be 2.8% in a 2013 study (based on the NHIS data between 1997 and 2004) (60). A Chinese study by Zhou et al. reported that the prevalence of COPD among non-smokers was 4.2% compared to 31.3% smoker of 40 packs per year, (61) while the prevalence among never-smokers in Korea was found to be7.7% (62). In a recent Canadian study (2014) the prevalence of COPD among never-smokers was reported at 2% compared to 14% among current smokers (63). In a Danish population-based study looking at Occupational COPD in never-smokers reported that non-smokers that were exposed to particles occupationally were three times more likely to have COPD compared to those not being exposed on their jobs (58). A Canadian review article, reported an association between pesticides and COPD or chronic bronchitis (64), while in a separate review article by Mamane et al. found a negative association between pesticides and obstructive lung diseases (64). Also, a Swiss study reported that a high level of occupational exposure to biological dust, gas/fumes, and

VGDF were significantly associated with stage II+ GOLD and lower limit normal (LLN) COPD (65).

Comorbidities are common among people with COPD. This study shows that 47.8% of patients diagnosed with COPD had between three and four comorbidities. In a cross-sectional family practice study done in Madrid, the authors reported ten comorbid conditions that were highest among COPD patients after controlling for age and sex (66). In a study by Mannino et al analyzing data from 20,296 participants age 45 and older at baseline in the Atherosclerosis Risk in Communities Study (ARIC) and the Cardiovascular Health Study (CHS) the authors found that participants with GOLD stage III or IV COPD had a higher prevalence of cardiovascular disease, hypertension, and diabetes (OR: 2.4; 95% CI: 1.9 - 3.0), (OR: 1.6; 95% CI: 1.3-1.9), and (OR: 1.5; 95% CI: 1.1-1.9) respectively (67). In a 2015 systematic review and meta-analysis, patients with COPD were reported to more likely to be diagnosed with cardiovascular disease (OR: 2·46; 95% CI: 2·02 - 3·00; p<0·0001), including a two to five times higher risk of ischaemic heart disease, cardiac dysrhythmia, heart failure, disease of the pulmonary circulation, and disease of the arteries. Additionally, patients with COPD reported hypertension more often (OR, 1·33; 95% CI: 1·13 - 1·56; p=0·0007), and diabetes (OR: 1·36; 95% CI: 1·21 - 1·53; p<0·0001) (68).Additionally, two studies, Dal Negro et al. and Fumagalli et al., reported that heart disease was higher among male COPD patients (69,70). In a survey administered by telephone to 1003 COPD patients aiming to evaluate the prevalence of comorbid conditions, the authors found hypertension (55%), hypercholesterolemia (52%), depression (37%), cataracts (31%), and osteoporosis (28%) to be the most prevalent comorbid diagnoses (71).

ACOS diagnosis

The prevalence of ACOS in this SOB study population was found to be 16.8%. ACOS patients were statistically significantly more likely to be older than 40 years, to have allergies, and to be previously diagnosed with asthma by the family-care physician (p=0.003, p=0.05, and p=0.003 respectively).

The prevalence of ACOS varies across countries and groups based on the criteria being used to define it. However, the prevalence has been shown to increase with age (72,73). In a longitudinal study by de Marco et al using the European Community Respiratory Health Survey II (ECRHS II) data on young adults of the general population collected between 1991-1993 (ages 20-44 years) and follow-up 1999-2001 found the prevalence of ACOS to be 3.12% (218 out of 6984 participants), asthma was 13.47% and COPD 2.37%. Subjects with COPD were older (60.4 years) compared to those with ACOS and asthma (50.5 and 44.2 years respectively), a significant difference. The authors also found that among the young adults ACOS was seen more of a form of severe asthma "characterized by more frequent hospitalizations, and to be the result of early-onset asthma that has progressed to fixed airflow obstruction" (73). In a most recent cross-sectional study investigating 'the prevalence of ACOS among 190 primary care asthmatics with a smoking history' by Kiljander et al in Finland, 27.4% of the patients had ACOS. These patients had no prior diagnosis of COPD and so they were considered to have ACOS if their FEV1/FVC ratio was less than 10%. These newly determined ACOS patients also had an average age of 60 and older. The authors concluded the main predictors for ACOS is age ≥60 with a >20 pack years smoking history(72).

A literature review was conducted by Wurst et al, with the aim of characterizing the "the prevalence of ACOS and the effect of different disease definitions on these estimates"; they found that ACOS prevalence varied widely (12–61%) among patients with COPD or asthma and that the variability is linked to the differences in COPD and asthma diagnostic criteria as well as age, gender and the population being studied. Specifically, the authors reported that after analyzing the literature published in English from 2000 to 2014 the prevalence of ACOS was estimated to range from 12.1% to 55.2% among patients with COPD and 13.3% to 61.0% among patients with asthma alone (74). A study published in 2014 by Hardin et al., reported the prevalence of ACOS in a study population of 10,000 subjects to be 4.5% and that 13% of the COPD patients in the study reported a history of doctor-diagnosed asthma. They also found that subjects with an overlap were significantly younger ($p<0.001$) compared to subjects with COPD only (75).

In the same way, a systematic review conducted by a team in Vancouver, with the aim of evaluating the prevalence of ACOS in COPD patients and the association between ACOS and exacerbation, hospitalization, health care utilization and HRQoL (76). Using nineteen studies in their review, the authors found the pooled prevalence of ACOS among the COPD patients to be 27% in population-based studies and 28% in hospital-based studies. ACOS patients were found to younger than those with COPD alone but older than those with asthma alone, similar to other studies (62,66).

Conclusions: Study 1 showed that most patients with SOB symptoms are prescribed inhalers without a PFT diagnostic workup; which may due in part to an inadequate understanding of PFT usage and interpretation by a family physician. Study 2 showed that ACOS patients are older than 40 years and seem to represent a form of

severe asthma with similar features of prior asthma and COPD. Asthma patients were less likely to have addition comorbidities while COPD patients, were more likely to have a wide range of comorbidities.

5.3 Strengths and limitations of the studies

The main strength of this thesis study is that it has provided, for the first time (to our knowledge), the estimates of PFT utilization for diagnosis of obstructive airway diseases in Canada. This Canadian study has concurred with other research, showing that that non- PFT usage in the management of SOB patients is associated with substantially fewer health benefits and increases the risk of over or under-diagnosis of OADs in shortness of breath patients. The main limitation is that the study was conducted as a cross-sectional study with no follow-up for intervention. In addition, recall bias, selection bias, as well as attrition bias may all be a factor in this study and, therefore, results may not be generalized.

5.4 Clinical Implications

In a group of community-based SOB patients being treated with inhalers, fewer than half ever had PFT performed, and a significant proportion had no lung disease or other conditions. Modest but significant agreement exists between family-care diagnosis and expert guideline-derived diagnosis for SOB patients. These findings, however, point to the need for a more thorough diagnostic workup, including PFT for patients with presumed OADs.

5.5 Future Research

Based on numerous reports and guidelines on asthma, COPD and by extension ACOS (5,6,23,28,31) the knowledge and understanding of ACOS are limited and still in the early stages of research. A limitation of most studies being done is that patients with an unclear diagnosis of either asthma and or COPD have been excluded from studies and therefore diagnosis and proper management of this disease remain a challenge. Therefore, research is urgently needed in this area of study so as to better equip family-care physicians with easy to follow guide that easily and clearly outlines how to better recognize, diagnose and manage this progressive disease.

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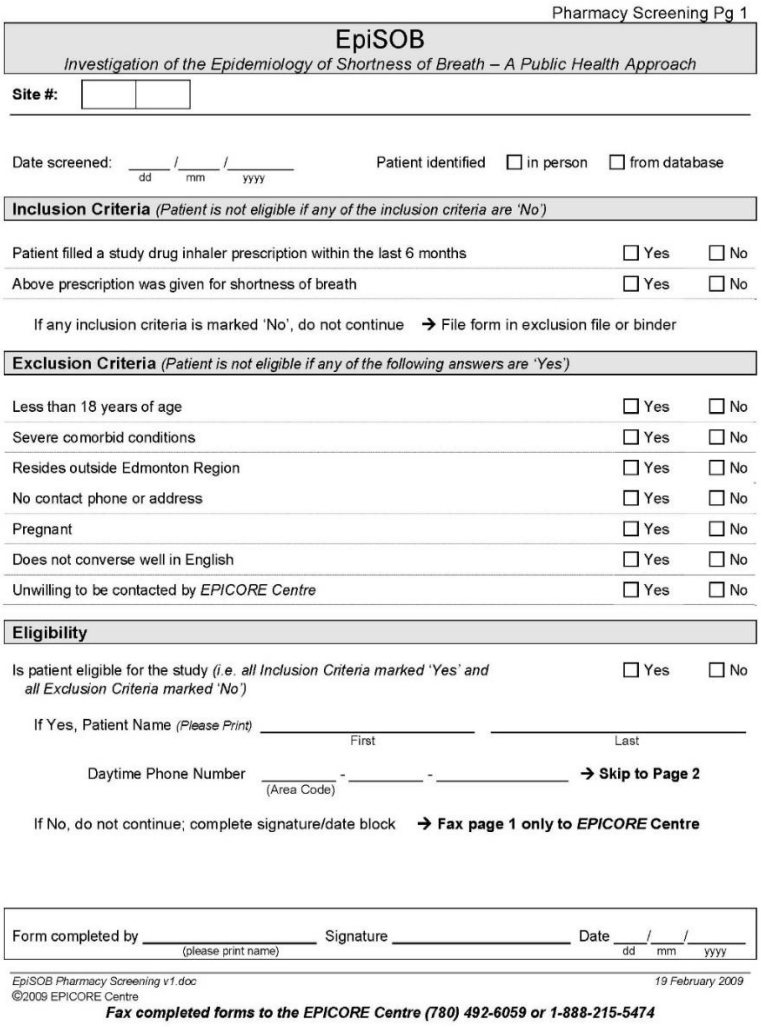
APPENDICES

Appendix A: Pharmacy Screening Forms



Pharmacy Screening Pg 1

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Site #: ☐☐

Date screened: ____ /____ /____ (dd / mm / yyyy) Patient identified ☐ in person ☐ from database

Inclusion Criteria *(Patient is not eligible if any of the inclusion criteria are 'No')*

