SEX AND GENDER
IN
CHRONIC OBSTRUCTIVE PULMONARY DISEASE

by

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ABSTRACT

Research on sex and gender in chronic obstructive pulmonary disease (COPD) has primarily focused on differences in pulmonary function. Detailed gender- and sex-based analyses of other aspects of COPD, including epidemiology, risk factors other than cigarette smoke, pathophysiology, and measurement tools are warranted. In **Chapter Two** we analyzed administrative health services data to compare the prevalence, mortality and use of drugs and spirometry in men and women with COPD. Contrary to recent predictions, we did not detect a dramatic increase in the prevalence or mortality of COPD over time in women compared to men. We discuss how different coding practices in medical billing can impact the results. In **Chapter Three** we examined sex differences in COPD phenotypes. We hypothesized that male smokers would have more emphysema whereas female smokers would have more airway wall remodeling using data from high resolution computed tomography (HRCT) scans. We did detect more emphysema in male smokers but there was no evidence of increased airway remodeling in women. We discuss the limits of HRCT to detect airway differences in women and men. In **Chapter Four** we examined the use of HRCT in assessing emphysema. We hypothesized that the computer-derived estimates of emphysema (the fractal value and the % low attenuation area (%LAA)) would differentiate COPD from non-COPD as accurately as the radiologist's emphysema scores, and would provide similar predictions in both men and women. Instead, we found that the subjective rating of emphysema best differentiated COPD, and the fractal value (a measure of

emphysematous lesion size) better differentiated COPD compared with an established objective measurement, the %LAA. These results were generally the same in men and women. In **Chapter Five** we examined characteristics of COPD in women exposed to biomass smoke. We hypothesized that biomass smoke would induce an airway disease-predominant phenotype. We found that women with biomass smoke-exposed COPD had greater airway remodeling and less emphysema than women with tobacco smoke-exposed COPD. In summary, these findings suggest that sex and gender differences are present in COPD epidemiology and pathophysiology. However, current research measurement tools may limit the ability to accurately measure these differences.

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CO-AUTHORSHIP STATEMENT

Sections of this thesis have been published or are in preparation for publication in refereed journals. These papers have multiple authors. Details of each author's contributions are provided below.

PUBLISHED REFEREED PAPERS

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Camp PG, Chaudhry M, Platt H, Roch M, Road J, Sin D, Levy RD. The gender factor; epidemiology and management of COPD in British Columbia. Reproduced with permission, Can Respir J (In press).

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The thesis author had primary responsibility for developing the research question, performed data analysis and interpretation of the summary data provided by the British Columbia Ministry of Health and wrote the manuscript. As the British Columbia Ministry of Health data analyst, Ms. Chaudhry performed the extraction, linkage, and analysis of the raw data, and assisted with the editing of the manuscript. Mr. Roch provided editorial comments on the manuscript. Dr. Platt provided editorial comments on the manuscript. Dr. Road provided editorial comments on the manuscript. Dr. Sin provided editorial comments on the manuscript. Dr. Levy provided guidance with the development of the research question and the interpretation of the summary data, and provided editorial comments on the manuscript.

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OTHER PUBLISHED PAPERS

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CHAPTER ONE. LITERATURE REVIEW AND INTRODUCTION TO THESIS[1]

1.1 INTRODUCTION

In this dissertation a program of research investigating the relationship of sex, gender, and chronic obstructive pulmonary disease (COPD) is presented. COPD is a prevalent condition associated with significant morbidity and mortality. Although cigarette smoking is the primary risk factor for COPD in developed countries, not all smokers develop COPD. Internal risk factors, such as genetics, lung development and overall health status interact with external risk factors, such as smoking behaviour, occupational exposures and socioeconomic status to affect the likelihood of developing COPD, as well as influence the health outcomes associated with this disease. Male, and more recently female, sex has also been cited as an independent risk factor for developing COPD and could have an influence on the natural history of the disease (1).

Previously, research on sex and gender in COPD has primarily focused on differences in pulmonary function. This area of research would benefit from an analysis that moves beyond differences in pulmonary function to a more detailed

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gender- and sex-based analysis of other aspects of COPD, including epidemiology, risk factors other than cigarette smoke, pathophysiology, and measurement tools.

This dissertation is part of the requirements for obtaining an Interdisciplinary PhD at the University of British Columbia. Interdisciplinary graduate programs enable students to conduct research that move beyond the boundaries of a single, established discipline. An interdisciplinary approach to sex and gender research is crucial, as it encourages the investigation of research problems from many disciplines, including medicine, epidemiology, and gender studies, from both a biomedical and a sociocultural perspective. The intent of an interdisciplinary degree is not to become an expert in many disciplines but instead draw on the strengths of multiple disciplines, including the use of measurement tools and analytic strategies to interpret the data.

This is a manuscript-based dissertation, which is an approved thesis style of the Faculty of Graduate Studies, University of British Columbia. It is comprised of an introductory chapter, followed by four research papers, each with its own introduction, methods, results, discussion and reference sections. As such there is some degree of repetition in this dissertation. The final chapter is a summary and discussion of the results of the research studies and recommendations for future research.

In this introductory chapter I provide an introduction to COPD, followed by a discussion of sex and gender health research in general and related to COPD in particular. This chapter concludes with a description of the structure of the thesis with an overview of the chapters which make up this body of work.

1.2 WHAT IS CHRONIC OBSTRUCTIVE PULMONARY DISEASE?

Chronic obstructive pulmonary disease is a progressive lung disorder characterized by chronic airflow limitation, an increase in shortness of breath, known as *dyspnea*, and eventually, severe disability and death (1). In developed countries the most common risk factor for COPD is exposure to tobacco smoke (2). A small percentage (1-2%) develop emphysema and airflow limitation as a result of a genetic disorder known as alpha-$_1$ antitrypsin deficiency (3).

Although the exact pathophysiological processes have not been determined, it is generally understood that the progressive loss of lung function that defines COPD is due to an exaggerated inflammatory response to a chronic exposure of toxic particles or gases. In the lungs of genetically-susceptible individuals (Figure 1-1) this inflammatory response leads to two main pathophysiologic mechanisms – parenchymal destruction and loss of elastic recoil of the lung, and small airway wall inflammation, remodeling and narrowing (bronchiolitis). Although the two processes are considered distinct they often occur simultaneously, although it is likely that one process is the dominant phenotype in a given patient. Both result in expiratory airflow limitation, which make it difficult to determine the relative contribution of each process to abnormal lung function in a given individual.

COPD has been defined in various ways over the decades. In an attempt to standardize the definition of COPD, the international organization Global Initiative for Obstructive Lung Disease (GOLD) defined COPD as:

> "…a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases." (1)

GOLD also developed spirometric criteria for defining COPD (Table 1-1) (1). The GOLD criteria rely on two lung function measurements obtained from a post-bronchodilator spirometry test. In this test, an individual inhales fully, to their total lung capacity. They then exhale as rapidly as possible into a mouthpiece and keep exhaling until they cannot force any more air from their lungs. The amount of air exhaled in the first second is the forced expiratory volume in the first second (FEV_1), and the total amount of air exhaled is the forced vital capacity (FVC). Both the FEV_1 and the FVC are influenced by the sex, height, and age of an individual; therefore, reference equations are available which allow these values to be expressed in terms of the percent predicted (4).

In healthy younger individuals, the FEV_1 is approximately 80% of the FVC although it falls toward 70% during normal aging. A reduction in the ratio of FEV_1/FVC below 0.70 is an early indication of COPD. As the disease worsens, there is a progressive worsening in the percent predicted FEV_1. Further decrements of FEV_1 are used to categorize COPD disease severity.

1.3 COPD: THE BURDEN OF DISEASE

COPD is a very common disorder, although estimates of the prevalence of

COPD vary widely by country and method used. Data from the Canadian Community Health Survey estimate that based on self-report, 4.4% of Canadians have COPD (5), although self-report studies may underestimate the true prevalence of COPD. Randomly-sampled population-based studies that use spirometry to diagnose COPD have demonstrated much higher values. For example, Canadian data from the Burden of Lung Disease (BOLD) study show that 19.3% of individuals 40 years and older have COPD (6). This study includes in the estimate individuals with no symptoms and only mild decreases in lung function who would not report physician-diagnosed COPD. The estimated American prevalence of moderate and severe COPD based on spirometry ranges from 7.2% in those age 45-54 years to 22.9% in those older than 75 years, based on data from the National Health and Nutrition Examination Survey (NHANES) study (7). COPD accounts for over 60,000 hospitalizations in Canada per year resulting in health care costs of over 570 million dollars (8). In addition, COPD is associated with increased mortality --it is currently the fourth leading cause of death in Canada and the United States and is expected to be third leading cause of death worldwide by 2020 (3). It is the only leading cause of death that has seen a substantial increase over the last 30 years (9).

Individuals who have COPD have considerable morbidity; patients experience dyspnea, chronic cough with sputum, repeated respiratory infections, low activity tolerance and poor quality of life (3). Treatments include inhaled medications, smoking cessation, and exercise rehabilitation with the primary aim of minimizing symptoms and improving health status. Oxygen therapy (10) and lung transplant

(11) in carefully selected individuals are the only treatments shown to improve survival.

1.4 GENDER AND SEX IN HEALTH RESEARCH

1.4.1 Definitions

Although often used interchangeably, ‘sex’ and ‘gender’ are considered by some to be distinct concepts (12). ‘Sex’ refers to the primary and secondary sex characteristics that distinguish males and females. More commonly, this term is expanded to encompass all anatomical and physiological attributes which may differ between males and females. ‘Gender’ is the result of the societal, environmental, cultural and individual influences which may be termed ‘masculine’ or feminine’ and which allow an individual to identify themselves as either male or female. In addition, society encourages specific roles and affords opportunity and power, based on gender. Gender is therefore relative to person, place, and era. In health research, the term ‘gender bias’ is also used. For example, gender bias in diagnosis occurs when a man (or woman) is more likely to receive a diagnosis because of his/her sex, instead of being diagnosed based on the clinical evidence. Gender bias in measurement occurs when a test or measurement method is less valid or reliable in one gender versus the other.

The investigation of sex and gender differences in COPD parallels the current trend in health research overall. Ten years ago, the first articles were published that described the differing outcomes between men and women following myocardial

infarction or cardiac surgery (13, 14). Studies have subsequently followed which have explored differences between men and women in other health areas such as the experience of pain (15) or stress responses (16). Although the empirical study of sex differences in disease may now seem *de rigeur*, the theoretical discussion regarding what it means to include sex as a primary study variable has lagged behind. In a given study we routinely count how many subjects are male and how many are female, yet we rarely reflect on the theoretical reasoning behind the inclusion of the variable. This is even more apparent when we control for sex in a multivariate analysis – what are we are controlling for? What does the male/female sex designation actually represent? Is it a biological process, yet unknown, or a sociocultural/environmental impact, or an interaction of both?

Theoretically, we may consider 'sex' and 'gender' to be distinctly different with independent effects on health but in reality there is a great deal of overlap. For example, gender may impact our biological health by influencing our behaviors, our access to resources, and our overall position in society. It is also commonplace to consider 'sex' and 'gender' as dichotomous variables, i.e., we are either 'male' or 'female'. Again, theoretically this may allow for convenience in the statistical analysis but in reality there are instances of ambiguous sex determination (i.e., hermaphroditism). Gender is considered by many *not* to be dichotomous, but instead should be viewed as an identity located on a continuum of characteristics. For example, there may be examples of men who exhibit feminine characteristics or vice versa, or characteristics that are considered masculine in one culture may be quite common among women in another. Although these definitions have been

proposed, in reality most health research examining differences between men and women does not distinguish between sex and gender. Although ‘gender’ is often used when describing physiological differences between men and women, the term ‘sex’ would be more appropriate.

1.4.2 Gender and Sex-Based Analysis in Health Research

A number of analysis strategies have been described to best investigate how gender and sex independently and together affect health outcomes (17). The term ‘gender and sex-based analysis (GSBA)’ has been proposed and ”…is in part a response to research that either fails to account for sex and gender differences or presumes they exist without evidence” (17). It is a research approach that investigates the relationship between sex and gender and how this relationship affects risk factors and health outcomes. GSBA strategies do not merely address the similarities and differences between men’s and women’s health but also considers the underlying mechanisms behind differences. For example, differences may be real but they may also be influenced by gender bias in measurement, either in the selection of measurement tool, or in the selection of the variables themselves. Messing et al (18) noted that "there is a risk of overemphasizing sex differences in relation to other anatomical and physiological contributions to population variation . . . the relevant source of variation may be size difference, not the sex difference, and may not apply to small men or large women. It is undeniably easier to record sex rather than measure the relevant body dimensions, but it may not be as good a predictor”. GSBA techniques expand the investigation of sex and gender-based

differences by emphasizing greater attention to the construction of measurements and variables in research.

1.5 GENDER AND SEX IN COPD

Health outcomes in COPD are influenced by internal factors, such as pulmonary physiology, susceptibility to disease, and response to treatment. They are also influenced by external factors, such as environmental and occupational exposures. A theoretical framework of the factors influencing health outcomes in COPD is presented in Figure 1-2. Sex and gender, both together and individually have the capacity to influence how these factors impact health outcomes in COPD.