Patient filled a study drug inhaler prescription within the last 6 months	☐ Yes	☐ No
Above prescription was given for shortness of breath	☐ Yes	☐ No

If any inclusion criteria is marked 'No', do not continue → File form in exclusion file or binder

Exclusion Criteria *(Patient is not eligible if any of the following answers are 'Yes')*

Less than 18 years of age	☐ Yes	☐ No
Severe comorbid conditions	☐ Yes	☐ No
Resides outside Edmonton Region	☐ Yes	☐ No
No contact phone or address	☐ Yes	☐ No
Pregnant	☐ Yes	☐ No
Does not converse well in English	☐ Yes	☐ No
Unwilling to be contacted by *EPICORE Centre*	☐ Yes	☐ No

Eligibility

Is patient eligible for the study *(i.e. all Inclusion Criteria marked 'Yes' and all Exclusion Criteria marked 'No')* ☐ Yes ☐ No

If Yes, Patient Name *(Please Print)* _____ (First) _____ (Last)

Daytime Phone Number ____ (Area Code) - _____ - _____ → **Skip to Page 2**

If No, do not continue; complete signature/date block → **Fax page 1 only to *EPICORE* Centre**

Form completed by _____ (please print name) Signature _____ Date ____/____/____ (dd / mm / yyyy)

EpiSOB Pharmacy Screening v1.doc *19 February 2009*

Fax completed forms to the EPICORE Centre (780) 492-6059 or 1-888-215-5474

Appendix A (continued)

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Site #: ☐☐

First SOB Episode Medication

What medication*(s)* were prescribed for the first *(index)* episode of SOB *(check all that apply)*

☐ Short-acting β_2 ☐ Short-acting anticholinergic ☐ Inhaled corticosteroid
☐ Long-acting β_2 ☐ Long-acting anticholinergic ☐ Combination (☐ Symbicort ☐ Advair)

Who prescribed these medication*(s)*

☐ Family Physician *(Regular)* ☐ Walk-in Clinic Physician ☐ Respirologist
☐ Family Physician *(New/occasional)* ☐ Emergency Physician ☐ Other Specialist, specify _____

Current Medications *(Pharmacy record of current medications dispensed within the last 6 months)*

Does patient agree to Pharmacy providing *EPICORE* Centre with their medication history ☐ Yes ☐ No

If Yes, ☐ confirm consent by asking patient to initial here → **OR**
☐ if verbal consent received by phone, pharmacist to confirm by initialing here → _____ Initials

☐	ACE inhibitor	☐	Long-Acting β_2
☐	ARB	☐	Inhaled Corticosteroid
☐	Beta Blocker	☐	Steroid, Oral
☐	Calcium Channel Blocker	☐	Combination/Symbicort
☐	Diuretic	☐	Combination/Advair
☐	Antidepressant	☐	Theophylline
☐	Antipsychotic	☐	LTRA *(Singulair)*
☐	Antihistamine	☐	Ketotifen/Nedocromil
☐	Anticholinergic, Long-Acting	☐	Other respiratory drug, specify _____
☐	Anticholinergic, Short-Acting	☐	Other respiratory drug, specify _____
☐	Short-Acting β_2	☐	Other respiratory drug, specify _____

PiKo-6 Test – To be completed **ONLY** for patients identified **in person**

Is patient willing to perform ***PiKo -6*** ☐ Yes ☐ No

If Yes, ask patient to initial the box below. Record values from two (2) ***PiKo-6*** readings

_____ Patient Initials

Reading #1	FEV_1 ___•___		FEV_6 ___•___		Ratio ___•___	
Reading #2	FEV_1 ___•___		FEV_6 ___•___		Ratio ___•___	

Comments _____

Form completed by _____ (please print name) Signature _____ Date ___/___/_____ dd mm yyyy

Fax completed forms to the EPICORE Centre (780) 492-6059 or 1-888-215-5474

Appendix B: Patient Invitation Letter

Insert Patient Address here

Dear (patient name):

Thank you for agreeing to participate in the program called "Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach" (EpiSOB). The appointment for your tests and interview will be on (date) at (time) , 404 College Plaza, 8219-112 Street, Edmonton. Please allow about 2 hours for this appointment.

To prepare for the pulmonary function test, please do not take your respiratory inhalers for at least 6 hours before your test, if you can tolerate it. Note the Garneau Lung Lab is a fragrance-free clinic. Please refrain from wearing scents/fragrances out of respect to other patients with scent sensitivities/allergies.

Please find attached the following information:

- A map showing how to get to College Plaza
- A medication list – please document all the medications you have been taking or have been prescribed in the last 6 months.
- A copy of the Patient Information for the study for you to read and prepare any questions you may have.
- Travel
  - ☐ Parking information: There are two entrances to the College Plaza parkade; one on the south side (82rd avenue) and one on the north side (on 83rd avenue) of the building. You will be provided with a parking pass upon completion of your testing. When you leave the parkade, insert this parking pass first and then the parking stub you received at the gate when you entered the parkade.
  - ☐ Taxi: Enclosed you will find a form that will allow to take a taxi to College Plaza free of charge. Please call 780-484-8888 (Checker Cab) to book your taxi. The taxi driver will keep the white and yellow copies. Please bring the pink and goldenrod copies to your appointment. You will be given another set at your appointment for your trip home.
  - ☐ BUS/DATS: Enclosed you will find ETS ticket(s) that will allow you to take your bus/or DATS to College Plaza free of charge. You will be given more at your appointment for your trip home.

If you have any questions regarding your appointment call Giselle at 780-433-5891 or Carolyn at 780-492-4428. If you have any questions or concerns at all about this study please call Carolyn Nilsson at 780-492-4428.

Thank you,

Sincerely,
Carolyn Nilsson,
Project Coordinator

EPICORE Centre - Division of Cardiology - Department of Medicine

220 College Plaza • University of Alberta • Edmonton, Alberta, Canada • T6G 2C8
Telephone: (780) 492-8525 Fax: (780) 492-6059 http://www.epicore.ualberta.ca

Appendix C: Patient Study Information and Survey

UNIVERSITY OF ALBERTA

Appendix III: Patient Information Sheet

Title of Study Program: Investigation of the Epidemiology of Shortness of Breath – A public health approach

Principal Investigator: Ross Tsuyuki, PharmD

Co-Investigator (s): Irvin Mayers, MD; Heather Sharpe, RN, MN, Dilini Vethanayagam, MD; Michael Chan, MD; William Midodzi, PhD; Brian Rowe, MD; Carolyn Nilsson, CCHRA(c)

Program Coordinator(s): Epidemiology Coordinating and Research (EPICORE) Centre, Department of Medicine, University of Alberta, 220 College Plaza, Edmonton, Alberta, T6G 2C8,

Background: Shortness of breath is a symptom that occurs with many medical conditions, including asthma, chronic obstructive pulmonary disease (COPD) or heart failure. Often, people with shortness of breath are prescribed inhaled medications such as salbutamol (Ventolin® and others), ipratropium (Atrovent®, others), tiatropium (Spiriva®), *(LABA), (ICS)*, symbicort or advair. You have been prescribed one or more of these medications. We are interested in determining what conditions these medications are used for.

Purpose: The purpose of this study is to determine the conditions associated with shortness of breath.

Procedures: This is what will happen if you agree to take part in this research program:

1. The reason you are being asked to be part of this program is because you have been prescribed one of the medications for shortness of breath sometime during the last 6 months.
2. Your pharmacist has asked if you are interested in being part of this program. He /she will give us your name and phone number.
3. You have talked to a research assistant by phone about the study and to make an appointment for a pulmonary function test and interview.
4. For most of the people in the study, that appointment should be the only time you have to do anything.
5. At this appointment you will meet with the program coordinator. We would like to get information about you, your health and which medications you are taking. This will take about 20 minutes. A few patients at random will be chosen to see a physician for a separate physical exam, and this will take an extra 20 minutes or so.
6. A respiratory technician will ask you to do a pulmonary function test (PFT). This is a special test to see how well your lungs are working. In this test, you take deep breaths and then blow into a machine. The machine measures how deeply you can breathe and how fast you can move air in and out of your lungs. Meds prior to test? This may take up to 30 minutes.
7. A blood test will be taken.
8. We will ask you to provide a urine sample.
9. We will check NetCare to see if you have had a chest x-ray in the last 6 months.

10. Lung specialists will receive the results from these tests and they will decide if you have one of the conditions that causes shortness of breath. They will send you a letter about what they have found. If you agree, they will also send a letter to your family doctor to let them know what the tests show and what medications would be best for you.
11. Most of the time, these tests will be enough. However, if the specialists are not able to decide what you have from these test results, you will be contacted to come in for an appointment with the specialist. They may ask you to have another test. All of the results and information will be shared with you and your family doctor.

Possible Benefits: The benefit for you being in this program is that you may be able to find out more about your condition. You will also help us to determine the reasons why people are given these medications. This will give us a clearer picture of the treatment of shortness of breath in the community.

Possible Risks: There is little risk involved in this program. Decisions about your health care are still made by you and your family doctor as usual. There is some commitment, inconvenience and discomfort in having a lung function test performed (you have to blow as hard as you can into the tube), but the test is short.

Confidentiality: Personal health records relating to this project will be kept confidential. Any information collected about you during this program will not identify you by name, only by your initials and a coded number. Your name will not be disclosed outside the research clinic. Any report published as a result of this program will not identify you by name.

For this program, the study doctors may need to access your personal health records for health information such as past medical history and test results. He/she may also need to contact your family physician and your other health care providers to obtain additional medical information. The health information collected as part of this program will be kept confidential unless release is required by law, and will be used only for the purpose of the research program. By signing the consent form you give permission to the project staff to access any personally identifiable health information which is under the custody of other health care professionals as deemed necessary for the conduct of the research.

The personal health information collected in this program will need to be checked from time to time against your medical records. In addition to the investigators(s), the Health Research Ethics Board may have access to your personal health records to monitor the research and verify the accuracy of program data.

By signing the consent form you give permission for the collection, use and disclosure of your medical records. Study information is required to be kept for 7 years. Even if you withdraw from the program, the medical information which is obtained from you for study purposes will not be destroyed. You have a right to check your health records and request changes if your personal information is incorrect.

Voluntary Participation: You are free to withdraw from the research program at any time, and your continuing medical or pharmacy care will not be affected in any way. If the program is not undertaken or if it is discontinued at any time, the quality of your medical care will not be affected..

Reimbursement of Expenses: You will be provided with parking coupons at each visit. The project office will provide transportation for you if are unable to get to the clinic.

Compensation for Injury: If you become ill or injured as a result of participating in this program, necessary medical treatment will be available at no additional cost to you. By signing this

consent form you are not releasing the investigator(s) and institution(s) from their legal and professional responsibilities.

Contact Names and Telephone Numbers:
If you have concerns about your rights as a participant, you may contact the Patient Relations Office of Capital Health, at 482-8080 This office has no affiliation with the study investigators.

Please contact any of the individuals identified below if you have any questions or concerns:

Dr. Ross Tsuyuki, Principal Investigator, Professor of Medicine: 780-492-8526 or toll-free at 1-877-876-9888.

Appendix D: Medication Information Form

Initials ___ ___ ___ Study # ___ ___ ___

EpiSOB Program

Medication, Allergy List and Information Page

Name: _____

Alberta Health Care Number: ___ ___ ___ ___ ___ - ___ ___ ___ ___

To the best of your ability, please list all medications you have been on or have been prescribed in the last 6 months:

Name of Medication	Name of Medication

Allergies:

_____

_____

_____

Physician Information:

Physician name: _____

Physician phone number: _____ Fax: _____

Address: _____

City _____ Postal Code _____

Please bring this with you to your appointment.

Appendix E: Patient Consent Form

UNIVERSITY OF ALBERTA

Title of Study Program: Investigation of the Epidemiology of Shortness of Breath – A public health approach

Principal Investigator:

Ross Tsuyuki, PharmD, MSc, Division of Cardiology, University of Alberta	780-492-8526

Co-Investigator (s):

Irvin Mayers, MD; Pulmonary Medicine	780-407-1854
Dilini Vethanayagam, MD; Pulmonary Medicine	780-407-1479
Michael Chan, MD; Cardiology	
William Midodzi, PhD; EPICORE Centre	780-492-9714
Brian Rowe, MD; Emergency Medicine	780-407-6707
Heather Sharpe, PhD (c); University of Calgary	
Carolyn Nilsson, CCHRA(c), EPICORE Centre	780-492-4428

Study Coordinator(s): Epidemiology Coordinating and Research (EPICORE) Centre, Department of Medicine, University of Alberta, 220 College Plaza, Edmonton, Alberta, T6G 2C8, Canada

---

To be completed by the research participant:

Do you understand that you have been asked to be in a research program?	☐ Yes	☐ No
Have you read and received a copy of the Patient Information Sheet?	☐ Yes	☐ No
Do you understand the benefits and risks involved in taking part in this research program?	☐ Yes	☐ No
Have you had an opportunity to ask questions and discuss this program?	☐ Yes	☐ No
Do you understand that you are free to withdraw from the study at any time, without having to give a reason and without affecting your future medical care?	☐ Yes	☐ No
Has the issue of confidentiality been explained to you?	☐ Yes	☐ No
Would you like the final results of these tests and examinations sent to your family physician?	☐ Yes	☐ No

☐ This program was explained to me by: Ms. Carolyn Nilsson, EPICORE Centre

---

I agree to take part in this program: ☐ Yes ☐ No

Signature of Research Subject	Date:	Witness
Printed name		Printed Name

I believe that the person signing this form understands what is involved in the program and voluntarily agrees to participate.

Signature of Investigator or Designate	Date

Appendix F: Asthma Control Questionnaire (ACQ) Form

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Study ID # ____ ____ – ____ ____ ____ (Site Number – Patient Number) **Patient Initials** ____ ____ ____ (First Middle Last)

Please answer questions 1 - 6.

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you **woken by your asthma** during the night?
   - 0 Never
   - 1 Hardly ever
   - 2 A few times
   - 3 Several times
   - 4 Many times
   - 5 A great many times
   - 6 Unable to sleep because of asthma

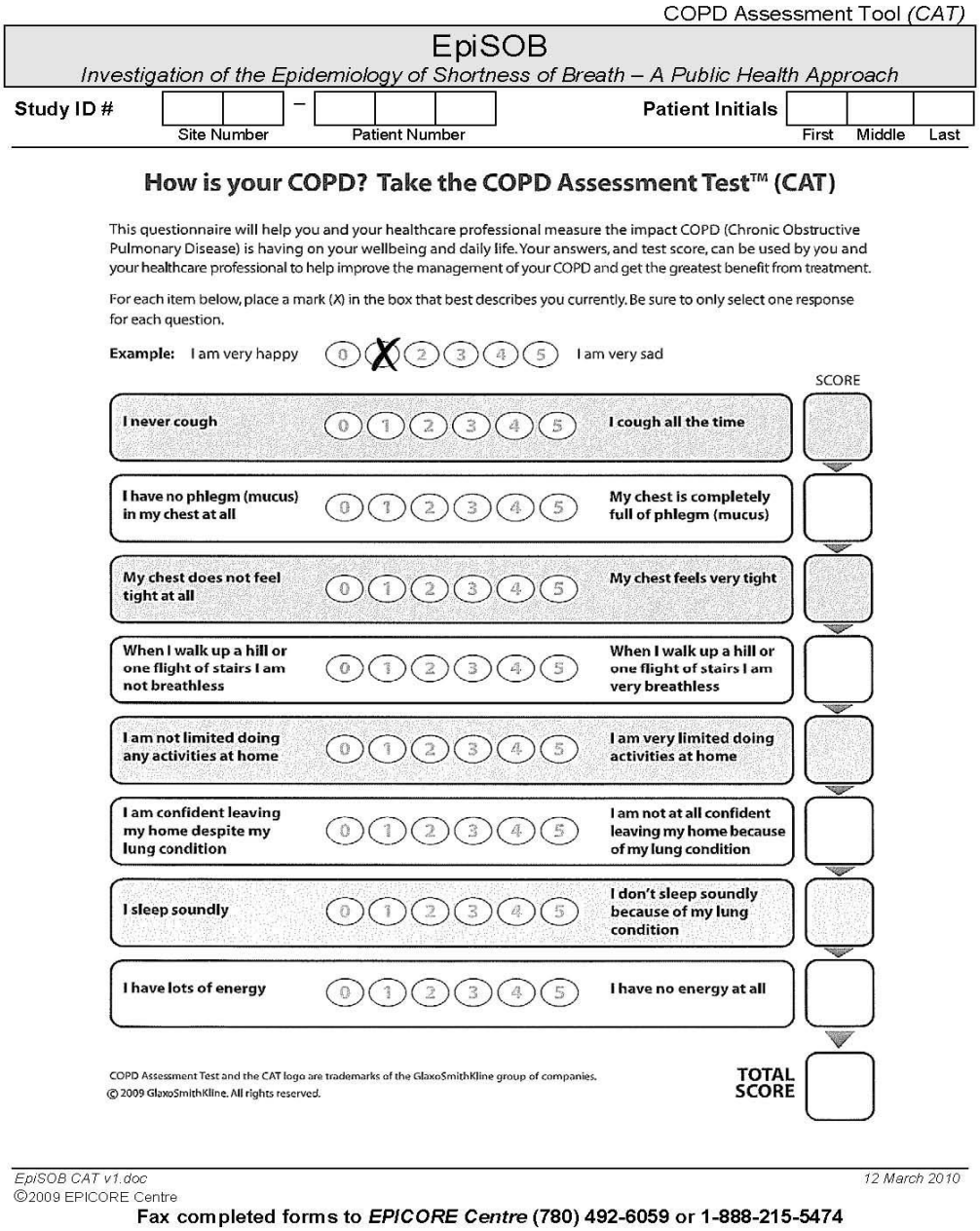
2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?
   - 0 No symptoms
   - 1 Very mild symptoms
   - 2 Mild symptoms
   - 3 Moderate symptoms
   - 4 Quite severe symptoms
   - 5 Severe symptoms
   - 6 Very severe symptoms

3. In general, during the past week, how **limited were you in your activities** because of your asthma?
   - 0 Not limited at all
   - 1 Very slightly limited
   - 2 Slightly limited
   - 3 Moderately limited
   - 4 Very limited
   - 5 Extremely limited
   - 6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?
   - 0 None
   - 1 A very little
   - 2 A little
   - 3 A moderate amount
   - 4 Quite a lot
   - 5 A great deal
   - 6 A very great deal

Asthma Control Questionnaire (ACQ) Juniper, EF, O'Byrne, PM and Guyatt, GH (1999)
EpiSOB ACQ v1.doc *16 July 2009*

Appendix G: COPD Assessment Tool (CAT) Form



COPD Assessment Tool *(CAT)*

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Study ID # Site Number – Patient Number **Patient Initials** First Middle Last

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (*X*) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy (0) (X) (2) (3) (4) (5) I am very sad

		SCORE
I never cough	(0) (1) (2) (3) (4) (5) **I cough all the time**	
I have no phlegm (mucus) in my chest at all	(0) (1) (2) (3) (4) (5) **My chest is completely full of phlegm (mucus)**	
My chest does not feel tight at all	(0) (1) (2) (3) (4) (5) **My chest feels very tight**	
When I walk up a hill or one flight of stairs I am not breathless	(0) (1) (2) (3) (4) (5) **When I walk up a hill or one flight of stairs I am very breathless**	
I am not limited doing any activities at home	(0) (1) (2) (3) (4) (5) **I am very limited doing activities at home**	
I am confident leaving my home despite my lung condition	(0) (1) (2) (3) (4) (5) **I am not at all confident leaving my home because of my lung condition**	
I sleep soundly	(0) (1) (2) (3) (4) (5) **I don't sleep soundly because of my lung condition**	
I have lots of energy	(0) (1) (2) (3) (4) (5) **I have no energy at all**	
	TOTAL SCORE	

Fax completed forms to *EPICORE Centre* (780) 492-6059 or 1-888-215-5474

Appendix H: Patient Interview Form

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Study ID # ☐☐ – ☐☐☐ (Site Number / Patient Number) **Patient Initials** ☐☐☐ (First Middle Last)