Sex and gender research in COPD has primarily focused on differences in susceptibility. Prior to the mid-1980s, COPD was still considered by many to be a man's disease and men were thought to have a higher risk of developing COPD. Yet there has been a gradual shift in thinking over the last 15-20 years. Indeed, the opposite theory has been presented, and women are considered by many investigators to have an increased susceptibility to cigarette smoke compared to men (19). Many different internal and external factors have been researched to test the 'increased susceptibility in women' hypothesis, including exposure, epidemiology, lung function, symptom and diagnosis-related variables. All of these factors have the capacity to be influenced by sex and/or gender. A review of the literature shows that in fact, although the differential susceptibility theory may be considered by some as an accepted fact (20), in reality there are considerable data

which both support and refute the hypothesis. The following sections outline the literature on sex and gender in COPD.

1.5.1 Gender and Exposure to Inhaled Risk Factors

1.5.1.1 Cigarette Smoking

In 1964, the U.S. Surgeon General Report reviewed the evidence to date and concluded that cigarette smoking is a sufficient cause of chronic bronchitis and a possible cause of emphysema (21). Male and female smokers were considered to have increased risk of developing COPD compared to non-smokers. These early studies focused on differences in the prevalence of COPD and symptoms between men and women. At that time, it was reported that men were more likely to report the symptoms of chronic bronchitis compared to women, but the authors of the Surgeon General Report did not discuss the plausible mechanisms behind these differences. One possible explanation for these early reported differences in disease prevalence or symptoms may be the lack of adjustment for smoking history in the analyses. Women's smoking rates were at a peak in the 1960's but generally women smokers had not actively smoked for as many years as men. Therefore their cumulative dose was much less – a measurement bias not appreciated at that time.

The 1964 report briefly commented on the observed differences in symptoms and lung function between men and women, but offered no compelling discussion as to why these differences occurred. Although incomplete assessment of and adjustment for smoke exposure continued in subsequent studies, researchers began to question whether there were differences between men and women smokers in the

pulmonary structure or function related to COPD. This is demonstrated in Thurlbeck's 1974 study (22) where they examined the lungs of almost 1800 random necropsies. Using standardized grading pictures, each lung was graded for the severity of emphysema. Thurlbeck concluded that male smokers had greater emphysema scores and a higher prevalence of emphysema compared to female smokers. Although detailed smoking histories were not available for all subjects and the investigators did not adjust for cumulative smoking history, they were quite sophisticated in their speculation of the possible cause of the difference. The investigators cited several factors that may have contributed to a greater degree of emphysema in men, some biological in nature, such as differences in hormonal influences, others behavioral or environmental, such as exposure to occupational agents.

The 1980 Surgeon General Report discussed the health consequences of smoking in women specifically. They acknowledged the flaws of previous work in their comment:

> 'In these studies, conducted during the past three decades, relative mortality risks among female smokers appeared to be less than those of male smokers. It is now clear, however, that these studies were comparing the death rates of a generation of established, lifelong male smokers with a generation of women who had not yet taken up smoking with full intensity.'(23)

The 1980 report identified a marked increase in female mortality due to COPD compared to men between the years 1960 and 1977. Although men still accounted for the largest number of COPD-related deaths, the mortality rate increased 5.3 times in white women compared to 2.2 times in white men (23, 24). While the risk of COPD in female smokers was clearly established, the identification of distinct male-

female differences in the susceptibility to and progression of COPD remained elusive. The authors of the 1980 Surgeon General Report concluded:

> …it is not clear whether these differences (in mortality rates) are due to intrinsic differences in the way men and women respond to environmental injury or to the differences in the degree of environmental injury experienced by men and women."(23) (parentheses added)

Cigarette smoking is the primary risk factor for COPD in developed countries. While earlier studies on the health consequences of smoking tended to categorize smoking exposure into "heavy", "moderate" or "light", this method was eventually replaced with the measurement of pack years. Initially the measurement of pack years was merely the number of packs per day multiplied by the number of years of smoking. However, the calculation of pack years was later modified to reflect the fact the number of cigarettes in a pack is not consistent. The generally-accepted calculation of pack years is to multiply the average number of cigarettes smoked per day by the number of years smoked, standardized to a pack size of 20 cigarettes. This modified pack year measurement is a more accurate estimate of cigarette smoke exposure than categories but it does not take into account other smoking behaviours (Table 1-2). Although the modified pack years measurement may be adequate for confirming the risk of COPD in smokers, it may not capture differences in smoking behaviour between men and women. There is evidence that other aspects of smoking behaviour are influenced by gender, such as type of cigarette, and individual smoking patterns.

Type of Cigarette. Cigarettes sold in North America are of different lengths. The standard cigarette is approximately 85mm long. King size cigarettes are longer,

and cigarettes of 100mm and 120mm are also produced. In general, longer cigarettes are marketed toward women (25). Marketing schemes focused on the length and slimness of king size and 100mm cigarettes in an attempt to draw a parallel between societal expectations of personal beauty and the cigarette chosen. This campaign was largely successful, with industry marketing surveys reporting an increased use of longer cigarettes, as well as menthol-flavoured cigarettes, among women compared to men (25). It is unclear if king size cigarettes have more tobacco than regular length cigarettes, and there is no evidence that smoking king size cigarettes provides any additional risk of lung disease. Although more women than men smoke menthol cigarettes, menthol cigarettes do not increase the risk of mortality in COPD (26) and are not thought to confer any additional risk to smokers (27), although a sex-menthol cigarette interaction has not been tested.

Individual Smoking Patterns. Other factors that can affect smoking exposure relate to individual patterns of smoking, such as the frequency of puffs, and the depth of inhalation. Cigarette brand can affect these behaviours. In general, low-tar cigarettes have been successfully marketed toward women (25, 28, 29). Studies have shown that smokers of low-tar cigarettes tend to compensate for the decreased nicotine and tar by inhaling more deeply and taking more puffs per cigarette, which results in a larger dose of inhaled smoke than individuals who smoke regular-tar cigarettes (30). Whether this smoking behaviour is wide-spread or specifically related to cigarette type is not known. There remains a need to adequately investigate gender differences in smoking behaviour.

1.5.1.2 Indoor Air Pollution

COPD does occur in the absence of active cigarette smoking, with more women than men with COPD reporting to be lifelong non-smokers. In the Caucasian population, 13% of men and 27% of women with GOLD Stage 2 or more are reported never-smokers, based on data from the NHANES study (31). These numbers are higher in the African-American population, with 20% of men and 39% of women with Gold Stage 2 or greater reporting to be never-smokers. The reason for this gender difference is not clear, but other sources of exposure may be a factor. Although the link between exposure to environmental tobacco smoke (ETS) and the development of COPD has not been established (32), women are more likely to be exposed to ETS compared to men (33). Most studies that investigate sex or gender difference in COPD measure active cigarette smoking only, and most studies of ETS measure risk of COPD in never-smokers. Whether exposure to ETS adds an important additional burden to the lungs of female cigarette smokers is not known.

Another key pollutant that women are differentially exposed to is indoor air pollution from biomass fuels. Biomass fuels are primary sources of energy for cooking, light and heat for approximately 50% of the world's population (34). Many families that use biomass fuels do so in dwellings without adequate ventilation. Cooking is often done on indoor fires without chimneys, resulting in smoky rooms throughout the day. Since women are primarily responsible for cooking in many of these communities, they, along with their young children, receive the largest burden of exposure, usually over their entire lifespan. Biomass exposure can often exceed

World Health Organization maximal exposure guidelines by as much as 400 times (34).

Biomass smoke, similar to cigarette smoke, is made up of thousands of chemicals and particles ranging in size from large to small, depending on the biomass fuel and the completeness of combustion. These particles can irritate eyes and nasal passages, and can be inhaled deeply into the lung. This exposure is associated with several acute and chronic conditions. Specifically, biomass smoke exposure has been linked to chronic bronchitis, COPD, and an increased risk of tuberculosis (34). It also increases the risk of acute childhood respiratory infections, particularly pneumonia (34). Other respiratory findings have been detected on computed tomography (CT) scans in women exposed to biomass smoke, including signs of fibrosis and severe bronchiolitis (35, 36).

Globally, biomass exposure accounts for 4-5% of all deaths that occur annually (34). The fact that women and children in developing nations have historically low tobacco smoking rates possibly has obscured the very real threat to their health from biomass smoke exposure. In addition, as the tobacco smoking rates for women and girls rise in developing countries, the additive effect of tobacco smoke on those already exposed to biomass smoke could lead to dramatic increases in morbidity and mortality.

1.5.1.3 Occupational Exposures

There is little information on sex/gender differences in the likelihood or outcomes of COPD due to occupational exposures. The reasons for this information

gap are several. First, most research on COPD measures active cigarette smoking and not occupational exposure as the primary risk factor. Second, much of the information on occupational risk factors for COPD comes from research on dusts and fumes. These exposures usually occur in manufacturing, welding, etc.; occupations which generally employ many more men than women. The few numbers of women available for study makes any investigation of sex or gender differences difficult. Third, there have been few studies on the risk for COPD in industries that have chemical and dust exposures but primarily employ women, such as the cleaning industry. Matheson et al (37) found a seven-fold increased risk for COPD in women exposed to biological dusts in the health care, food, textile, artistic and cleaning industries. This risk was not detected in men. Using data from the third National Health and Nutrition Examination Survey, Hnizdo et al (38) reported higher odds ratio for COPD in women working in agriculture, textile, rubber and plastic, and sales-related industries compared to men in the same industries. Further research is needed to address the female risk for developing COPD in male-dominated industries as well as identifying the risk for COPD in other industries where women are commonly exposed to chemical fumes or dust.

1.5.2 Gender Differences in the Epidemiology of COPD

There have been numerous studies on sex/gender differences in the epidemiology of COPD, including studies on prevalence, symptoms, diagnosis, mortality and hospitalizations.

1.5.2.1 Prevalence

COPD is a prevalent disease, yet the measurement and monitoring of the true burden of illness remains problematic. Prevalence estimates have relied on self-report, administrative databases, or lung function testing in large, population-based samples. Each method may contribute to under- or over-estimates of COPD in men and women. By self-report, women tend to have a higher prevalence of COPD compared to men. Data obtained from the 2005 Canadian Community Health Survey show that the prevalence of self-reported COPD diagnosed by a physician is 4.8% in women versus 3.9% in men, 35 years and older (5). Data from the United States National Health and Nutrition Examination Survey show an even larger discrepancy between men and women; in 2000, the prevalence of self-reported, physician-diagnosed COPD was 7.3% in women versus 4.6% in men (7). However, prevalence estimates based on spirometry performed in randomly-sampled population studies continue to show a greater prevalence of COPD in men. Recent data from the Burden of Obstructive Lung Disease (BOLD) study show that in each of eleven cities in countries from North America, Asia, Europe and Africa, men had a higher prevalence of COPD than women (6).

1.5.2.2 Symptoms

For many patients the pathway to a COPD diagnosis begins with the reporting of respiratory symptoms to their physician; therefore gender differences in symptoms are important to consider. Symptoms of COPD include respiratory-related symptoms such as dyspnea, cough, sputum production, wheezing and chest

tightness, as well as associated conditions, such as anxiety, depression, and weight loss (1).

Several studies have examined gender differences in symptom reporting (Table 1-3). Women with COPD are more likely to report dyspnea (39-41) and chronic cough (42) but less likely to report phlegm production (40, 43). In addition, women with COPD are more likely to have depression and anxiety compared to men, even after adjusting for lung function (41, 44). The mechanisms behind these differences are not clear. Differences between men and women in respiratory symptoms may be due to sex differences in lung pathophysiology, hormonal differences in ventilatory control, differences in afferent neural processing or gender-related factors in symptom reporting. Respiratory symptom questionnaires are available but have not been scrutinized in terms of gender differences in reporting, irrespective of actual differences in the prevalence of symptoms. Since there are few objective measures available for respiratory symptoms, it may be difficult to distinguish pathophysiological differences from gender differences in the perception or reporting of symptoms.

1.5.2.3 Gender Bias in Diagnosis

Even if men and women report similar respiratory symptoms to their physician, little is known about how a physician may interpret those symptoms. Gender bias in the diagnosis of COPD can affect estimates of prevalence, recruitment into research studies and treatment outcomes. Chapman et al (45) conducted a study in the United States and Canada which was repeated in Spain by

Miravitlles et al (46). In these studies, physicians were presented with hypothetical case scenarios. Half of the physicians were told that the hypothetical patient was female; the other half were told the patient was male. Physicians were asked to give the most likely diagnosis based on the case summary (symptoms, past medical history, smoking history). They were then given hypothetical spirometry results (indicating COPD) and asked again for a most likely diagnosis. Finally, the physicians were told that a one-week course of oral corticosteroids did not improve symptoms in the patient, and were again asked their most likely diagnosis. The results of both studies are summarized in Table 1-4.