Date of Interview _____ / _____ / _____ (dd / mm / yyyy) ☐ Not done

If not done, complete signature/date block → Fax page 1 only to *EPICORE* Centre

Form completed by _____ (please print name) Signature _____ Date ____/____/_____ (dd mm yyyy)

Demographics

Date of Birth _____ / _____ / _____ (dd / mm / yyyy) Sex ☐ Male ☐ Female

Postal Code _ _ _ _ _ _

Marital Status *(check one only)*

- ☐ Single *(never married)*
- ☐ Currently married
- ☐ Common Law/living with a partner
- ☐ Separated
- ☐ Divorced
- ☐ Widowed

Highest level of education *(check one only)*

- ☐ Less than Grade XII
- ☐ High school diploma
- ☐ Some post secondary
- ☐ Post secondary certificate/diploma/degree
- ☐ Not stated

Ethnicity *(check all that apply)*

- ☐ Caucasian
- ☐ Black
- ☐ Aboriginal
- ☐ Hispanic
- ☐ Oriental
- ☐ South Asian *(e.g. East Indian)*
- ☐ Middle Eastern
- ☐ Other, specify _____
- ☐ Not stated

Drug Insurance Coverage *(check all that apply)*

- ☐ Private *(through employment, etc.)*
- ☐ Government *(Child Benefit, Social Services, AISH, Gp 66, Gp 1, etc)*
- ☐ Other, specify _____
- ☐ None

Smoking History

- ☐ Current — # of years _____ # of cigarettes/day _____
- ☐ Past — # of years _____ # of cigarettes/day _____
- ☐ Never smoked

Second-hand exposure to cigarette smoke ☐ Yes ☐ No

If Yes, type *(check all that apply)*

☐ Childhood ☐ Adult ☐ Work-related/Other

Appendix H (continued)

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Study ID # ☐☐ – ☐☐☐ (Site Number – Patient Number) **Patient Initials** ☐☐☐ (First Middle Last)

Comorbidities/Patient-reported *(check all that apply)*

☐ Allergies	☐ High cholesterol
☐ Asthma *(# of years _____)*	☐ Heart Failure
☐ Bronchitis, chronic	☐ Arrhythmias ☐ A Fib/Flutter ☐ Other arrhythmia
☐ COPD *(# of years _____)*	☐ Malignancy
☐ Sinusitis or nasal polyps	☐ Osteoporosis
☐ Diabetes Type I	☐ Depression ☐ Current ☐ Prior
☐ Diabetes Type II	☐ Anxiety ☐ Current ☐ Prior
☐ CAD *(Ischemia, History of MI, Angina, CABG, PCI)*	☐ GERD/Heartburn
☐ Hypertension	☐ Anemia
☐ None of the above	

Family history *(1st degree)* of any of the following *(check all that apply)*

☐ COPD/Other	☐ Asthma
☐ Heart Disease	☐ Cystic Fibrosis
☐ None of the above	

Medications *(currently using or started within the last 6 months)*

Patient Report	Pharmacist Report	Name of Medication	Patient Report	Pharmacist Report	Name of Medication
☐	☐	ACE inhibitor	☐	☐	Anticholinergic, Long-Acting
☐	☐	ARB	☐	☐	Anticholinergic, Short-Acting
☐	☐	Beta Blocker	☐	☐	Short-Acting β_2
☐	☐	Calcium Channel Blocker	☐	☐	Long-Acting β_2
☐	☐	Diuretic	☐	☐	Inhaled Corticosteroid
☐	☐	Antidepressant	☐	☐	Steroid, Oral
☐	☐	Antipsychotic	☐	☐	Combination/Symbicort
☐	☐	Antihistamine	☐	☐	Combination/Advair
☐	☐	Other, specify _____	☐	☐	Theophylline
☐	☐	Other, specify _____	☐	☐	LTRA *(Singulair)*
☐	☐	Other, specify _____	☐	☐	Ketotifen/Nedocromil

Appendix H (continued)

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Study ID # ☐☐ – ☐☐☐ (Site Number / Patient Number) **Patient Initials** ☐☐☐ (First / Middle / Last)

Symptoms

Index	Current		**New York Heart Association Functional Classification** *(check one only)*
☐	☐	1	No symptoms and no limitation in ordinary physical activity, *(e.g. shortness of breath when walking, climbing stairs)*
☐	☐	2	Mild symptoms *(mild shortness of breath and/or angina)* and slight limitation during ordinary activity.
☐	☐	3	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances *(20-100 meters)*. Comfortable only at rest.
☐	☐	4	Severe limitations. Experiences symptoms even while at rest. Mostly bed-bound.

Index	Current		**MRC Dyspnea Scale** *(check one only)*
☐	☐	1	Not troubled by breathlessness except on strenuous exercise.
☐	☐	2	Short of breath when hurrying or walking up a slight hill.
☐	☐	3	Walks slower *(than contemporaries)* on level ground because of breathlessness or has to stop for breath when walking at own pace.
☐	☐	4	Stops for breath after walking about 100 meters or after a few minutes on level ground
☐	☐	5	Too breathless to leave the house, or breathless when dressing/undressing

Index	Current	**Triggers** *(check all that apply)*
☐	☐	Inhalant allergens *(cats, animals, dust mites, indoor mold, environmental)*
☐	☐	Occupational allergens *(refer to occupational trigger list)*
☐	☐	Irritants *(tobacco smoke, household chemicals, perfumes, pollution, wood-burning stove/fireplace)*
☐	☐	Other *(ASA/NSAIDS, endocrine, exercise, food/additives, GERD, respiratory infections, weather, etc.)*

Index	Current	**Cough Symptoms** *(check all that apply)*
☐	☐	Cough *(Daytime)* (# of days/week: Index _____ Current _____)
☐	☐	Cough *(Nocturnal)* (# of days/week: Index _____ Current _____)
☐	☐	Sputum production
☐	☐	Chest tightness
☐	☐	Wheeze

Index	Current	**Other symptoms** *(check all that apply)*
☐	☐	Edema
☐	☐	Fatigue
☐	☐	Bilateral ankle edema
☐	☐	Fever or flu symptoms at time of prescription
☐	☐	Absence from work or school *(due to shortness of breath)*
☐	☐	Most recent hospitalization or ER visit due to SOB (*Date:* ____ / ____ / _____) *dd mm yyyy*

Appendix H (*continued)*

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Study ID # [ ][ ] – [ ][ ][ ] (Site Number / Patient Number) **Patient Initials** [ ][ ][ ] (First / Middle / Last)

Work History

Not for Database

Present Occupation _____

Past Occupations _____

_____

_____

_____

Occupational/Environmental History

Patient has been **regularly** exposed to *(check all that apply)*

- ☐ **1** Wood or cotton dust
- ☐ **2** Asbestos, silica, coal, talc
- ☐ **3** Manufacture of stone, glass, clay
- ☐ **4** Welding or pottery-making
- ☐ **5** Manufacture of plastics or rubber
- ☐ **6** Grains
- ☐ **7** Hooved farm animals *(sheep, goats, cattle, horses, pigs)*
- ☐ **8** Non-hooved farm animals *(chickens/turkeys)*
- ☐ **9** Hooved wild animals *(deer/moose)*
- ☐ **10** Animal hide or wool processing
- ☐ **11** Gases from formaldehyde, ammonia, chlorine
- ☐ **12** Paint, lacquer, hair spray, pesticide, acid, solvent
- ☐ **13** Latex gloves
- ☐ **14** Cigarette smoke
- ☐ **15** Landscaping or gardening soil
- ☐ **16** None of the above

Physical Exam

Weight ___ ___ ___ kg

Height ___ ___ ___ cm

Heart Rate ___ ___ ___ bpm

Respiratory Rate ___ ___ / min

Blood Pressure *(seated)* ___ ___ ___ / ___ ___ ___ mmHg (systolic / diastolic)

Oxygen Saturation ___ ___ ___ %

Appendix H (continued)

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Study ID # [ ][ ] – [ ][ ][ ] (Site Number / Patient Number) **Patient Initials** [ ][ ][ ] (First / Middle / Last)

Patient Awareness

Has your family physician ever given you a diagnosis for your SOB symptoms ☐ Yes ☐ No

If Yes, what diagnosis *(check all that apply)*

☐ Asthma ☐ COPD ☐ Heart Failure ☐ Other, specify _____

Have you ever seen a specialist for your SOB symptoms *(i.e. Respirologist, Cardiologist, Internal Medicine, etc.)* ☐ Yes ☐ No

If Yes, approximate date of most recent visit *[enter month (mm) and year (yyyy)]* 01 /_____ (mm) /_____ (yyyy)