The results indicate that in the absence of spirometry, physicians may be more likely to diagnose males as having COPD than females, all other factors being equal. In the Spanish study, the proportion of female cases diagnosed with COPD was the same as males after spirometry results were given; however in the Canada / United States study, the gender bias persisted, even after information on the failed course of steroids was given.

As suggested by these studies, an objective measure of lung function should be administered to reduce the possibility of gender bias. However the utilization of spirometry is low. Anthonisen et al (47) reported that in patients coded as having COPD, the use of spirometry ranged from 27% in patients with only one physician visit per year to 53% for patients with greater than 19 visits per year. In the Chapman study, when given the option only 22% of physicians requested a spirometry test (45). Compounding the gender bias, women in particular may be less likely to receive a spirometry test -- Watson et al (40) found that the odds ratio

of being given a spirometry test is 0.84 for women compared with men (95% confidence interval 0.72-0.98).

Without spirometry testing, symptomatic women with COPD may be diagnosed with asthma. Dales et al (48) found that the prevalence of physician-diagnosed asthma was twice as high among women as men; however, bronchodilator responsiveness did not differ between the two sexes. Others have also reported a greater likelihood for women with COPD to be incorrectly diagnosed with asthma than men (19, 40). Adult women have a higher prevalence of asthma compared to men (5). The reasons for this may be due to intrinsic differences in airway behavior, but it is possible that a misdiagnosis of asthma instead of COPD is occurring to a greater degree in women.

1.5.2.4 Mortality

COPD is associated with a high mortality rate – it is the 4th leading cause of death in Canada and is expected to be the 3rd leading cause of death worldwide by 2020. In the United States, it is the only leading cause of death where the mortality rate has increased over the period 1965-1998 (3).

Mortality data for COPD is available from the Public Health Agency of Canada and Statistics Canada (http://204.187.39.30/surveillance/Mapdb/Infobase_e.htm). Using the International Classification of Disease -Version 10 (ICD-10) codes for COPD (J40-44), the 1997 Canadian mortality rate for COPD as the primary cause of death was 45.03 per 100,000 adults 50-74 years. This rate dropped to 40.07 per 100,000 adults in 2001, due to a 16% reduction in the male mortality rate from 1997

to 2001; the female mortality rate remained unchanged over this time. This rate likely underestimates the true burden of COPD-related mortality since pneumonia or other respiratory tract infections may be listed as the primary cause of death in COPD patients. In British Columbia, there was a striking increase in mortality for COPD in the female 75+ year age group, with an 80% increase in COPD-related mortality for women from 1984 to 2001, while the male mortality rate decreased. Again, these mortality rates likely underestimate the impact of COPD mortality on high-risk groups. When looking at Canadian data, the highest rates for COPD mortality were in the Northwest Territories, with rates almost 3 times higher than those in British Columbia (49). The large aboriginal population in northern communities may be bearing a much larger burden of mortality than is indicated in British Columbia provincial data. A large increase in COPD mortality in women has also been observed in other countries (7).

1.5.3 Gender, Sex and Lung Function

The majority of studies investigating sex/gender differences in COPD have used lung function parameters as indicators of disease susceptibility. Many studies have used lung function measurements to argue that women have an increased susceptibility to COPD; i.e., for a given amount smoked, women have worse lung function. The possible mechanisms for this are complex. There is evidence that there are sex differences in lung anatomy and physiology which may influence the development of lung disease. Over a lifetime, the female lung tends to be smaller than the male lung in individuals of the same height, with smaller caliber airways, yet

female lungs have higher forced expiratory flow rates, and higher FEV_1/FVC ratios even after standardizing for differences in body size (50). Yet there is little understanding on how these differences in lung anatomy might impact overall susceptibility to COPD.

Early studies have reported inconsistent results. In 1976, Tager et al (51) found an increased prevalence of chronic bronchitis in men but no differences in the effect of smoking on lung function. In 1979, Buist et al (52) reported that the single-breath nitrogen test (a test of small airways function) and the FEV_1/FVC were abnormal more than twice as often in female smokers compared to male smokers. Similar to Tager, Beck et al (53) found the loss of FEV_1 as a function of pack years was similar in men and women. More recent work has continued with the inconsistent results – Silverman et al (54) reported an increased risk for reduced FEV_1/FVC in female smokers who had a sibling with severe COPD, but no such risk in the male smokers (54). Gan et al (55) found that female smokers over the age of 55 years had a greater decline in FEV_1 compared to male smokers, but this effect was not seen in the ex-smokers; whereas Martinez et al (56) reported no difference in lung function between men and women with severe emphysema.

The many different lung function parameters used (FEV_1; rate of decline in FEV_1; single breath nitrogen test; FEV_1/FVC) make it difficult to reach a consistent conclusion regarding sex/gender differences in COPD susceptibility. Measurement bias may also contribute to the inconsistent findings. For example, Xu et al (57) investigated differences between men and women in the effects of smoking on pulmonary function, using data collected from 3,287 individuals as part of the Beijing

Respiratory Health Study. They reported that female lifetime nonsmokers had a greater mean FEV_1 % predicted than male lifetime nonsmokers, and female smokers had lower FEV_1 % predicted values compared to male smokers. These values were adjusted for age, education level, use of an indoor coal stove for heating, passive smoke exposure, occupational dust and gas/fume exposure, and residence. The investigators hypothesized that the measured differences in lung function between men and women could be partially attributed to the incomparability of the reference groups used to generate the lung function predictions. They argue that this incomparability may result from differences in the proportion of "unhealthy" male and female subjects in the lifetime nonsmoker reference group. The higher the proportion of "unhealthy lifetime nonsmokers" in the reference group, the lower the reference values and the more likely that lung function in the smokers' group will be overestimated when compared to this reference group (see Table 1-5 for illustration of this effect). They provide support for their hypothesis by summarizing the results of different studies with respect to smoking prevalence and gender differences in lung function. A trend is apparent, with the larger the disparity between men and women in terms of nonsmoking prevalence the more likely the conclusion that women smokers will have greater reduced lung function. This explanation for differences in lung function moved the discussion beyond physiology and opened the door for further discussion of gender bias in measurement, but unfortunately, little has been done to further develop this hypothesis.

1.6 RATIONALE FOR STUDY

Based on this review of the literature, three important factors emerge which form the themes for this program of research. First, COPD is a complex chronic disease, arising from two main pulmonary pathophysiological pathways -- parenchymal inflammation and destruction, and airway inflammation and remodeling. It is evident that our current understanding of sex and/or gender in COPD has focused primarily on changes in lung function and epidemiology (Figure 1-3 – highlighted area). Returning to the diagram of the pathophysiological processes of COPD, it is evident that symptoms, epidemiology, and lung function are downstream health effects of these processes. Gender influences how and why men and women smoke and there has been some investigation into the gender differences in exposure. There remains a poor understanding of sex differences in pulmonary pathophysiology once a male or female lung is exposed to cigarette smoke. We don't know if sex and gender determine or influence which pathophysiological process occurs. It is possible that the dominant pathophysiological process in a given COPD patient can influence downstream effects such as symptoms, lung function and morbidity. Gender likely interacts with these processes to further impact these outcomes. The first theme of this research program is based on the question: is a predisposition to parenchymal destruction versus airway wall remodeling influenced by sex?

Second, another important factor often overlooked in previous research is the concept of gender-sensitive or gender-neutral measurement tools.

Rarely is the impact of the measurement tool on the results of the study discussed. In this thesis, we will consider how the measurement tools used may have influenced the conclusions of the studies.

Third, most of the research on sex and gender in COPD has focused on differences between male and female cigarette smokers. Relatively little research has addressed COPD in populations with exposures unique to either men or women. The third theme in this study will consider how unique exposures, specifically biomass smoke exposure, impact the lung health of women.

1.7 OBJECTIVES AND HYPOTHESES OF THE THESIS

In this thesis I will investigate the epidemiology and pathophysiology of COPD using a sex- and gender-based analysis strategy.

Study 1.

Objective. To describe the differences between men and women with COPD in prevalence, mortality, diagnostic testing utilization and medication use.

Study 2.

Objective 1. To examine differences between male and female smokers in the two pathophysiological processes of COPD – emphysema and airway wall remodeling.

Objective 2. To examine differences between male and female smokers in the reporting of dyspnea and the level of lung function.

Hypothesis. Female smokers will be more likely to have evidence of decreased lung function and airway wall remodeling and be more likely to report dyspnea, whereas male smokers will be more likely to have evidence of emphysema.

Study 3.

Objective. To compare the relationship of three different measures of emphysema (one subjective, two objective) with reduced lung function and to test for gender-neutrality in these measures.

Hypothesis. Objective measures of emphysema will better predict reduced lung function in smokers. These measures will perform equally well in both male and female smokers.

Study 4.

Objective. To compare the phenotypic characteristics of COPD in women previously exposed to biomass smoke with women who have previous history of active cigarette smoking.

Hypothesis. COPD due to biomass smoke is associated with an airway disease-predominant phenotype whereas COPD due to cigarette smoking is associated with an emphysema-predominant phenotype.

1.8 SCOPE OF THE THESIS

This thesis includes four studies detailed in the following four chapters, followed by a discussion chapter which summarizes the findings and discusses the future implications for this work. As such there is some repetition between the thesis chapters. **Chapters Two** to **Four** focus on identifying sex and gender differences in men and women with or at risk for developing COPD. In **Chapter Two** I describe the results of a study on gender differences in the epidemiology of COPD. I used summary data on COPD provided by the British Columbia Ministry of Health (MOH). Due to privacy issues, the MOH data analyst extracted the individual-level data and summarized the data by age group, year, and gender. As a member of the COPD expert advisory committee to the Ministry, I participated in the development of the case definition for COPD and assisted with the interpretation of the summary data. I had the primary responsibility of developing the research questions related to gender differences in the epidemiology of COPD, guided and conducted the analysis related to those questions, and was first author on the published paper. I investigated if the predicted increase in prevalence and mortality of COPD in women relative to men was evident in British Columbia, using administrative health services data from 1992/1993 – 2003/2004. I also tested for gender differences in referral for diagnostic (lung function) testing and use of COPD medications. In **Chapter Three** and **Chapter Four** I analyzed individual-level data obtained from the COPD Genetics Network, a previous multi-centre study on genetics and COPD. This study was a multi-centre study which began data collection in 2000. I was the research manager for the Vancouver data collection and was involved in all aspects of data

collection and data cleaning for that site. For this thesis, I then obtained data from all ten sites which participated in the genetics study, and was primarily responsible for data cleaning for all sites. In **Chapter Three,** I had the primary responsibility of developing the research questions related to sex differences in COPD phenotypes. To test for these differences, I used data from high resolution computed tomography (HRCT) scans, lung function tests and questionnaires and conducted all analyses. I hypothesized that male smokers would have more emphysema, whereas female smokers would have more airway wall remodelling and experience more dyspnea. In **Chapter Four** I also used data from the COPD Genetics Network and investigated the research methodology used in assessing emphysema. In this study, I compared subjective scoring of emphysema with two objective methods, all derived from the HRCT scan, to determine which method best predicted COPD in both men and women. For this study, I had primary responsibility for developing the research question related to sex and COPD and conducted the analyses. In **Chapter Five** I focussed my attention on the impact of COPD on women exposed to biomass smoke. In countries where smoking rates remain low for women, COPD may not be considered a threat. Considering tobacco smoke as the sole risk factor for COPD neglects the tremendous risk of this disease for women in developing countries who are dependent on biomass fuel for cooking and heating. There is a lack of research detailing the long term effects of biomass smoke on the lungs of women. In **Chapter Five** I investigated the effects of biomass fuel on the lungs of women with COPD. There is a long-standing collaboration between investigators at the James Hogg iCAPTURE Centre of Cardiovascular and Pulmonary Research at

St. Paul's Hospital, Vancouver, and the National Institute for Respiratory Research, Mexico City. For this study, I travelled to Mexico City to work with the investigators there to develop the research question, research methodology, and analysis strategies. I met women with cigarette smoke or biomass smoke exposure and toured the testing facilities. The investigators in Mexico City provided day-to-day responsibility for data collection and sent the raw data to Vancouver for analysis. The CT scans were sent to Vancouver and the qualitative and quantitative CT scan data analysis was done in Vancouver. I was responsible for the development of the research question, data management, cleaning and analysis. I hypothesized that women with COPD due to biomass smoke exposure will be more likely to have an airway disease-dominant phenotype.

Table 1-1. Global Initiative for Obstructive Lung Disease – Classification of COPD Severity by Spirometry (1)

Stage	Criteria
Stage 1 : Mild	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted
Stage 2: Moderate	$FEV_1/FVC < 0.70$ $50\% \leq FEV_1 < 80\%$ predicted
Stage 3: Severe	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 < 50\%$ predicted
Stage 4: Very Severe	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted *plus* chronic respiratory failure

Table 1-2. Factors Affecting Tobacco Smoke Exposure

Active Smoking Exposure
• Age of onset of smoking habit • Intensity of smoking (does 1 pack per day x 40 years = 2 packs per day for 20 years in terms of effect on the pulmonary system?) • Type of tobacco product – cigarette, cigar, pipe • Number of cigarettes/cigars/pipes smoked per day • Number of years of smoking habit • Tar level of tobacco • Frequency of puffs • Whether smoke is inhaled into the lungs • Volume of inhalation per puff • For cigarettes: Length of the cigarettes smoked • For cigarettes: Amount of cigarette butt left at the end of each cigarette smoked
Secondhand Smoke Exposure
• Amount of smoked tobacco products exposed to per day • Number of years of exposure • Size of area in which exposure occurred • Ventilation of area in which exposure occurred • Tar level of tobacco

Table 1-3. Gender Differences in COPD-related Symptoms

Symptoms	**Study & Year**	**Study Design**	**Summary**
Dyspnea	de Torres et al, 2005 (39)	Cross-sectional; 53 men and women with COPD recruited from pulmonary clinic and matched on lung function	Women with COPD report more dyspnea on the American Thoracic Society-Modified Medical Research Council scale than men (p=0.0003)
	Watson et al, 2004 (40)	Cross-sectional; randomly-sampled population-based telephone survey; self-report of COPD diagnosis	Women with self-reported COPD report severe dypsnea on the Medical Research Council scale more frequently than men ($p<0.05$)
	Di Marco et al, 2006 (41)	Case-control; COPD patients attending a pulmonary clinic compared with non-COPD patients on prevalence of symptoms	Women with COPD report more severe dyspnea on the Medical Research Council scale for a given lung function compared to men (p=0.003)
Chronic Cough	Watson et al, 2006 (42)	Longitudinal study; Placebo arm of randomized clinical trial of budesonide	Higher prevalence of 'being woken by an attack of coughing' ($p < 0.001$) and 'chronic cough during winter' ($p = 0.03$) in women compared to men.

Table 1-3. Continued.

Symptoms	Study & Year	Study Design	Summary
Sputum Production	Cydulka et al, 2005 (43)	Secondary analysis of prospective cohort of patients presenting to emergency with an acute exacerbation of COPD	Men more likely to report productive cough on most days compared to women (p = 0.02)
	Watson et al, 2004 (40)	Cross-sectional; randomly-sampled population-based telephone survey; self-report of COPD diagnosis	Women less likely to report sputum.
Depression	Di Marco et al, 2006 (41)	Case-control; COPD patients attending a pulmonary clinic compared with non-COPD patients on prevalence of symptoms	High prevalence of depression compared to controls; women had higher levels of depression and worse symptom-related quality of life compared to men
Anxiety	Di Marco et al, 2006 (41)	Case-control; COPD patients attending a pulmonary clinic compared with non-COPD patients on prevalence of symptoms	High prevalence of anxiety compared to controls; women had higher levels of anxiety compared to men.
	Gift et al, 1999 (44)	Cross-sectional study of patients attending a pulmonary clinic	Women and men were similar in their psychological symptoms except for anxiety, which was higher in women.

Table 1-4. Percentage of Patients Diagnosed with COPD by Gender – Results from Two Studies Examining Gender Bias in the Diagnosis of COPD

	Chapman et al (45) Canada / United States study		Miravitlles et al (46) Spain study	
	Patient is Male % diagnosed with COPD	Patient is Female % diagnosed with COPD	Patient is Male % diagnosed with COPD	Patient is Female % diagnosed with COPD
History and physical exam only	64.6	49.0	41.6	31.4
Above plus spirometry	76.0	64.6	74.0	74.1
Above plus oral steroid trial	85.4	78.1	73.2	72.4

Table 1-5. Illustration of How Gender Differences in Smoking Prevalence in Reference Group Could Impact Lung Function Calculations in Smokers' Group

Example 1 (using Xu et al 1994 data (57))

	Male	Female
Population n	1000	1000
% Current or ex-smokers	78	35
% Lifetime nonsmokers	22	65
# Lifetime nonsmokers	220	650
Hypothetical # of unhealthy lifetime nonsmokers*	50	50
% of unhealthy lifetime nonsmokers in lifetime nonsmoker population	23%	8%

* individuals who did not attempt to smoke due to respiratory problems

In this example, men have a greater proportion of unhealthy lifetime nonsmokers in their lifetime nonsmoker population and therefore the reference values derived from this population could be underestimated. Therefore the true effect of smoking on the male population could be underestimated when compared to this reference population, and it could be concluded that women have a greater reduction in lung function due to smoking compared to men.

Example 2 (from Camilli et al 1987 data (58))

	Male	Female
Population n	1000	1000
% Current or ex-smokers	72	58
% Lifetime nonsmokers	28	42
# Lifetime nonsmokers	280	420
Hypothetical # of unhealthy lifetime nonsmokers*	50	50
% of unhealthy lifetime nonsmokers in lifetime nonsmoker population	18	12

* individuals who did not attempt to smoke due to respiratory problems

In this example, the proportion of "unhealthy lifetime nonsmokers" is similar between men and women, and in this study it was concluded that male smokers had a greater reduction in lung function compared to female smokers.

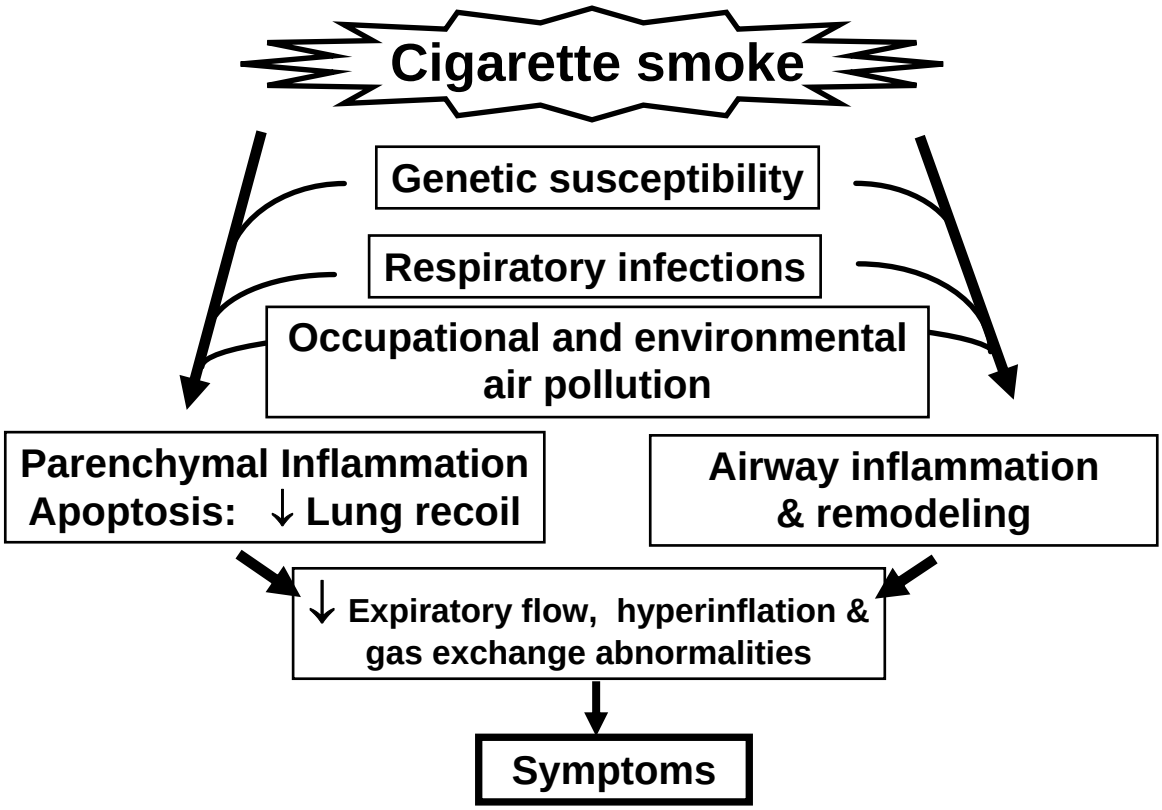

Figure 1-1. The Pathogenesis of COPD
This figure illustrates the pathogenesis of COPD due to exposure to cigarette smoke. In genetically-susceptible individuals, cigarette smoke exposure leads to parenchymal inflammation and destruction and/or airway inflammation and remodeling. Repeated respiratory infections and air pollution can also contribute to the development of COPD. Parenchymal destruction and airway remodeling both lead to decreased expiratory airflow, which eventually result in symptoms such as dyspnea, cough and reduced activity tolerance.

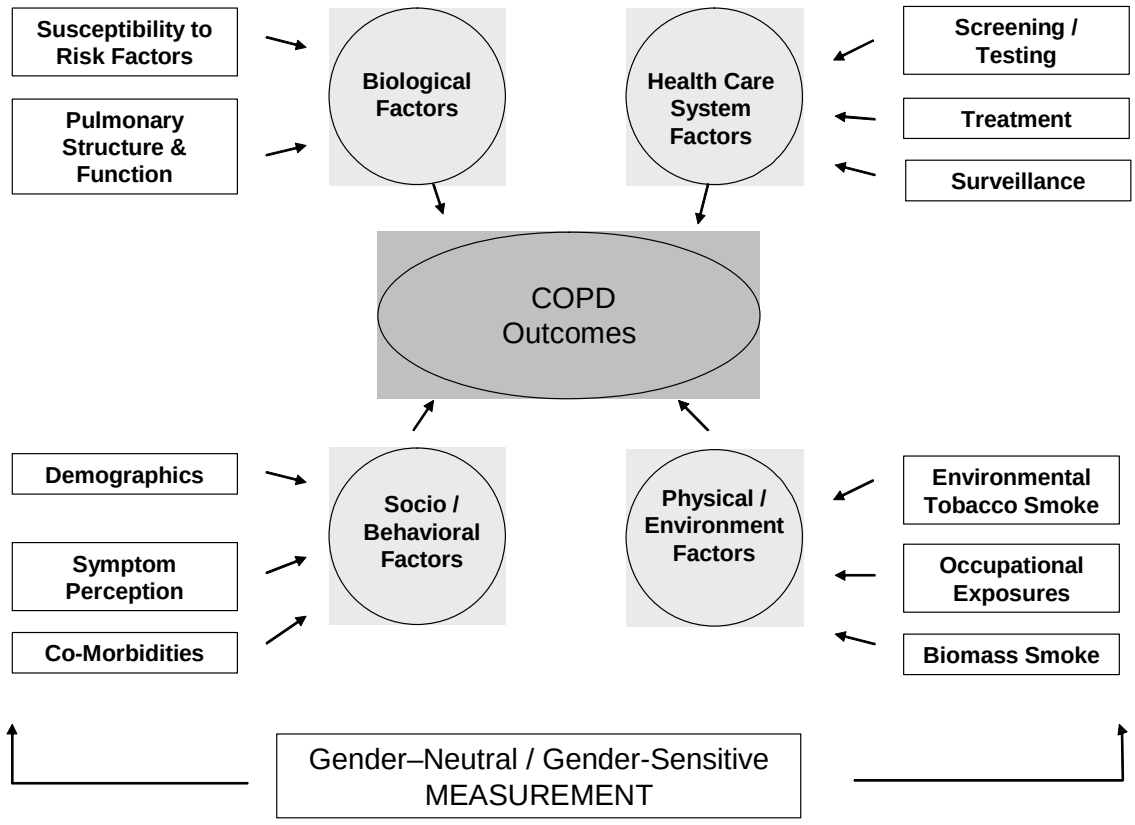

Figure 1-2. Factors Affecting Outcomes in COPD
Sex- and gender-related factors can influence COPD through many mechanisms. Some of these factors are individually-based, such as pulmonary structure and function or symptom perception, but many are externally-influenced, such as occupational exposures and surveillance and screening strategies. Sex and gender have the capacity to individually and together influence how these factors ultimately impact health outcomes in COPD.