Were you referred by your family doctor ☐ Yes ☐ No

Were you given a diagnosis for your SOB symptoms ☐ Yes ☐ No

If Yes, what diagnosis *(check all that apply)*

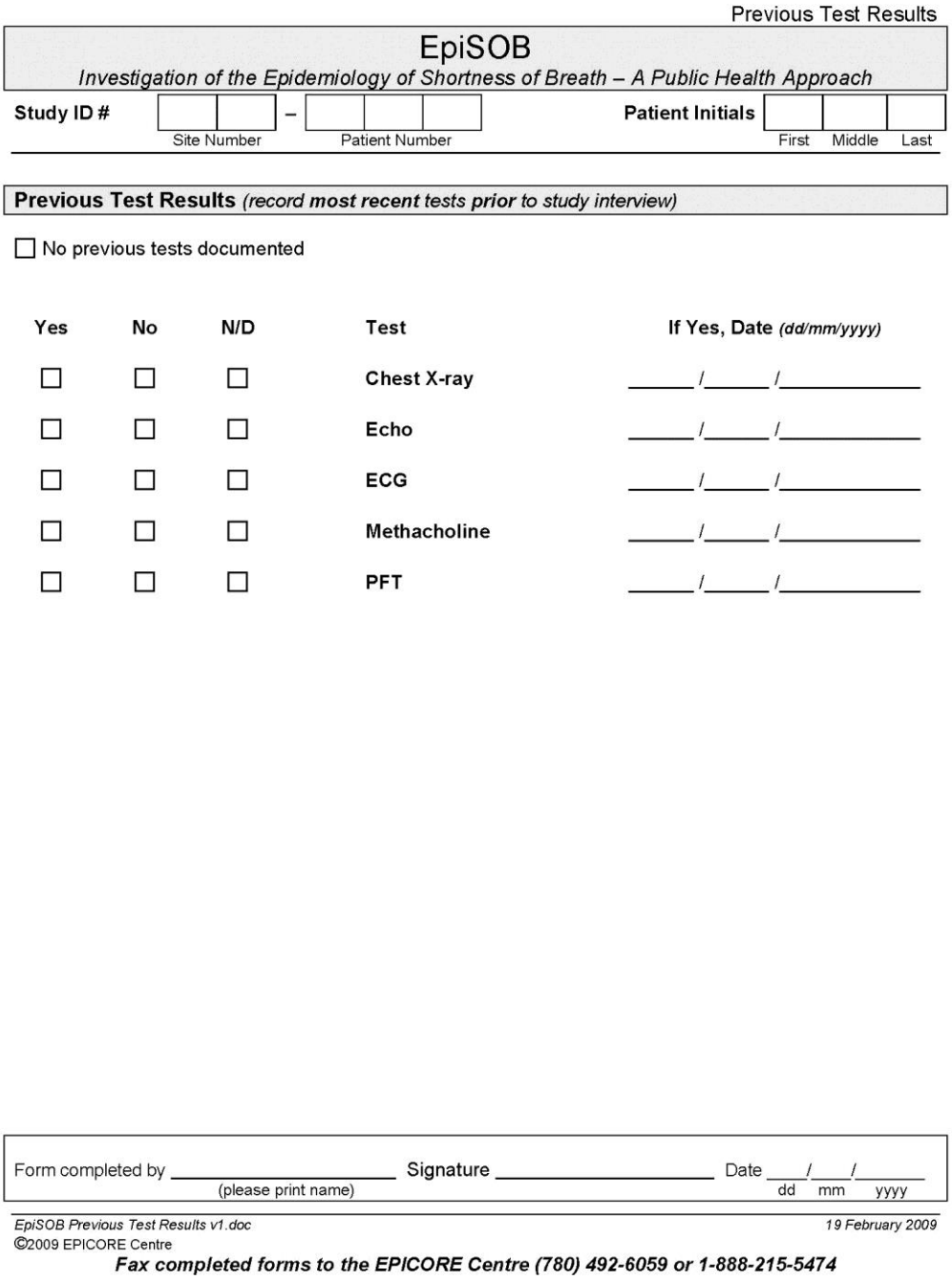
☐ Asthma ☐ COPD ☐ Heart Failure ☐ Other, specify _____

Have you ever had any of the following tests for your SOB symptoms

Test/Procedure				If Yes, Approximate Date of Most Recent Test *(enter month (mm) and year (yyyy))*
PFT	☐ Yes	☐ No	☐ Don't know	01 /_____ (mm) /_____ (yyyy)
Chest X-ray	☐ Yes	☐ No	☐ Don't know	01 /_____ (mm) /_____ (yyyy)
Echo	☐ Yes	☐ No	☐ Don't know	01 /_____ (mm) /_____ (yyyy)
ECG	☐ Yes	☐ No	☐ Don't know	01 /_____ (mm) /_____ (yyyy)
Methacholine	☐ Yes	☐ No	☐ Don't know	01 /_____ (mm) /_____ (yyyy)
Other	☐ Yes	☐ No	☐ Don't know	
If Yes, specify _____				01 /_____ (mm) /_____ (yyyy)

Form completed by _____ (please print name) Signature _____ Date ____/____/_____ (dd mm yyyy)

Appendix I: Previous Test Results Form



Previous Test Results

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Study ID # ☐☐ – ☐☐☐ (Site Number / Patient Number) **Patient Initials** ☐☐☐ (First Middle Last)

Previous Test Results *(record **most recent** tests **prior** to study interview)*

☐ No previous tests documented

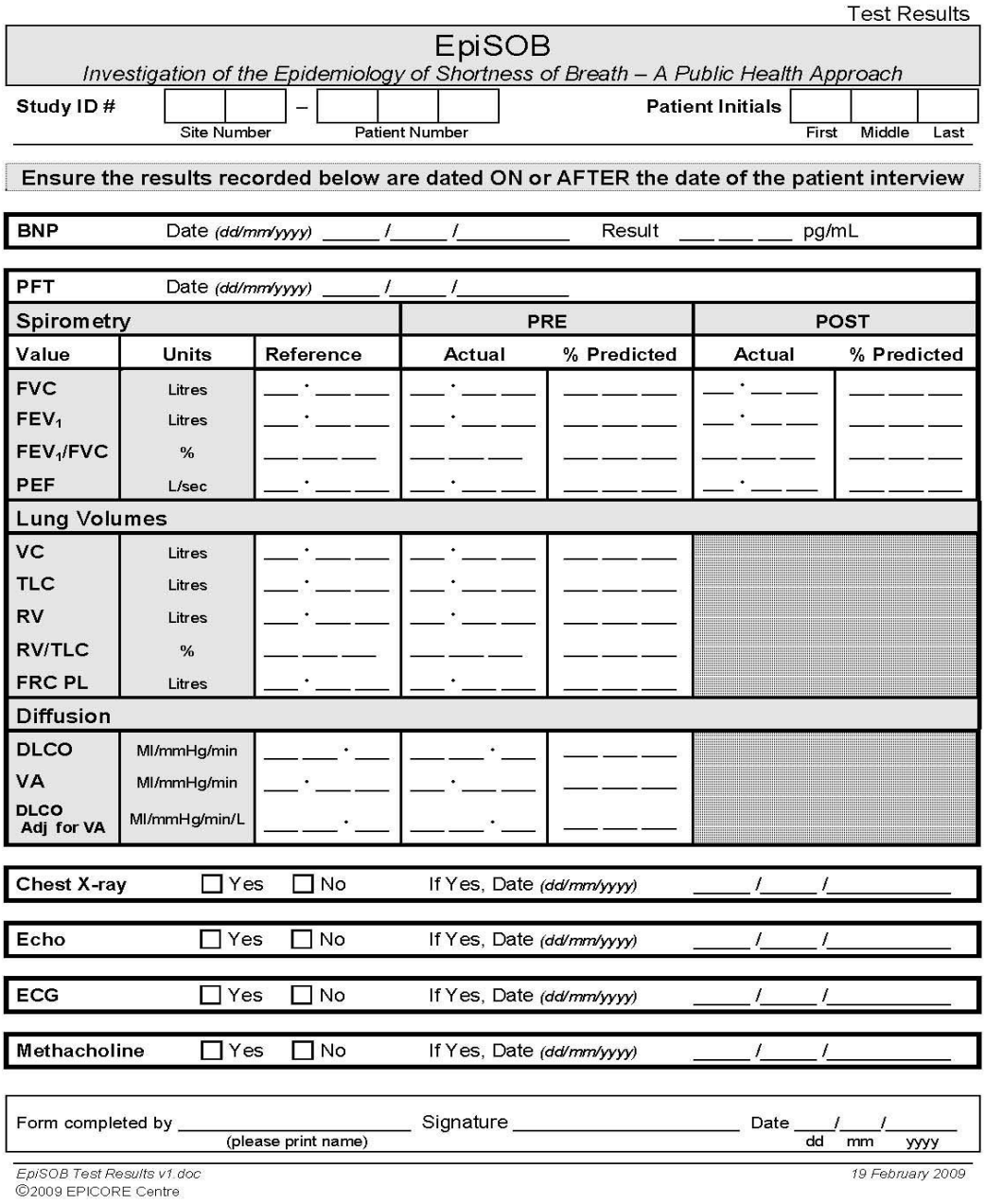
Yes	No	N/D	Test	If Yes, Date *(dd/mm/yyyy)*
☐	☐	☐	**Chest X-ray**	_____/_____/_____
☐	☐	☐	**Echo**	_____/_____/_____
☐	☐	☐	**ECG**	_____/_____/_____
☐	☐	☐	**Methacholine**	_____/_____/_____
☐	☐	☐	**PFT**	_____/_____/_____

Form completed by _____ (please print name) Signature _____ Date ____/____/_____ (dd mm yyyy)

EpiSOB Previous Test Results v1.doc *19 February 2009*

Fax completed forms to the EPICORE Centre (780) 492-6059 or 1-888-215-5474

Appendix J: Laboratory Results Forms



Test Results

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Study ID # ☐☐ – ☐☐☐ (Site Number / Patient Number) **Patient Initials** ☐☐☐ (First Middle Last)

Ensure the results recorded below are dated ON or AFTER the date of the patient interview

BNP Date *(dd/mm/yyyy)* _____/_____/_____ Result ___ ___ ___ pg/mL

PFT Date *(dd/mm/yyyy)* _____/_____/_____

Spirometry			PRE		POST	
Value	**Units**	**Reference**	**Actual**	**% Predicted**	**Actual**	**% Predicted**
FVC	Litres	___ . ___ ___	___ . ___ ___	___ ___ ___	___ . ___ ___	___ ___ ___
FEV_1	Litres	___ . ___ ___	___ . ___ ___	___ ___ ___	___ . ___ ___	___ ___ ___
FEV_1/FVC	%	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___	___ ___ ___
PEF	L/sec	___ . ___ ___	___ . ___ ___	___ ___ ___	___ . ___ ___	___ ___ ___
Lung Volumes						
VC	Litres	___ . ___ ___	___ . ___ ___	___ ___ ___		
TLC	Litres	___ . ___ ___	___ . ___ ___	___ ___ ___		
RV	Litres	___ . ___ ___	___ . ___ ___	___ ___ ___		
RV/TLC	%	___ ___ ___	___ ___ ___	___ ___ ___		
FRC PL	Litres	___ . ___ ___	___ . ___ ___	___ ___ ___		
Diffusion						
DLCO	Ml/mmHg/min	___ ___ . ___	___ ___ . ___	___ ___ ___		
VA	Ml/mmHg/min	___ . ___ ___	___ . ___ ___	___ ___ ___		
DLCO Adj for VA	Ml/mmHg/min/L	___ ___ . ___	___ ___ . ___	___ ___ ___		