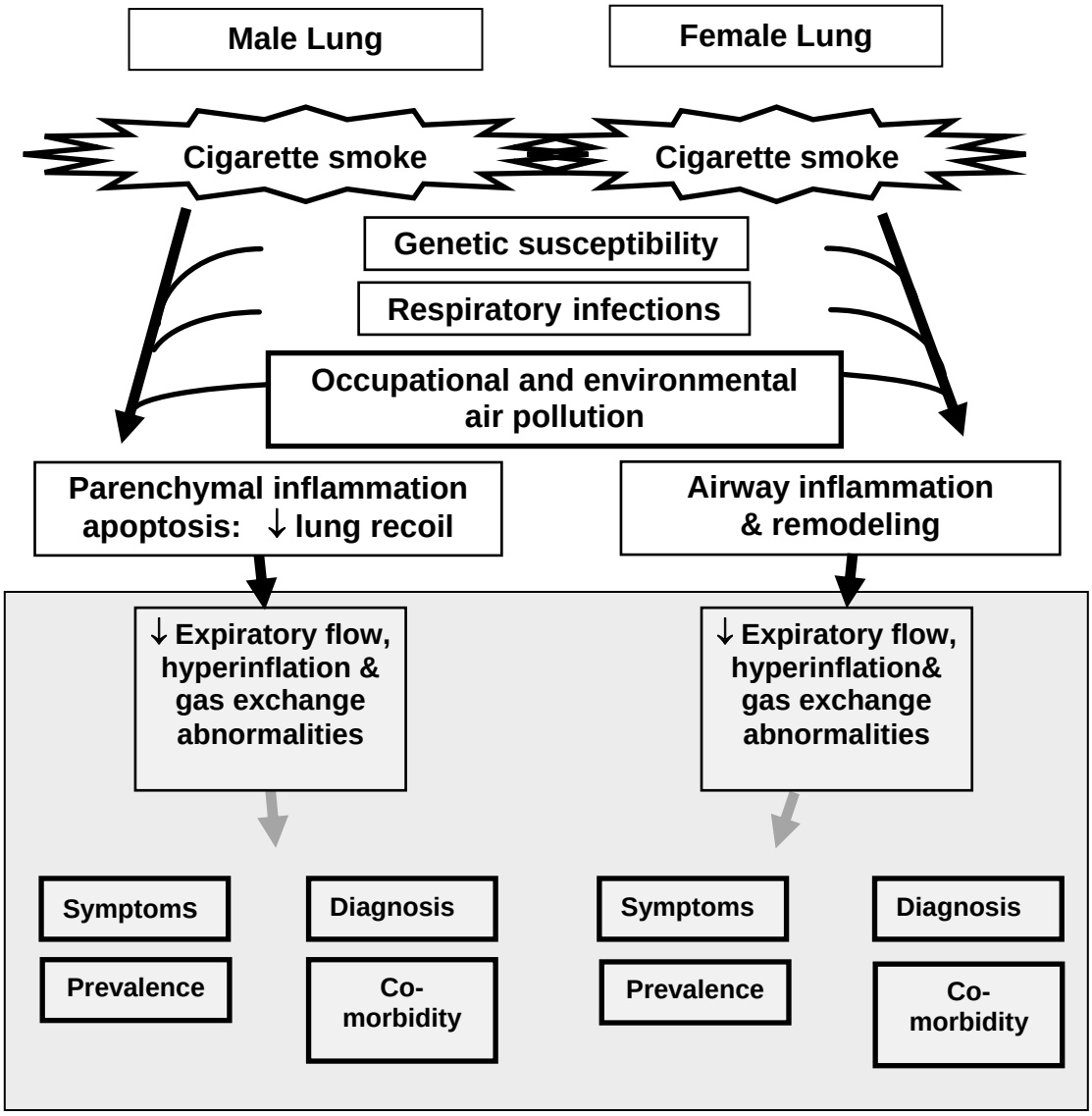

Figure 1-3. Revised Diagram of the Pathogenesis of COPD

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CHAPTER TWO. THE GENDER FACTOR: EPIDEMIOLOGY AND MANAGEMENT OF COPD IN BRITISH COLUMBIA[1]

2.1 INTRODUCTION

The prevalence of chronic obstructive pulmonary disease (COPD) is increasing in women (1, 2) and is likely due, in part, to changes in cigarette smoking patterns and possibly a greater susceptibility for women to develop COPD (3-6). In 2001, Health Canada released a report entitled 'Respiratory Disease in Canada' predicting that by 2002 the epidemiological trends of COPD would shift, with prevalence, hospitalizations and mortality for women with COPD surpassing those for men (1). There have been few studies to determine if these predicted gender differences have been realized on a population-based scale and if these differences translate into gender differences in diagnostic testing or treatment. To date, Canadian estimates for prevalence have been largely based on self-report of diagnosis. It is not known whether an increased susceptibility for COPD in women can be detected in larger, population-based administrative data.

Administrative health databases provide a valuable method for identifying gender differences in the epidemiology of COPD, since they provide large sample sizes, have strong statistical power, are relatively inexpensive studies to conduct, and can link information on diagnosis, treatment and mortality. These databases

[1] A version of this paper has been accepted for publication:

Camp PG, Chaudhry M, Platt H, Roch M, Road J, Sin D, Levy RD. The gender factor: epidemiology and management of COPD in British Columbia. Reproduced with permission Can Respir J (In press).

may represent the 'real world' more accurately and characterize gender differences more fully than do other data sources.

The purpose of this study was to determine if administrative health data from British Columbia could detect the predicted increase in women in prevalence and mortality of COPD from 1992/1993 – 2003/2004 compared to men. We also tested for gender differences in referral for diagnostic (lung function) testing and use of COPD medications.

2.2 METHODS

We abstracted COPD cases from the British Columbia (BC) Ministry of Health (MOH) administrative health service databases. The BC MOH maintains several sources of data on the medical services provided to the province's residents as part of providing comprehensive medical insurance. Each eligible resident receives a unique Personal Health Number (PHN) upon registering for provincial medical insurance. Individuals without unique PHNs include inmates in federal penitentiaries, members of the Canadian Armed Forces and the Royal Canadian Mounted Police, foreign students, new residents who have resided in the province less than 3 months, aboriginals living on reserves, and in some circumstances, individuals who are wards of the province. Other jurisdictions have estimated this group to be approximately 1% of the population (7). Insurance coverage and registry data were linked to become the Population Registry and were used to derive population estimates. Information on disease prevalence was derived from two

sources. The first is the Medical Services Plan (MSP) Billing Database which contains data on visits to physicians who bill on a fee-for-service basis (~ 96% of all practicing physicians in BC (8)). Each physician who bills the provincial government for a patient visit provides a diagnostic code, based on the International Classification of Diseases, 9th edition (ICD-9), that best describes the purpose of the visit along with the PHN number of the patient. The second source of data on diagnoses is the Discharge Abstract Database (DAD) which contains data on hospitalizations and day surgeries. A record is created for each patient upon discharge from the hospital. This record includes the PHN and sixteen ICD-9 (prior to 2000) or twenty-five ICD-10 (2000 onwards) diagnostic codes. Data on emergency room visits were not available. Population estimates for the denominators were obtained from the Population Registry database.

Lung function testing included one or more of: simple spirometry (with or without lung volumes), pre- and post-bronchodilator spirometry, flow volume loops, diffusion capacity and detailed pulmonary function tests. Tests which were performed in non-accredited physician's offices or at the hospital bedside are not routinely billed and as such were not captured in this data.

Individuals were considered to be COPD cases if they were aged 45 or older and had at least one hospitalization or two physician visits coded with an ICD9/10 code for COPD (Table 2-1) within any 365-day window between April 1, 1992 and March 31, 2004. For cases ascertained from hospital data, the ICD9/10 code for COPD could be any one of the diagnoses from the hospital discharge summary. Individuals whose gender was unknown were excluded. Upon meeting these

criteria, individuals were considered to have COPD until death or emigration from BC. Prevalent cases of COPD for each year were defined as cumulative incident cases of COPD from April 1, 1992 to the end of each fiscal year, less those lost due to death or emigration before the start of the fiscal year. Population estimates for the denominators were obtained from the MOH registry of insured residents. Rates were age-standardized to the 2001 BC census population estimates using direct standardization and five-year age-groups. Cases may have had codes for other chronic lung diseases in addition to COPD, such as asthma, tuberculosis, or interstitial lung disease; however, overlap with other chronic lung diseases was not measured in this study.

Some studies (9-12) have included the code ICD-9 490 (bronchitis not specified as acute or chronic) in their COPD case definition, but the validity of including this ICD-9 code has been questioned (13). Therefore, we measured COPD prevalence, medication and spirometry use by gender with and without ICD-9 490 included in the case definition to determine the impact of this ICD-9 code on gender differences in prevalence. As with the other COPD codes, individuals with ICD-9 490 were required to have two physician visits or 1 hospitalization coded with ICD-9 490 within any 365 day window. We did not include individuals with two physician claims where one visit was coded with ICD9-490 and the other visit was coded one of ICD9-491, 492, or 496.

Data on lung function testing were retrieved from the Medical Services Plan Database which includes records on outpatient billable diagnostic tests or procedures. We compared the prevalence of lung function testing ever between

1992 and 2004, for men and women with COPD who were alive and residing in BC in the 2003/2004 fiscal year.

Medication usage data were obtained from the PharmaNet database which contains records for all prescriptions filled in BC. To be considered a user of COPD medications, an individual had to fill at least two prescriptions of any medication within any of 12 major medication categories (Table 2-2) during the time period. Using the 2003/2004 prevalent cases, we compared the odds between men and women of filling prescriptions for COPD medications from April 1, 2002 to March 31, 2004.

All-cause mortality data was obtained from the MOH for all COPD cases by gender and age category for the years 1992/1993 – 2003/2004. In addition, we compared the all-cause mortality for COPD versus non-COPD.

Trends for age-standardized prevalence of COPD between April 1, 1992 and March 31, 2004 were estimated by dividing prevalent cases by the number of insured residents in BC for each fiscal year, and expressed by gender. Comparisons between genders for prevalence, medication use or lung function testing utilization are expressed using proportions or unadjusted odds ratios using the software package SAS (SAS Institute, version 9). The study was approved by the BC Ministry of Health and the University of British Columbia.

2.3 RESULTS

2.3.1 Prevalence

There were 1,713,759 insured individuals in BC who were 45 years of age or older in the fiscal year 2003/2004. Approximately 5341 of these individuals did not have gender listed in the database, leaving 1,708,418 individuals who made up the total population denominator for analysis. Of these, 38,458 men (crude prevalence 4.7 %) and 34,960 women (crude prevalence 4.0%) met the case definition for COPD at some time between 1992 and 2004 and were still alive and residing in BC in 2003/2004. Age-standardized prevalence increased for both men and women from 1992/1993 to 2003/2004 (Figure 2-1) but there was no substantial relative increase in prevalence in women compared to men. Data on a concurrent diagnosis of asthma were not available for this analysis.

2.3.2 Lung Function Testing & Medication Utilization

Approximately 55% of the 2003/2004 COPD population had lung function testing billed during the period 1992/1993 to 2003/2004. Only 45% of the 2003/2004 prevalent COPD cases had filled prescriptions for COPD-related medications in the period 2002-2004. Similar proportions of men and women underwent lung function testing.

The majority of filled prescriptions (53%) were for short-acting bronchodilator medications (beta-$_2$ agonists and anticholinergics) followed by inhaled corticosteroids (21%) and long-acting bronchodilators (10%). Women were slightly

more likely than men to have filled a prescription for any COPD medication (odds ratio 1.16, 95% confidence interval 1.13,1.20). Long-acting bronchodilator medication made up 10% of all COPD prescriptions filled for men but only 5% of prescriptions filled for women. In the period 2002-2004, long-acting beta-$_2$ agonists which were available to all COPD patients in British Columbia. Long-acting anticholinergics (tiotropium) were available but not paid for under the government prescription reimbursement program; hence, few tiotropium prescriptions were filled.

2.3.3 Mortality

From 1992/1993 to 2003/2004 there was a steady decline in the age-standardized mortality rate for both genders, although this trend reached a plateau by 1999/2000 (Figure 2-2). We did not observe a progressive increase in the numbers of female deaths or in any age-specific female mortality rate in COPD cases over the study period.

Individuals with COPD had a much higher risk of all-cause mortality than individuals without COPD for all age groups, but the excessive risk was most striking in the younger age groups (Figure 2-3). For all ages combined, the COPD versus non-COPD risk of all-cause mortality was higher for men than for women but this appeared to be largely driven by a higher risk for mortality in COPD versus non-COPD males in the 45-49 and 50-54 year age groups. A higher risk for all-cause mortality in COPD versus non-COPD patients was seen for women compared to men in the 55-59, 65-59 and 70-74 year age groups.

2.3.4 Inclusion of ICD-9 490 (Bronchitis, not specified as acute or chronic) in the Case Definition

The inclusion of ICD-9 490 in the COPD case definition doubled the prevalence of COPD in BC (Table 2-3). When ICD-9 490 was included in the case definition, the prevalence of COPD cases fulfilling the case definition due to a hospital contact decreased from 44% to 3%. There were important gender differences in the prevalence of COPD by age group when ICD-9 490 was included in the case definition. In those aged 65 years and older, the prevalence of COPD was greater in men than in women, regardless of inclusion or exclusion of ICD-9 490. However, in those age 45-64 years, women had a higher prevalence of COPD compared to men when ICD-9 490 was included. Gender differences in this younger age group disappeared when ICD-9 490 was excluded from the COPD case definition. Lung function testing and COPD medication use was much lower in those coded with ICD-9 490 exclusively compared to those with ICD-9 codes 491, 492, and/or 496.

2.4 DISCUSSION

In this study, we used administrative health services data from BC to estimate gender differences in COPD prevalence, mortality, lung function testing and the use of medication. Specifically, we aimed to see if the predicted increase of COPD prevalence and mortality in women could be detected in the BC population using administrative health data. We did not see evidence of a dramatic shift in the

epidemiologic trends of COPD in this province but discovered that differences in medical coding may be influencing COPD prevalence estimates. In addition, our study did not demonstrate any difference in the use of lung function testing between men and women and only a small increase in the likelihood of women with COPD filling prescriptions for COPD medications.

COPD prevalence has been estimated in a number of ways, including self-report or measurement of airflow obstruction. All methods have problems with their validity. Self-report likely underestimates the true prevalence of COPD since many affected individuals may not see a doctor until the disease is quite advanced. Population-based random sampling and subsequent measurement of airflow obstruction is likely the most accurate method of determining the true prevalence of COPD in an area, but have limited external validity beyond the community that is sampled. In addition, the enormous expense of conducting such studies precludes the repeated measurement that is required to identify epidemiological trends.

We used administrative data as an alternative method of estimating the prevalence of COPD. Administrative data is routinely used in COPD for morbidity and hospitalization surveillance (Public Health Agency of Canada Chronic Disease Infobase http://204.187.39.30/surveillance/Mapdb/Infobase_e.htm). A key issue in using this data source is the validity of the case definition in accurately identifying COPD cases. The validity of administrative data for epidemiologic studies of COPD has been tested in several studies. Two Canadian studies (14, 15) found that COPD patients identified from medical records were accurately coded in physician service claims data. Another study (16) from the United Kingdom found moderate

agreement between administrative database-identified COPD patients and their medical records. Lacasse et al (13) did question the validity of using administrative data to identify COPD cases but used as their gold standard the self-report prevalence data from the National Population Health Survey, in itself a source which has not been validated against medical records. Their prevalence estimate was also based on a less stringent case definition that required only one contact for COPD within the 5 year period.

Our estimates were different than those recently reported by Health Canada using survey data (17). Their survey estimated prevalence by asking a random, population-based sample if they had COPD as diagnosed by a physician. Their 2005 prevalence estimate for women 45 years and older was 5.7% while their estimate for men 45 years and older was 4.9%. It has been suggested that gender bias in the diagnosis of COPD could occur (18) and this bias could result in a lower estimate of prevalence for women. However, if this bias did occur in our sample we would also expect that it could be detected in the self-report data on health professional-diagnosed COPD, yet women had a higher prevalence of COPD compared to men in the Health Canada estimates. Whether differences in self-report behaviours between men and women result in different prevalent estimates is unknown.

Our prevalence estimates are much lower than those estimated from studies using randomly-sampled, population-based lung function measurement. In the United States, the 1988-1994 prevalence of COPD as measured by lung function was 7.4% and 5.8% for moderate disease for men and women, respectively (2). In Canada, results of the Burden of Lung Disease (BOLD) study (19) estimate that

19.3% of those 40 years of age and older and living in Vancouver, B.C. had airflow obstruction consistent with COPD. Even when the diagnosis was limited to GOLD Stage 2 or greater (likely signifying clinically significant disease) the prevalence of COPD was 8.2% -- a much higher prevalence than in our study. The reasons why administrative health data estimates of COPD prevalence are much lower than population-based studies are not clear. It is possible that symptoms do not begin and diagnosis is not made until the disease reaches GOLD Stage 3 or 4. An additional factor may be that COPD is underdiagnosed or coded at either the general practitioner or hospital level. Recent data from other jurisdictions support the latter hypothesis as it has been suggested that as many as 75% of Europeans and 50% of Americans with COPD are undiagnosed (20).

Our mortality data differ from those recently released by Health Canada (17) in that we report all-cause mortality of individuals previously coded for COPD, whereas the Health Canada data reported mortality rates of death thought to be due to COPD itself. Nevertheless, our results show a trend of decreasing age-standardized mortality rates from 1992/1993 to 2000/2001, and then a stable mortality rate from 2001 onward for both men and women with COPD, whereas Health Canada reported an increase for women older than 80 years and an increase followed by a decrease for men over 80 years over a similar time period. As we used all-cause mortality data, decreasing trends in mortality in our COPD patients could be due to decreasing trends in mortality in other causes of death, such as cardiovascular disease, or decreased exposure to risk factors, such as cigarette

smoking. However, there was no similar trend of decreasing mortality in the non-COPD group over the same time period (data not shown).

It was surprising that the COPD versus non-COPD risk for all-cause mortality was higher in women than in men for several age groups. Why men would have a higher risk than women in the younger age groups (45-49 years, 50-54 years) and women would show the higher risk in the older age groups up to 75-79 years is unclear. Of note, the onset of menopause has been linked to more rapid decline in lung function in female COPD patients who continue to smoke (6). Whether such an effect would result in increased mortality in women with COPD is unknown, but our data highlight the importance of measuring mortality in men and women by age group in addition to reporting aggregate results.

We found that including ICD-9 490 (bronchitis, not specified as acute or chronic) had a substantial effect on estimates of COPD prevalence, nearly doubling it in our cohort. However, these individuals coded with ICD-9 490 may not have COPD as only 11% of individuals coded solely with ICD-9 490 were on COPD medications. However, COPD cannot be ruled out in this group, which had an even lower prevalence of lung function testing than the COPD patients coded with ICD-9 491, 492 or 496. Although it seems likely that these individuals do not yet have clinically significant COPD, they may represent an 'early' COPD group, i.e. it is possible that these individuals may have chronic bronchitis but may or may not have airflow obstruction. Since lung function testing was rarely performed, it is difficult to ascertain whether they have COPD. As chronic cough is also a feature of asthma, this may also represent an untreated asthma group.

The inclusion of ICD-9 490 had a large impact on the gender differences in prevalence of COPD in the younger age groups, where the prevalence of COPD in women was much higher than that of men. Whether these younger women who have repeated episodes of bronchitis (at least 2 doctor's visits for bronchitis within 1 year) represent the beginning of the 'female COPD epidemic' is unknown, but longitudinal studies on the outcomes of this group could provide valuable information on this issue. Specifically, further investigation on the concurrent diagnosis of asthma, the use of respiratory medications over time (including antibiotics), health care utilization and hospitalization rates would help determine if these individuals have clinically significant disease.

Only 55% of the COPD population had lung function testing over the 10 year period. Our results reflect outpatient lung function testing only, as administrative health services data from BC does not capture bedside spirometry which may occur during a hospital admission. However, it is recommended that spirometry to confirm a diagnosis of COPD should be done when the patient is stable with no recent history of an exacerbation (21). Therefore, we would expect that the majority of lung function testing associated with good clinical practice, including during the diagnostic period, would occur on an outpatient basis. Similarly, less than half of our COPD population had filled prescriptions for COPD-related medications. This may reflect mild disease severity in this population, or be due to poor adherence to COPD guidelines. Although we do not have data on disease severity, we can assume that on an individual basis the disease had progressed to the point of the patient experiencing symptoms which necessitated a physician visit. It is possible that

COPD is undertreated. Foster et al (22) found that only 25% of American primary care physicians reported using guidelines to aid decision-making in treating COPD, and of those, only 50% would use long-acting bronchodilators to treat persistent dyspnea. Similarly, in a 2003 Japanese study Takahashi et al (23) reported that 31% of COPD patients with moderate to severe COPD did not receive any clinical intervention. Clearly this is an area which bears further investigation.

In this study we estimated prevalence by calculating the cumulative incidence of COPD for each year from 1992/1993 to 2003/2004. A patient remained in the COPD database even if the physician subsequently changed the diagnosis. This accumulation of false positives would overestimate prevalence and also could explain the increase in prevalence we measured over the study time period. Conversely, it is likely that our estimates have also included individuals with predominantly symptomatic moderate and severe COPD but have not captured the milder cases, which could underestimate prevalence. In addition, our relatively short observation period (~10 years) could have limited our ability to detect gender differences in the epidemiology of COPD.

2.5 CONCLUSION

We utilized data from large administrative health databases to describe the gender differences in COPD prevalence, mortality, lung function testing and the use of medication. We did not see strong evidence of a rapid increase in prevalence or mortality from COPD in women over the period 1992/1993 to 2003/2004. Similar

proportions of male and female COPD patients underwent lung function testing and had filled prescriptions for COPD medications. Finally, the reversal of male versus female prevalence in the younger age group when ICD-9 490 was included in the case definition brings up the possibility that this group of younger individuals with 'bronchitis' may represent early COPD. Further studies of these individuals, including patterns of health care utilization, may better characterize this group.

Table 2-1. International Classification of Disease (ICD) Codes Used in COPD Case Definition

ICD-9 Description	Code	ICD-10 Description	Code
Chronic bronchitis	491	Simple and mucopurulent chronic bronchitis	J41
Emphysema	492	Unspecified chronic bronchitis	J42
Chronic airways obstruction, not elsewhere classified	496	Emphysema	J43
		Other chronic obstructive pulmonary disease	J44

Table 2-2. COPD Medication Categories

Medication Category
• Bronchodilators – solution • Bronchodilator – short-acting inhaler • Bronchodilator – long acting inhaler • Bronchodilator – oral • Anti-cholinergics – short-acting inhaler • Anti-cholinergics – short-acting solution • Anti-cholinergics – long-acting inhaler • Bronchodilator/Anti-cholinergic combination therapy inhaler • Leukotriene receptor agonists • Corticosteroids – inhaler • Corticosteroids – solution • Bronchodilator/corticosteroid combination therapy inhaler

Table 2-3. ICD-9 490 Analysis (Bronchitis, not Specified as Acute or Chronic)

	COPD Prevalence: ICD-9 491, 492, 496		COPD Prevalence: ICD-9 491, 492, 496 AND 490	
	Male	**Female**	**Male**	**Female**
Prevalence - All Ages	4.7 %	4.0 %	9.5 %	10.5 %
Prevalence - Age 65 years and older	10.8 %	7.9 %	16.3 %	15.1 %
Prevalence - Age 45-64 years	1.9 %	1.6 %	6.3 %	7.8 %
	Subgroup: ICD-9 491, 492, 496 ONLY		**Subgroup: ICD-9 490 ONLY**	
COPD Medication Use	45%		11%	
Lung Function Testing	55%		23%	