Chest X-ray ☐ Yes ☐ No If Yes, Date *(dd/mm/yyyy)* _____/_____/_____

Echo ☐ Yes ☐ No If Yes, Date *(dd/mm/yyyy)* _____/_____/_____

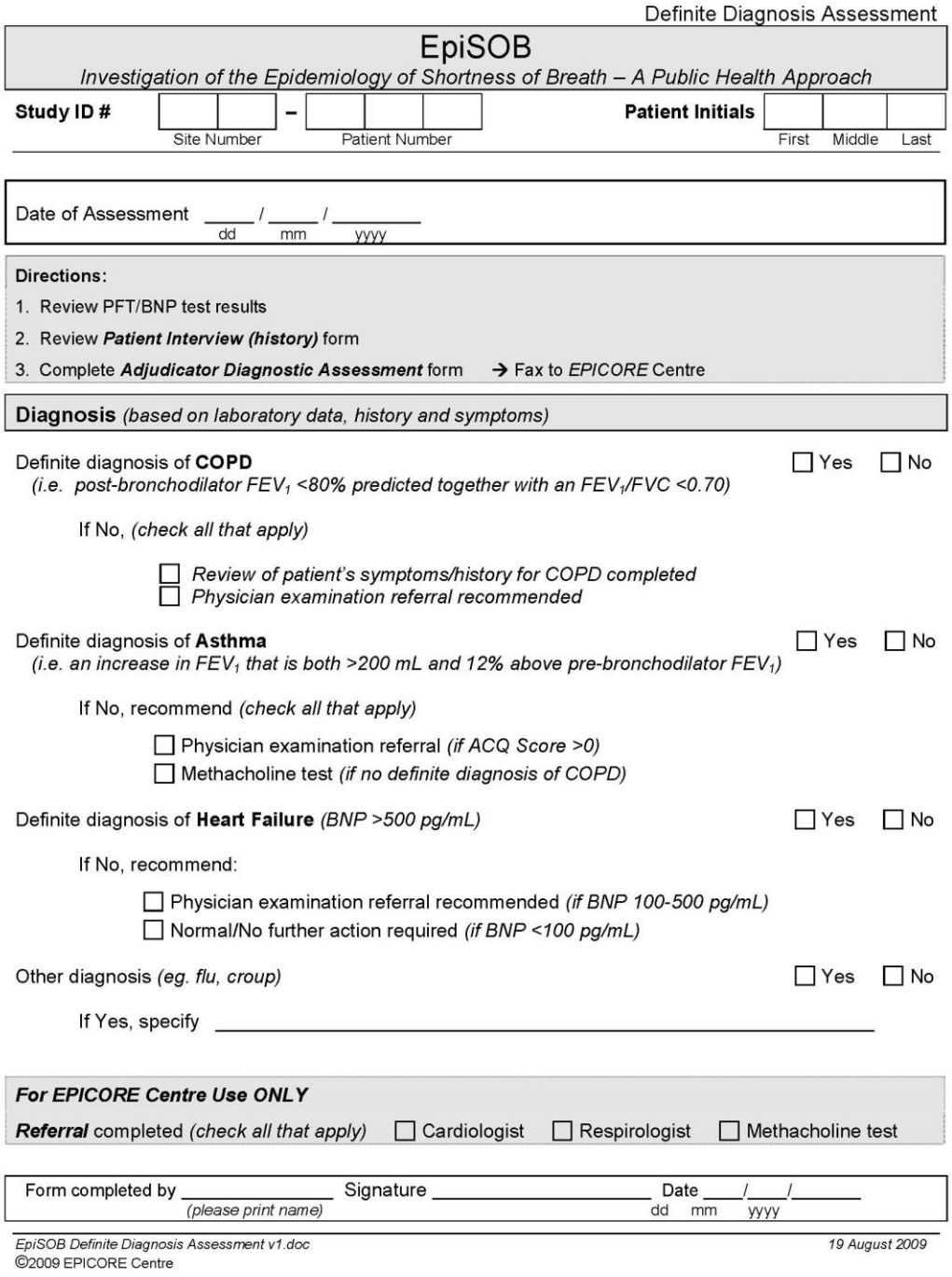
ECG ☐ Yes ☐ No If Yes, Date *(dd/mm/yyyy)* _____/_____/_____

Methacholine ☐ Yes ☐ No If Yes, Date *(dd/mm/yyyy)* _____/_____/_____

Form completed by _____ (please print name) Signature _____ Date ____/____/_____ (dd mm yyyy)

EpiSOB Test Results v1.doc *19 February 2009*

Appendix K: Diagnosis Assessment Form



Definite Diagnosis Assessment

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Study ID # ☐☐ – ☐☐☐ (Site Number – Patient Number) **Patient Initials** ☐☐☐ (First Middle Last)

Date of Assessment _____ / _____ / _____ (dd mm yyyy)

Directions:

1. Review PFT/BNP test results
2. Review ***Patient Interview (history)*** form
3. Complete ***Adjudicator Diagnostic Assessment*** form → Fax to *EPICORE* Centre

Diagnosis *(based on laboratory data, history and symptoms)*

Definite diagnosis of **COPD** ☐ Yes ☐ No
(i.e. post-bronchodilator FEV_1 <80% predicted together with an FEV_1/FVC <0.70)

If No, *(check all that apply)*

- ☐ *Review of patient's symptoms/history for COPD completed*
- ☐ *Physician examination referral recommended*

Definite diagnosis of **Asthma** ☐ Yes ☐ No
(i.e. an increase in FEV_1 that is both >200 mL and 12% above pre-bronchodilator FEV_1)

If No, recommend *(check all that apply)*

- ☐ Physician examination referral *(if ACQ Score >0)*
- ☐ Methacholine test *(if no definite diagnosis of COPD)*

Definite diagnosis of **Heart Failure** *(BNP >500 pg/mL)* ☐ Yes ☐ No

If No, recommend:

- ☐ Physician examination referral recommended *(if BNP 100-500 pg/mL)*
- ☐ Normal/No further action required *(if BNP <100 pg/mL)*

Other diagnosis *(eg. flu, croup)* ☐ Yes ☐ No

If Yes, specify _____

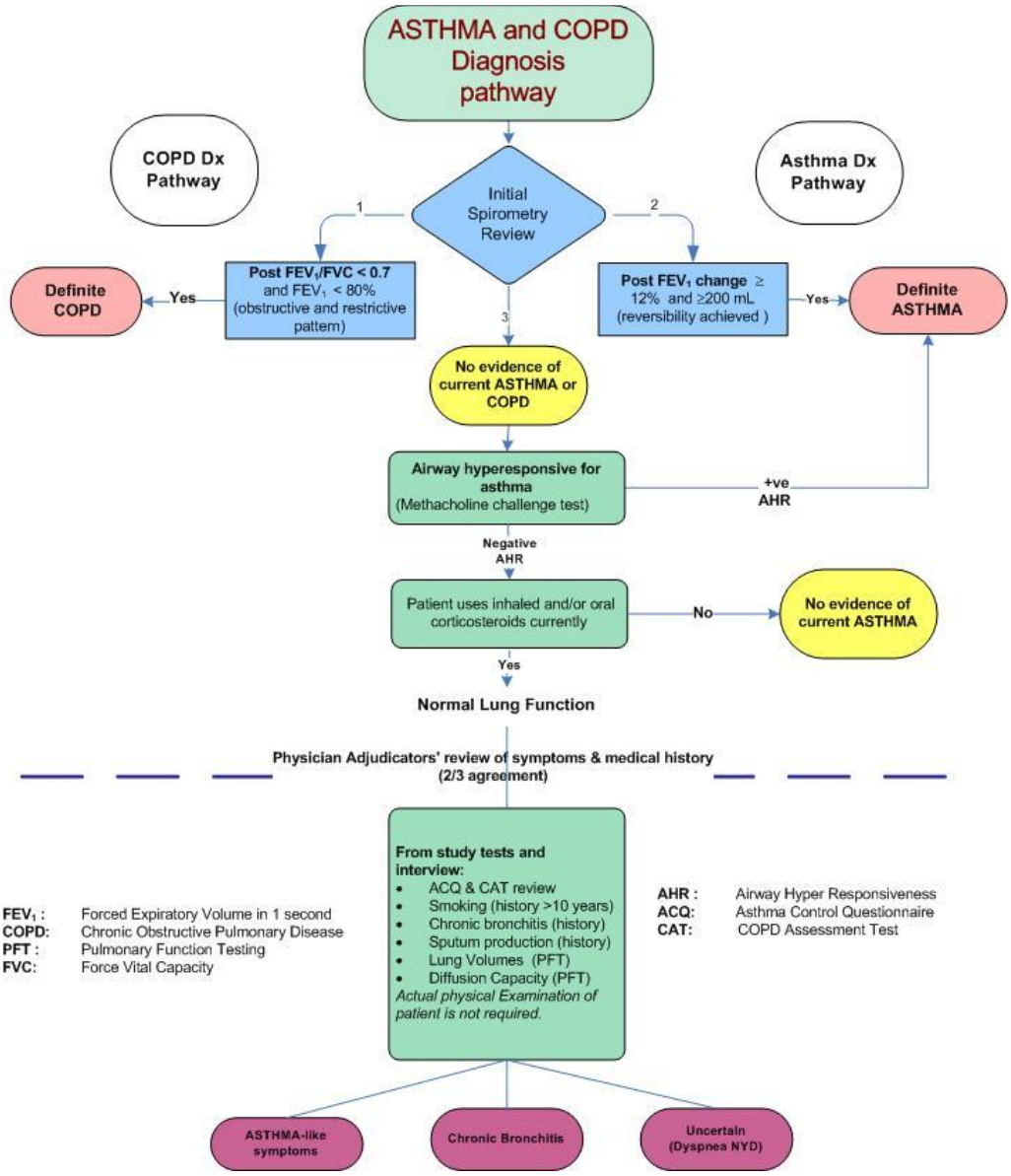
For EPICORE Centre Use ONLY

Referral completed *(check all that apply)* ☐ Cardiologist ☐ Respirologist ☐ Methacholine test