Definition of Abbreviations: ICD=International Classification of Diseases

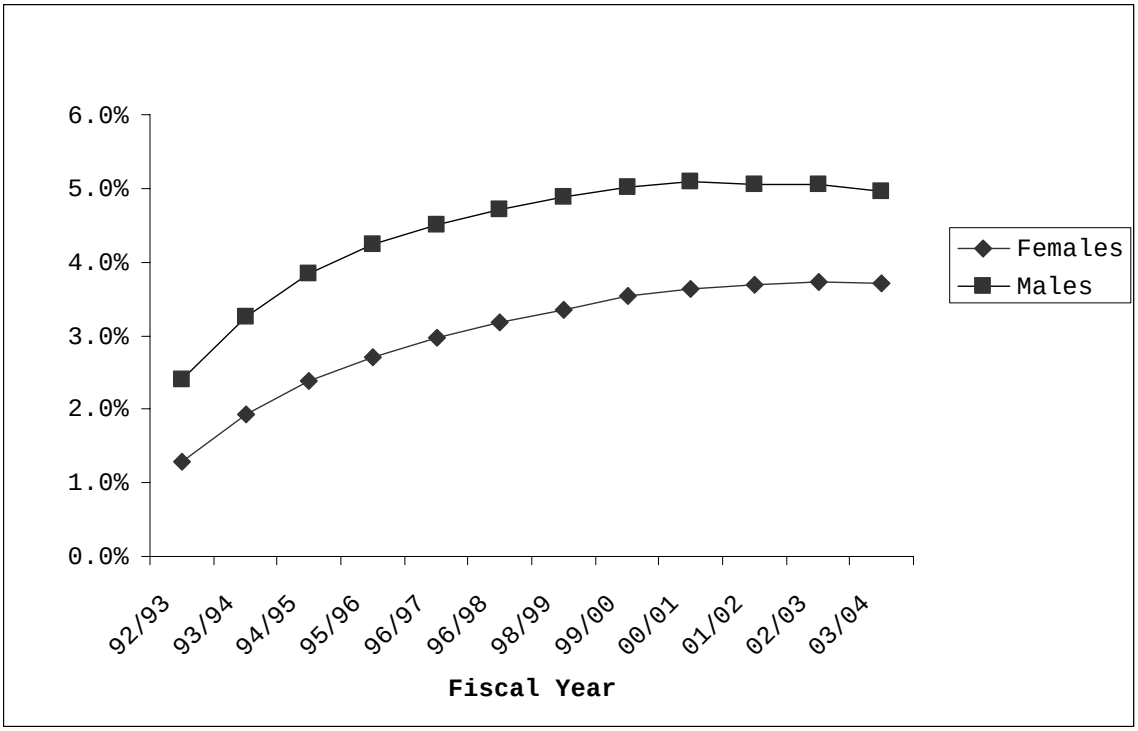

Figure 2-1. Age-Standardized Prevalence of COPD by Gender, 1992/93 to 2003/04

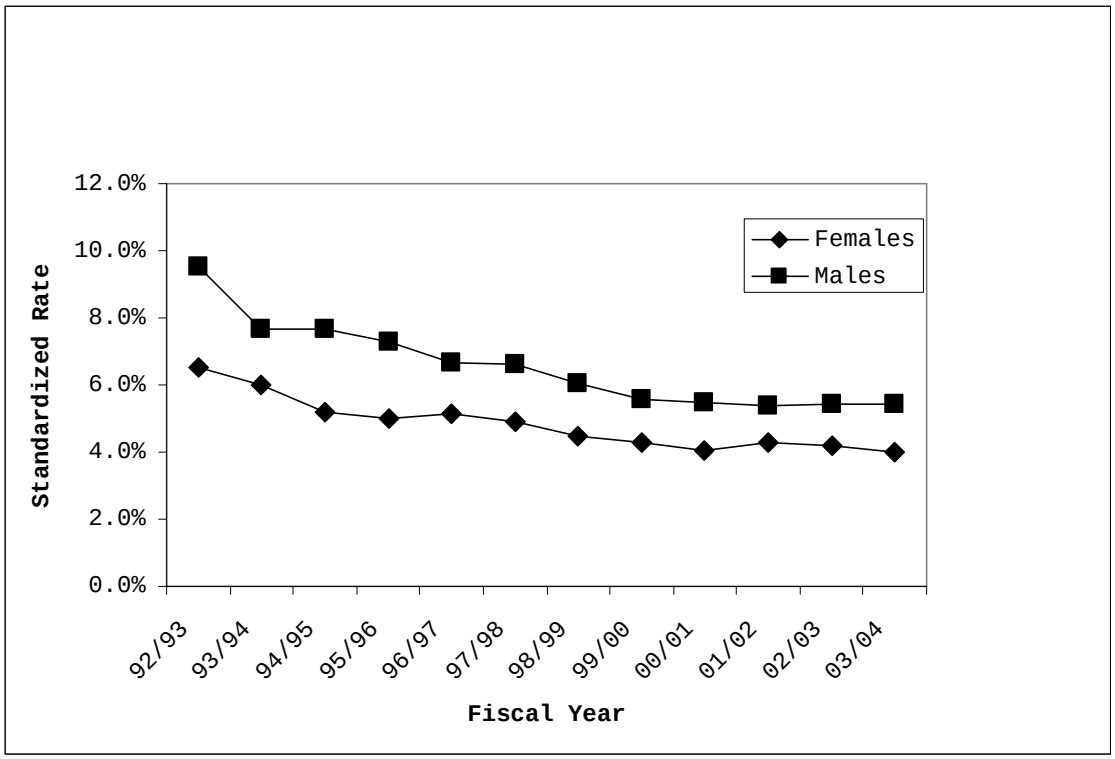

Figure 2-2. Age-Standardized All-Cause Mortality of COPD by Gender, 1992/93 to 2003/2004

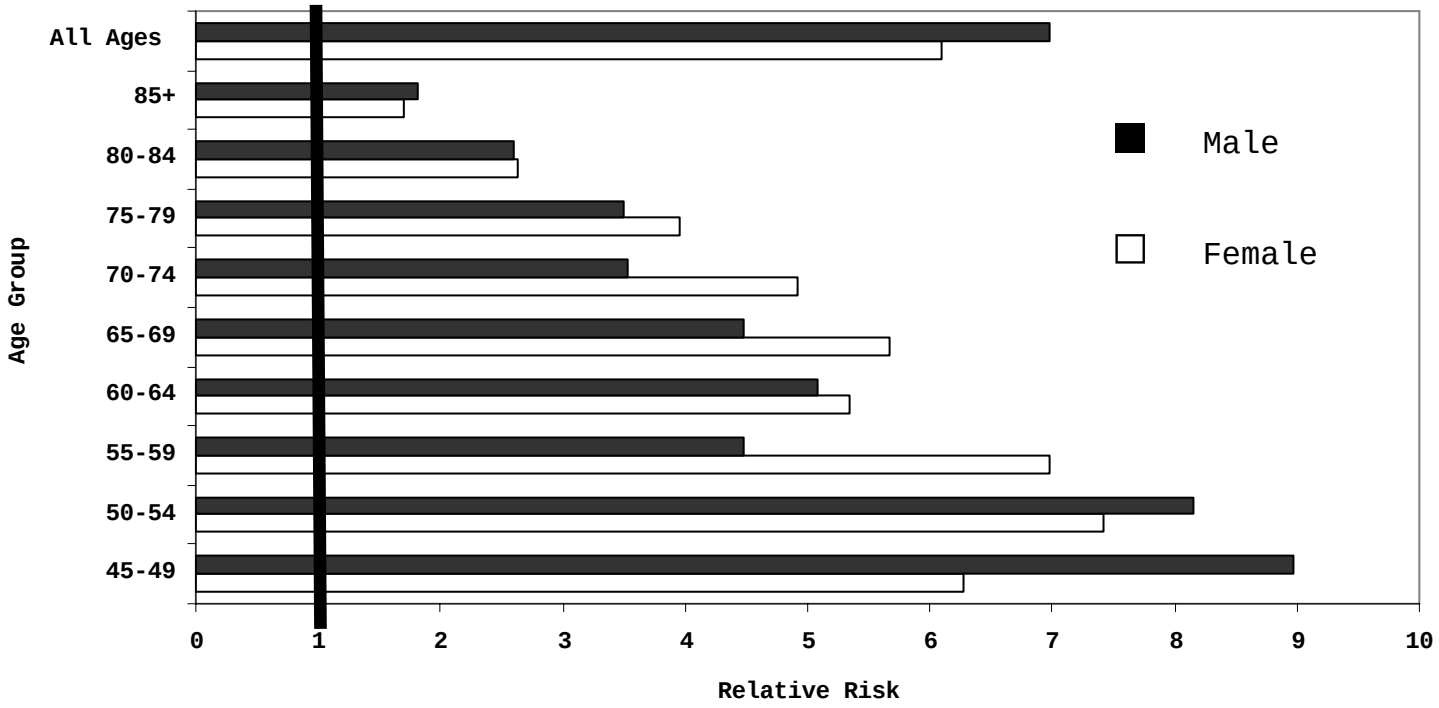

Figure 2-3. Risk of All-cause Mortality for COPD Individuals Compared to non-COPD Individuals, by Gender, 2003/2004

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CHAPTER THREE. SEX DIFFERENCES IN EMPHYSEMA AND AIRWAY DISEASE IN SMOKERS[1]

3.1 INTRODUCTION

Although COPD has long been considered a man's disease, there has been a dramatic increase in COPD prevalence and mortality in women over the last 20 years (1). This increase has been largely attributed to an increase in the prevalence of smoking among women over the last 50 years. However, recent reports have suggested that women may be more susceptible to cigarette smoke and more likely to develop early-onset COPD (2-4), although not all studies have reached this conclusion (5, 6).

Many studies have relied on spirometric measures, such as forced expiratory volume in the first second (FEV_1) or the ratio of FEV_1 to forced vital capacity (FEV_1/FVC), when investigating sex differences in COPD. These decreases in expiratory flow which characterize, and define, COPD can occur because of one, or a combination of the pathological processes which underlie COPD; emphysematous destruction of the lung parenchyma and remodeling and narrowing of the conducting airways. Sex differences in susceptibility to cigarette smoke could be due to relative differences in the development of these phenotypes.

[1] A version of this chapter will be submitted for publication:
Camp PG, Coxson HO, Muller NL, Levy RD, Pillai S, Vestbo J, Kennedy SM, Silverman EK, Lomas DA, Pare PD, on behalf of the International COPD Genetics Network (ICGN). Sex differences in emphysema and airway disease in smokers.

Historically, emphysema has been reported to be more prevalent in men than women. A 1974 autopsy study by Thurlbeck (7) found that men had more emphysema than women, and this finding was similar in both non-smokers and heavy smokers. However, the investigators were not able to adjust for pack years or occupational risk factors so it is possible that the increased emphysema in men was related to these unmeasured exposures.

Data from the Lung Health Study (4) show that women with mild COPD have a greater prevalence of airway hyperresponsiveness (AHR) than men. The authors concluded that the increased prevalence of AHR in women is related to their smaller airway caliber; when combined with airway wall inflammation and/or secretions in the airway lumen, the smaller airways cause a greater increase in airway resistance and risk for AHR.

More recently, two studies that utilized high resolution computed tomography (HRCT) scans have reported sex differences in COPD phenotypes. Martinez et al (8) and Dransfield et al (9) found that men had a greater severity of emphysema compared to women. In the Martinez study, which analyzed data from the National Emphysema Treatment Trial (NETT), men had significantly larger emphysematous spaces on HRCT scans compared to women, whereas on histology, women had disproportionately thicker airway walls. Women were also more likely to report dyspnea for a given emphysema severity, level of lung function and smoking history.

Since the NETT subjects were selected for lung volume reduction surgery and therefore were required to exhibit severe, upper lobe predominant emphysema, it is difficult to extrapolate these sex differences to the COPD population at large. In

addition, in the small sub-sample in which airway dimensions were assessed the measurements were confined to the airways in the resected tissue which represents the areas most severely affected by emphysema. It is not known if similar sex differences are present in individuals with less severe COPD or with more homogeneous emphysema. Similarly unknown is whether sex differences in airway dimensions exist in areas of lung less severely affected by emphysema.

To address these issues, we analyzed emphysema and airway wall measurements obtained from HRCT scans in a large sample of male and female smokers with a wide range of disease severity (Global Obstructive Lung Disease (GOLD) (10) classification levels 0-4 (Appendix 1)). We hypothesized that on HRCT, male smokers would exhibit more emphysema and female smokers would have thicker airway walls after adjusting for confounders. In addition we expected that women would report greater dyspnea after adjusting for lung function, emphysema and airway measurements.

3.2 METHODS

3.2.1 Subject Selection

We analyzed data from the participants in the GlaxoSmithKline International COPD Genetics Network (11), a multi-centre study designed to investigate genetic susceptibility for COPD. This study recruited individuals (probands) with relatively early-onset severe COPD (defined as post-bronchodilator FEV_1 < 60% predicted, FEV_1/VC (vital capacity) < 90% predicted, and age 45-65 years) and a minimum 5

pack-year smoking history. Siblings of these COPD patients who had a minimum 5 pack-year smoking history were also recruited. We excluded individuals with alpha-1 antitrypsin deficiency and other chronic pulmonary diseases such as tuberculosis. Ten sites participated in this study (four in North American, two in Great Britain, and four in Continental Europe). All subjects provided written, informed consent and the study was approved by the ethics review board at each study centre.

3.2.2 Pulmonary Function and Epidemiological Data

Each subject participated in a structured interview administered by trained research assistants. Spirometry was conducted pre- and post-bronchodilator (salbutamol 180 µg administered via an Aerochamber® spacer) using a SurveyTach™ portable spirometer (WE Collins, Braintree, MD) by trained personnel in accordance with American Thoracic Society standards (12). A minimum of three recordings were made and the higher of the slow or forced VC, as well as the FEV_1, were expressed as a percentage of predicted values (13). Information on symptoms, medical history, and smoking exposure was collected using the modified version of the American Thoracic Society/Division of Lung Diseases (ATS/DLD) Respiratory Epidemiology Questionnaire (14). Questions on breathlessness were translated into a Medical Research Council Dyspnea Scale (15) score as per the algorithm in Table 3-1.

3.2.3 HRCT Scans

All subjects were asked if they were willing to receive a HRCT scan as part of the study. Subjects were not excluded from the overall study if they refused the scan and were under no obligation to participate in this aspect of the study. If there was a scan that was acquired for other reasons within the last 2 years these scans were obtained for analysis. The scans were acquired at suspended full inspiration (apex to base) using 1 or 1.25 mm slice thickness, a 20 mm gap and the smallest field of view that included both lungs. Scans were performed on General Electric or Siemens scanners in order to provide comparable data for analysis. Six sites had General Electric or Siemens scanners and suitable numbers of men and women to allow for statistical comparisons. The images were reconstructed using a high spatial frequency reconstruction algorithm and saved in the DICOM 3.0 format. The images were then archived onto optical media and transferred to the James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research (Vancouver General Hospital site, Vancouver, Canada). Scans were analyzed using a custom software package (Emphylx-J, James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research, Vancouver, Canada).

Emphysema measurements are based on estimates of lung density, which are affected by the amount of air in the lungs. A poor maximal inspiratory effort may underestimate emphysema on HRCT. In addition, a maximal inspiratory effort is needed to ensure full airway opening and accurate airway measurement. Although all sites followed a standardized scanning protocol, it is possible that some subjects did not follow instructions precisely. To exclude individuals who obviously did not

take an adequate inspiration during HRCT scanning we excluded scans (n=64) for analysis of parenchyma and airways on which the air volume on HRCT was less than 54% of the predicted total lung capacity (TLC) for that subject (AirVolumeHRCT/predicted TLC). Predicted values for TLC were based on recommended reference equations from the European Respiratory Society and American Thoracic Society (16). Fifty-four percent is the average value for predicted functional residual capacity as a percent of predicted total lung capacity.

Quantitative analysis of the lung parenchyma was performed using a previously described technique (17, 18). The lung parenchyma was segmented from the chest wall and large central blood vessels using a contour-following algorithm. Emphysema was measured using a 'density mask' cut-off of -950 Hounsfield units (HU), which is appropriate for this CT acquisition technique (19) and defined as the % low attenuation area (%LAA). We also calculated the fractal value, the inverse slope of the log-log relationship between the number and the size of the emphysematous spaces. A smaller fractal value indicates larger low attenuation spaces.