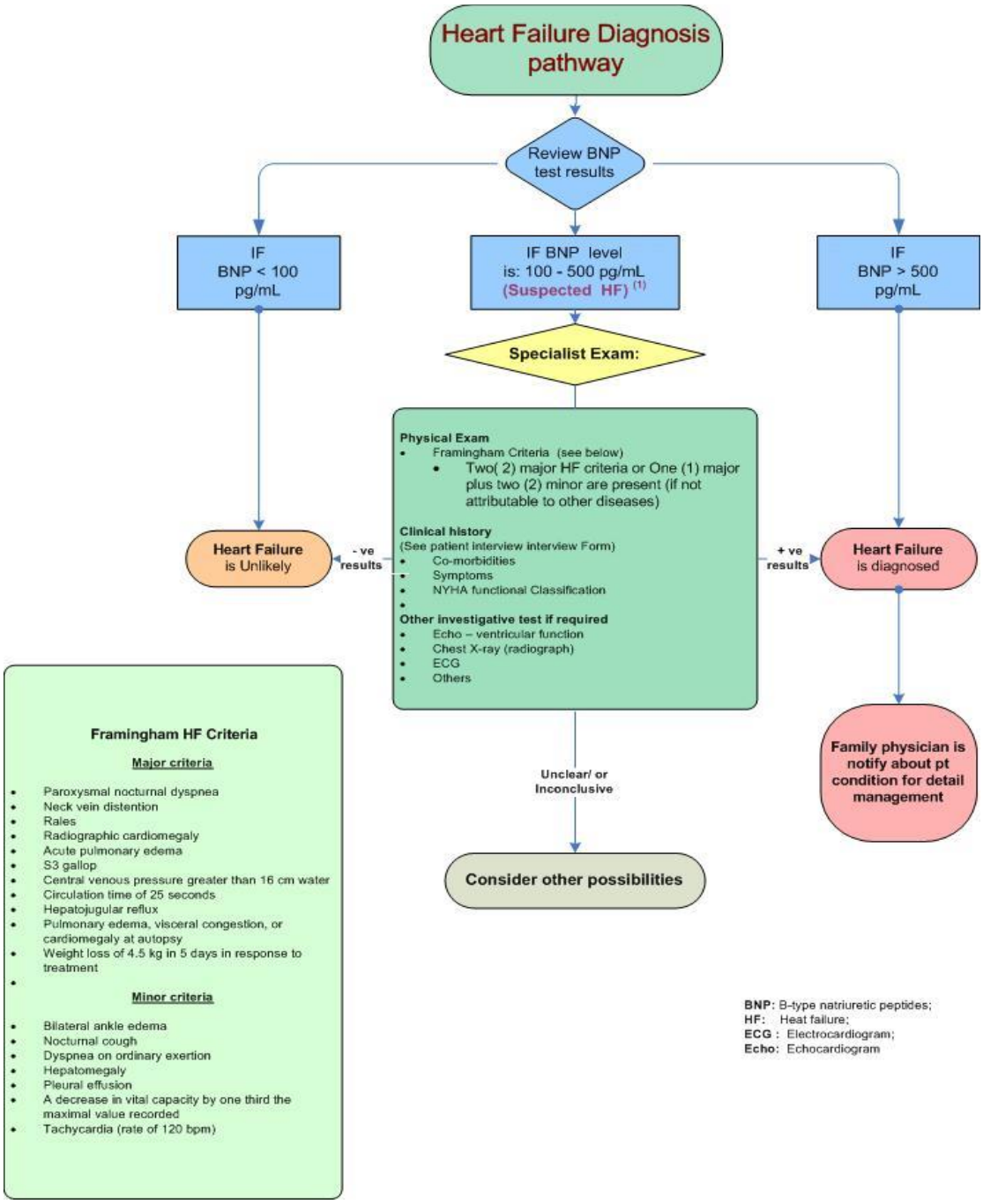
Form completed by _____ *(please print name)* Signature _____ Date ____/____/_____ (dd mm yyyy)

EpiSOB Definite Diagnosis Assessment v1.doc *19 August 2009*

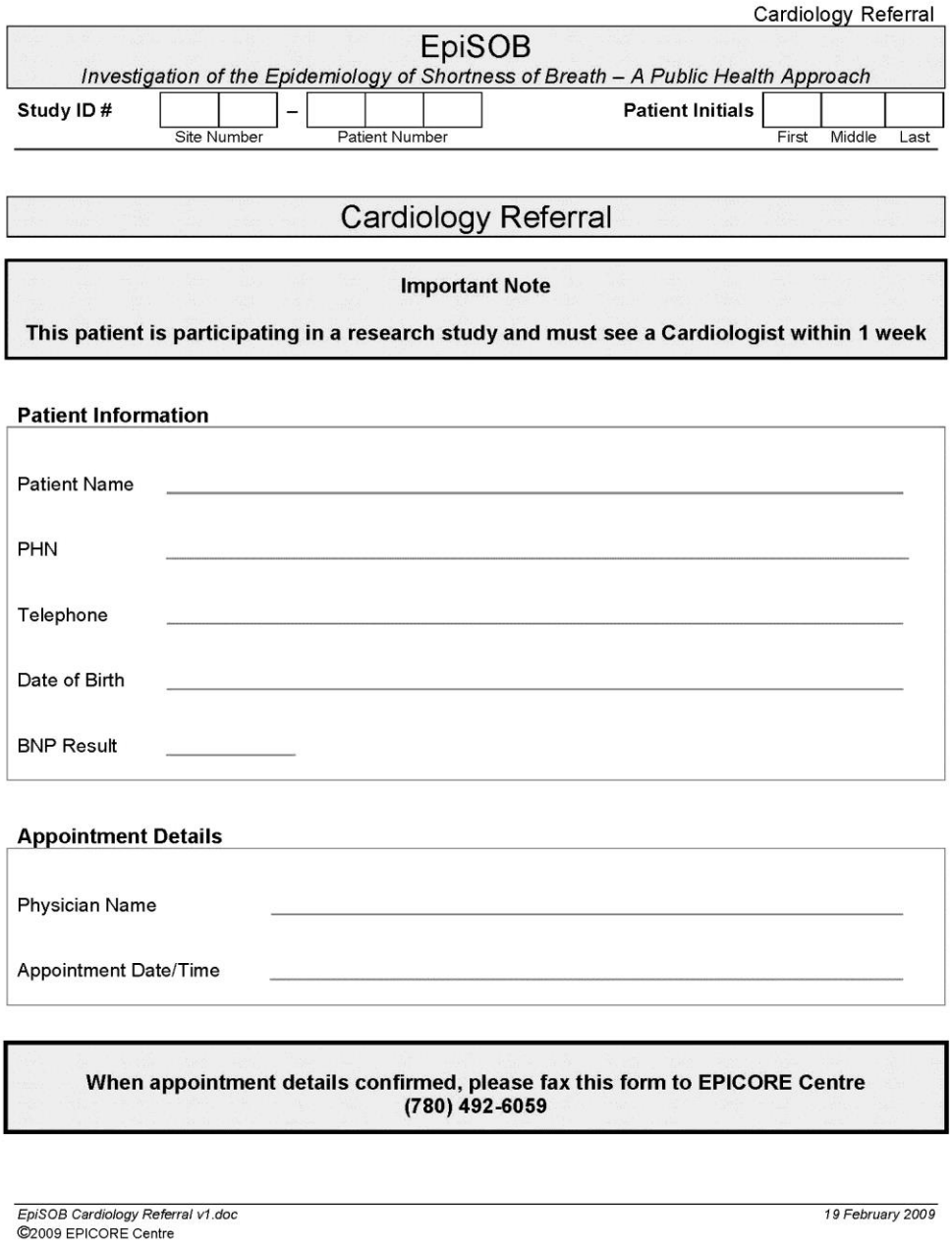
Appendix L: Diagnostic Algorithm for Asthma and COPD



Appendix M: Diagnostic Algorithm for Suspected Heart Failure



Appendix N: Physician Referral and Assessment Forms



Cardiology Referral

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Study ID # [ ][ ] – [ ][ ][ ] (Site Number / Patient Number) **Patient Initials** [ ][ ][ ] (First Middle Last)

Cardiology Referral

Important Note

This patient is participating in a research study and must see a Cardiologist within 1 week

Patient Information

Patient Name _____

PHN _____

Telephone _____

Date of Birth _____

BNP Result _____

Appointment Details

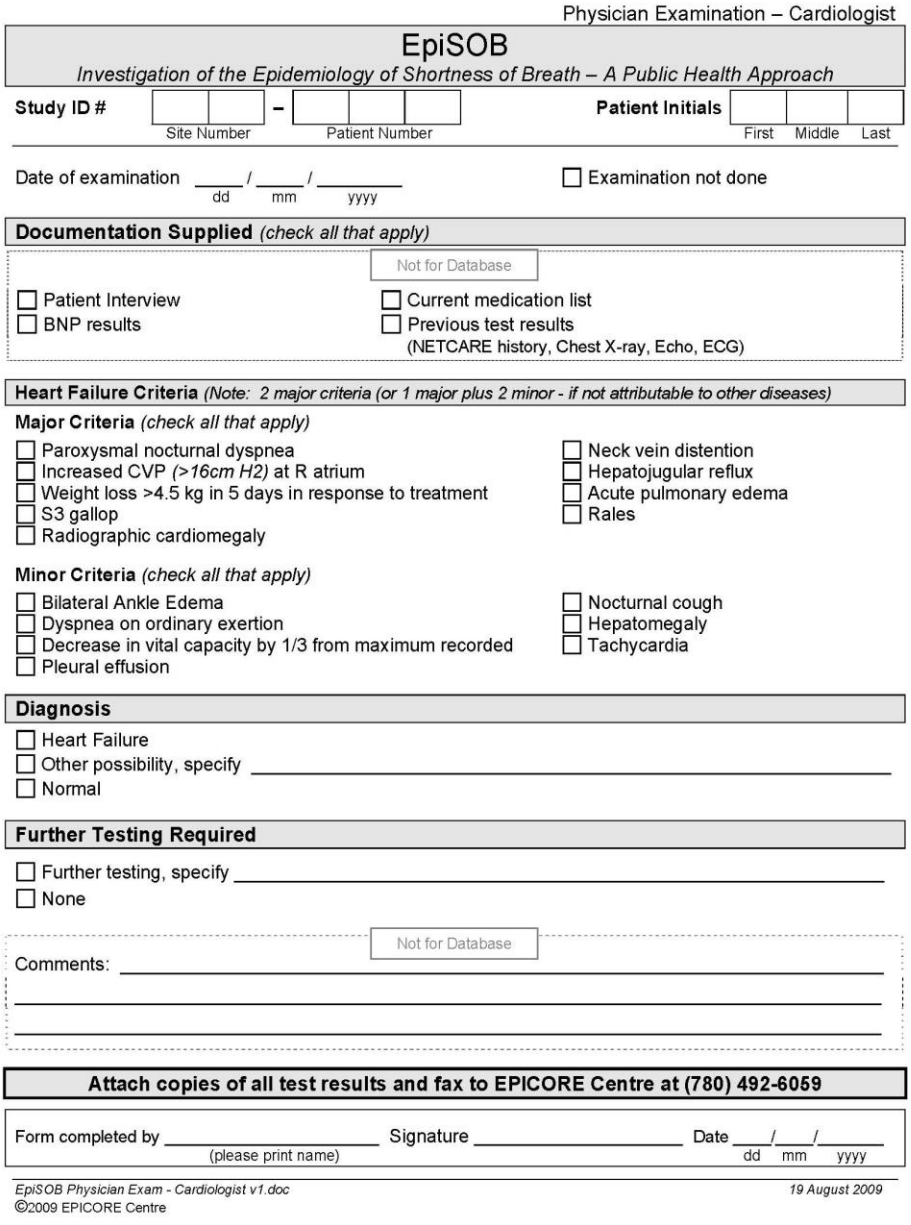
Physician Name _____

Appointment Date/Time _____

When appointment details confirmed, please fax this form to EPICORE Centre (780) 492-6059

EpiSOB Cardiology Referral v1.doc *19 February 2009*

Appendix O: Cardiologist Physical Examination Form



Physician Examination – Cardiologist

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Study ID # ☐☐ – ☐☐☐ (Site Number / Patient Number) **Patient Initials** ☐☐☐ (First Middle Last)

Date of examination ____ / ____ / ____ (dd mm yyyy) ☐ Examination not done

Documentation Supplied *(check all that apply)*

Not for Database

☐ Patient Interview
☐ BNP results
☐ Current medication list
☐ Previous test results (NETCARE history, Chest X-ray, Echo, ECG)

Heart Failure Criteria *(Note: 2 major criteria (or 1 major plus 2 minor - if not attributable to other diseases)*

Major Criteria *(check all that apply)*

☐ Paroxysmal nocturnal dyspnea
☐ Increased CVP *(>16cm H2)* at R atrium
☐ Weight loss >4.5 kg in 5 days in response to treatment
☐ S3 gallop
☐ Radiographic cardiomegaly
☐ Neck vein distention
☐ Hepatojugular reflux
☐ Acute pulmonary edema
☐ Rales

Minor Criteria *(check all that apply)*

☐ Bilateral Ankle Edema
☐ Dyspnea on ordinary exertion
☐ Decrease in vital capacity by 1/3 from maximum recorded
☐ Pleural effusion
☐ Nocturnal cough
☐ Hepatomegaly
☐ Tachycardia

Diagnosis

☐ Heart Failure
☐ Other possibility, specify _____
☐ Normal

Further Testing Required

☐ Further testing, specify _____
☐ None

Not for Database

Comments: _____

Attach copies of all test results and fax to EPICORE Centre at (780) 492-6059

Form completed by _____ (please print name) Signature _____ Date ____/____/____ (dd mm yyyy)

EpiSOB Physician Exam - Cardiologist v1.doc *19 August 2009*

Appendix P: Respirologist Referral Form

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Study ID # [ ][ ] – [ ][ ][ ] (Site Number / Patient Number) **Patient Initials** [ ][ ][ ] (First / Middle / Last)

Respirology Referral

Important Note

This patient is participating in a research study and must see a Respirologist within 1 week

Patient Information

Patient Name _____

PHN _____

Telephone _____

Date of Birth _____

PFT attached ☐ Yes ☐ No

Appointment Details

Physician Name _____

Appointment Date/Time _____

When appointment details confirmed, please fax this form to EPICORE Centre
(780) 492-6059

Appendix Q: Respirologist Physical Examination Form

Physician Examination – Respirologist

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Study ID # ☐☐ – ☐☐☐ (Site Number / Patient Number) **Patient Initials** ☐☐☐ (First / Middle / Last)

Date of examination _____ / _____ / _____ (dd / mm / yyyy) ☐ Examination not done

Physician completing examination

☐ Dr. Mayers ☐ Dr. Vethanayagam ☐ Dr. Rowe

Documentation supplied *(check all that apply)*

Not for Database

☐ Patient Interview
☐ Methacholine Challenge test result
☐ PFT plus BNP results
☐ ACQ
☐ Current medication list
☐ Previous test results (NETCARE history, Chest X-ray, Echo, ECG)

Note: All clear for asthma and COPD by PFT and methacholine

Physician Diagnosis *(check all that apply)*

☐ Asthma-like
☐ Bronchitis
☐ Other possibilities, specify _____
☐ Normal

Recommendation

Further testing ☐ Yes ☐ No

Not for Database

Comments: _____

_____

_____

_____

Attach copies of all test results and fax to Project Office

Form completed by _____ (please print name) Signature _____ Date ____/____/_____ (dd mm yyyy)

Fax completed forms to EPICORE Centre (780) 492-6059 or 1-888-215-5474

Appendix R: Final Diagnosis Form

Final Diagnosis

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Study ID # [ ][ ] – [ ][ ][ ] (Site Number – Patient Number) **Patient Initials** [ ][ ][ ] (First Middle Last)

Date of Review _____ / _____ / _____ (dd / mm / yyyy)

Final Diagnosis

Asthma ☐ Yes ☐ Probable ☐ No

If Yes or Probable, Diagnosis ☐ Diagnosis by guideline
☐ Physician diagnosis (Consensus panel)
☐ By airway hyperresponsiveness (Methacholine test)

COPD ☐ Yes ☐ Probable ☐ No

If Yes or Probable, Diagnosis ☐ Diagnosis by guideline
☐ Physician diagnosis (Consensus panel)

Heart Failure ☐ Yes ☐ Probable ☐ No

If Yes or Probable, Diagnosis ☐ Diagnosis by guideline
☐ Physician diagnosis

Other possibility ☐ Yes ☐ No

If Yes, Specify _____

☐ **Protocol Incomplete**

Not for Database

Comments: _____

_____

_____

_____

_____

_____

Form completed by _____ (please print name) Signature _____ Date ____/____/_____ (dd mm yyyy)

Fax completed forms to the EPICORE Centre (780) 492-6059 or 1-888-215-5474

Appendix S: Ethics Approval Letter

NEWFOUNDLAND AND LABRADOR
HREB
HEALTH RESEARCH ETHICS BOARD

Ethics Office
Suite 200, Eastern Trust Building
95 Bonaventure Avenue
St. John's, NL
A1B 2X5

March 07, 2016

300 Prince Philip Drive
St. John's, NL
A1B 3V6

Dear Miss Nugent:

Researcher Portal File # 20162410
Reference # 2016.054

RE: "Examining the similarities and differences in factors predicting physician diagnosis of COPD and asthma in patients with Shortness of Breath"

Your application received an expedited review by a sub-committee of the Health Research Ethics Board (HREB). ***Full approval*** of this research study is granted for one year effective **March 5, 2016**.

This is your ethics approval only. Organizational approval may also be required. It is your responsibility to seek the necessary organizational approval from the Regional Health Authority (RHA) or other organization as appropriate. You can refer to the HREA website for further guidance on organizational approvals.

This is to confirm that the HREB reviewed and approved or acknowledged the following documents (as indicated):

- Application, approved
- List of variables, approved

MARK THE DATE

This approval will lapse on March 5, 2017 . It is your responsibility to ensure that the Ethics Renewal form is submitted prior to the renewal date; you may not receive a reminder. The Ethics Renewal form can be found on the Researcher Portal as an Event form.

If you do not return the completed Ethics Renewal form prior to date of renewal:

- ***You will no longer have ethics approval***
- *You will be required to stop research activity immediately*
- *You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again*
- *Lapse in ethics approval* ***may result in interruption or termination of funding***

You are solely responsible for providing a copy of this letter, along with your approved HREB application form; **to Research Grant and Contract Services** should your research depend on funding administered

Appendix S (*continued)*

through that office.

Modifications of the protocol/consent are not permitted without prior approval from the HREB. **Implementing changes without HREB approval may result in your ethics appr revoked, meaning your research must stop**. Request for modification to the protocol/cons outlined on an amendment form (available on the Researcher Portal website as an Event for to the HREB for review.

The HREB operates according to the Tri-Council Policy Statement: Ethical Conduct for Res Humans (TCPS2), the Health Research Ethics Authority Act (HREA Act) and applicable la regulations.

You are responsible for the ethical conduct of this research, notwithstanding the approval c

We wish you every success with your study.

Sincerely,

Dr Fern Brunger (Chair, Non-Clinical Trials Health Research Ethics Board)
Ms. Patricia Grainger (Vice-Chair, Non-Clinical Trials Health Research Ethics Board)

CC: W. Midodzi

Appendix T: Methacholine Test

Methacholine Test (Summarized, taken from www.uptodate.com © 2015)

A series of methacholine chloride solutions are prepared, ranging from approximately 0.03 mg/mL (the most dilute) to 16 mg/mL (the most concentrated). After baseline spirometry the most dilute concentration of methacholine is administered by nebulizer, using either a tidal breathing or five breath dosimeter method. After inhalation of the aerosol by one of these methods, the FEV1 is measured at 30 and 90 seconds with careful coaching of the subject to obtain an acceptable quality FEV1. Each time two maneuvers are performed; if FEV1 is the only outcome being measured, it is acceptable to shorten the expiratory time to about 2 seconds (from the usual 6 seconds), The concentration is sequentially increased one concentration step at a time, until a decrease in FEV1 greater than 20 percent or a 35 to 40 percent decrease in specific airways conductance (SGaw) is observed. Typically, when there is a positive test, the FEV1 decreases more than 20 percent, so the dose of the inhaled agent that would provoke a 20 percent drop in FEV1 is determined by interpolation. This is referred to as the provocative concentration or PC20. Generally, a methacholine PC20 of 8 mg/mL (<4 mg/mL, for SGaw) or less is considered a positive test. A PC20 greater than 16 mg/mL is considered a negative test.