All airways that were cut in cross section were measured in all of the slices of the HRCT scans. This was performed by an operator who examined all the images and identified airways. When an airway was identified the computer mouse was used to mark a seed point in the lumen and 64 rays were projected out from this seed point 360^{o} around the airway. The X-ray attenuation was measured along each of the rays and the airway wall was defined using the full-width-at-half-maximal principle (20). The airway lumen (Pi) and outer airway wall perimeter (Po) were

measured by connecting the end points of each of the rays through the airway wall using a spline function. The lumen area (Ai) was defined as the area inside the internal perimeter. The total area of the airway (Ao) was defined as the area inside the outer perimeter. The airway wall area (Aaw) was defined as the area between these two perimeters and the wall area percent ((Aaw / Ao) x 100) which indicates the proportion of the total airway area that is taken up by the airway wall, was calculated.

Wall area and wall area percent (WA%) are directly and inversely related to the size of the airway respectively. Wall area is greater in larger airways, while WA% decreases as airway size increases (21). There are various methods to estimate airway wall thickness. By plotting the Pi of each airway against the square root of wall area for each individual subject, a linear regression equation can be derived (22). Using this equation, the square root of the wall area at a standard Pi (e.g. 10 or 20 mm) can be calculated for each subject. Calculating the square root of the wall area at Pi of 10mm (SQRTWA@Pi10) allows for the comparison of overall airway wall thickness between subjects while accounting for the different airway sizes measured in each subject. One limitation of this method is that all the airway measurements are condensed into one summary measure of wall thickness. Individuals with heterogeneous airway disease and more variation in SQRTWA for a given Pi may have a less accurate estimate of SQRTWA@Pi10 than individuals with a stronger linear relationship between SQRTWA and Pi. We used an alternate method that compares the SQRTWA and the WA% between men and women using all the airways measured, statistically adjusting for the intrasubject variability, airway

size, and other covariates, as described by Bosken et al (23). Instead of using one summary airway measure, such as SQRTWA@Pi10 for each subject, this method includes all the airways in a mixed regression model, and uses an individual identifier for each subject as a random variable to account for the clustering of individual airway sizes within the individual.

Although previous studies (24) have reported errors in measuring small airways which have a lumen perimeter less than 6mm on CT scan, systematically excluding small airways could bias the data against women, who have a greater proportion of their airways below this cut-off. We therefore performed the airway analyses with and without airways with an internal perimeter < 6mm.

3.2.4 Data Analysis

We chose the sibling group who had measurements of lung function (Main Group; n=1931) to test for sex differences in lung function, since this group was not selected for any spirometric criteria and therefore better represented a random sample of genetically-susceptible smokers. To test for differences in parenchymal or airways measurements, we included the entire sample of probands and siblings who had acceptable CT scans (CT Group; n=688). Creation of the Main Group and the CT group for analysis is illustrated in Figure 3-1a & b.

Continuous data and categorical data were compared using *t*-tests and chi-square tests, respectively. Multivariable linear regression models (PROC MIXED, SAS Version 9.1, SAS Institute, Cary, North Carolina) were used to test the relationships between sex and FEV_1 % predicted, %LAA and airway wall

measurements. Generalized estimating equations (PROC GENMOD, SAS Version 9.1) were used to test the relationship between sex and the presence of airflow obstruction, using both a cut-off of $FEV_1/FVC < 0.70$ as per GOLD criteria (10), or FEV_1/FVC less than the predicted lower limit of normal (LLN). The equations for the LLN of FEV_1/FVC are based on the 5^{th} percentile of the distribution of FEV_1/FVC from healthy, non-symptomatic, never-smoking participants in the National Health and Nutrition Examination Survey III (25), and take into account the normal loss of FEV_1 as a proportion of FVC that occurs with aging. PROC MIXED and PROC GENMOD are mixed models utilizing both random and fixed effects. 'Family membership' was considered a random effect in all mixed models to account for the potential clustering of data within families. Potential confounders were age, pack-years, smoking status (current smokers versus ex-smokers), height, weight (or body mass index (BMI)), and center of recruitment.

The number and size of the measured airways differed among subjects. Subjects had as few as 3 or as many as 100 airways measured (688 subjects = 18,177 airways measured; median number of airways measured = 24). As previously stated, airway wall measurements are dependent on the size of the airway measured, with airway measurements clustered within each individual. We used PROC MIXED (SAS Version 9.1) to compare wall area % and SQRTWA between men and women, and included "individual" as an additional random effect in the model to account for the clustering of airway measurements within each subject. Potential confounders were lumen perimeter, age, pack-years, smoking

status (current smokers versus ex-smokers), height, weight (or body mass index (BMI)), and center of recruitment.

3.3 RESULTS

3.3.1 Subject Characteristics

Three thousand and forty-three individuals were recruited across ten sites and had complete pulmonary function, questionnaire and smoking history data. Of these, 1112 were probands, and 1931 were siblings. These 1931 subjects were the sample group used for examining sex differences in lung function (Main Group). In this Main Group, men and women were similar in age and BMI. Women had fewer pack years, yet a greater proportion of women continued to smoke compared to men (Table 3-2).

3.3.2 Pulmonary Function

Compared to males, female subjects had a greater post-bronchodilator FEV_1 % predicted and FVC % predicted but a similar post-bronchodilator FEV_1/FVC. The distribution among GOLD groups was similar for men and women. After adjusting for age, pack years, smoking status, height and weight (or BMI) and center of recruitment women continued to have a marginally greater FEV_1 % predicted (difference in mean FEV_1 % predicted = 2.97%; 95% confidence interval (CI) 0.02, 5.92; p = 0.05). There was no difference between men and women in the likelihood of having a post-bronchodilator $FEV_1/FVC < 0.70$ after adjusting for age, pack years,

smoking status, height and weight (or BMI) and center of recruitment. Women were more likely than men to have an $FEV_1/FVC < LLN$ when BMI was entered into the model (odds ratio 1.31; CI 1.07, 1.60; p = 0.0088) but this difference was no longer significant when height and weight instead of BMI were in the model (odds ratio 1.18; CI 0.90, 1.56; p = 0.23), suggesting an interaction between sex, weight and/or height on the likelihood of having $FEV_1/FVC < LLN$.

3.3.3 Emphysema Assessment

A total of 1270 individuals had available scans, 1044 of which were digital scans. 752 of those individuals had spirometric, anthropometric, and smoking history data with complete HRCT measurements from either a General Electric or Siemens scanner, and enough men and women to allow for statistical comparisons. Of those, 688 individuals had an adequate inspiration during HRCT as judged by having a CT air volume greater than 54% of predicted TLC. The mean post-bronchodilator FEV_1 % predicted and mean FEV_1/FVC was lower and the number of pack years was slightly more in the CT Group than in the Main Group for both men and women; otherwise the CT group was similar to the Main Group in age and anthropometric measurements (Table 3-3). Sixty-four individuals were not included in the CT Group due to having a HRCT air volume/predicted TLC ratio < 0.54, i.e. there was a poor inspiratory effort on CT. We compared the characteristics of this group with the CT Group. Individuals with a poor inspiratory effort on CT were younger, with fewer pack years and a greater FEV_1 % predicted and FEV_1/FVC (Table 3-4). They were also more likely to be heavier and taller with a larger BMI

than the CT scan group. There were no differences in the proportion of women between the two groups.

The percentage of emphysema, measured as % LAA, was lower in women compared to men (Table 3-3) and this difference persisted after adjusting for age, pack years, current smoker status, BMI, post-bronchodilator FEV_1 % predicted and center (Table 3-5 – Model 1). Decreased BMI, and specifically decreased weight (Table 3-5 – Model 2), was also associated with increased emphysema. Separate multivariable analyses by sex showed a strong association between weight and % LAA for men (coefficient for weight -0.095; p=0.0037) whereas there was no relationship between weight and %LAA in women (coefficient for weight -0.048; p=0.09).

Measurements of the fractal value were available for 92% of the CT group. Women had a larger fractal value than men, indicating smaller emphysematous spaces (Table 3-3). This difference remained when adjusting for FEV_1 % predicted, but there were no differences between men and women in fractal value when the model was adjusted for %LAA (Table 3-6).

3.3.4 Airways Measurement

The WA % and the SQRTWA of the airways were smaller in women than in men (Table 3-3). These differences persisted after adjusting for lumen perimeter, age, pack years, current smoking status, BMI, FEV_1 % predicted and center (Table 3-7 and Table 3-8). Limiting the sample to only those airways with a lumen perimeter greater than 6mm yielded similar results (Table 3-9 and Table 3-10).

Increased weight was associated with a larger WA% and SQRTWA after adjusting for other covariates (Tables 3-7 and 3-8 - Model 2). Increased weight, especially abdominal obesity, could negatively affect an individual's ability to perform a maximal inspiration while supine and may result in an overestimation of airway wall measurements. We therefore repeated the analysis and entered into the model the ratio AirVolumeCT/predicted TLC which is an approximation for level of inspiration during the scan. In the CT subgroup, weight was a significant predictor of the Air Volume CT / predicted TLC ratio, after adjusting for family clustering (AirVolumeCT/predicted TLC = 1.0335 – 0.00311*(kg); $p<0.0001$). However, adjusting for level of inspiration did not affect the differences by sex in airway wall measurements nor did it impact the effect of weight on airway wall thickness (Table 3-11 and Table 3-12).

3.3.5 Dyspnea

We confined the dyspnea analysis to the CT subgroup in order to allow for adjustment by %LAA or airway wall thickness. There were 34 individuals (17 men, 17 women) who reported difficulty with walking due to a non-respiratory condition and did not answer questions about dyspnea. Of the 654 individuals remaining, 45% of the men and 53% of the women reported an MRC dyspnea scale of 3 or more (MRC Dyspnea Level 3 = 'walks slower than contemporaries on the level because of breathlessness, or has to stop for breath when walking at own pace') (Figure 3-2).

Women were more than twice as likely to report worse dyspnea compared to men after adjusting for age, pack years, current smoker status, BMI and FEV_1 % predicted (odds ratio 2.05; CI 1.47, 2.84; $p < 0.0001$) (Table 3-13). Yet when height and weight replaced BMI in the model, there was no longer a significant relationship between sex and dyspnea. An increase in height was protective against worsening dyspnea (odds ratio for increased dyspnea 0.95; CI 0.93, 0.98; p=0.0002 for each 1 cm increase in height). This pattern was repeated when % LAA and SQRTWA was used instead of FEV_1 % predicted; women reported significantly greater dyspnea when BMI, but not height and weight, was included in the model (Table 3-14 and Table 3-15). Interaction terms for height and sex or weight and sex were not significant.

3.4 DISCUSSION

This secondary analysis of a large cohort of men and women smokers who had a wide range of lung function (GOLD 0-4) was designed to test for differences between men and women in clinical and pathological phenotypes of COPD. For a given age, smoking history and smoking status, FEV_1 % predicted and anthropometric measures, men were more likely to have CT features of emphysema, whereas women were more likely to report dyspnea. Women did not have increased airway wall thickness compared to men, but we did see a strong independent influence of weight and height on wall area percent and SQRTWA.

Airway wall and parenchymal measurements derived from CT scans have been correlated with physiological and clinical findings, including lung function and

symptoms, in several studies. Unfortunately, none of these studies have reported differences between men and women or were designed to allow comparison between men and women of COPD phenotypes. Nakano et al (26) recruited men exclusively, while Fujimoto et al did not report their findings by sex (27). In additional studies there were too few men and women to allow for an appropriate statistical comparison (17, 20, 28). To our knowledge, this study represents the first analysis of both airway wall and parenchymal measurements on HRCT in a sample that included a large number of women (n=300+) over a wide range of disease severity (GOLD 0-4).

3.4.1 Sex Differences in Emphysema on HRCT

Men had a greater %LAA and larger emphysematous spaces after adjusting for age, pack years, smoking status, height, weight, and FEV_1 % predicted. For a given %LAA, however, there was no difference between men and women in the size of the emphysematous lesions. This finding is in agreement with previous studies which have reported increased emphysema in men. Martinez et al (8) reported that after adjusting for FEV_1 % predicted, men had an increased %LAA and larger emphysematous spaces compared to women. They did not compare the fractal value in men in women for a given severity of emphysema. In their study, the difference in %LAA was attributed to a significantly greater proportion of emphysema in the ‘peel’ or outer areas of the lung parenchyma in men whereas men and women had similar %LAA in the ‘core’ areas of the lung. Despite the less severe emphysema on HRCT, women had a lower diffusing capacity. The authors

hypothesized that the regional differences in emphysema contributed to the lower diffusing capacity measured in women. This conclusion was based on the study of Nakano et al (26) who reported a relationship between impaired diffusing capacity and the amount of emphysema in the 'core' of the lung; however, that study did not include women. Dransfield et al (9) analyzed CT data from approximately 400 heavy smokers ($\geq$ 30 pack years) enrolled in large, multi-centre lung cancer screening study. They reported that for all GOLD stages of COPD and in each of the upper, middle and lower regions of the lung, men had more CT emphysema than women. Subjects in GOLD stages 3/4 showed the greatest absolute difference between men and women (15.8% LAA vs. 8.7% LAA respectively; p=0.024).

It is not clear why sex should influence the phenotypic expression of COPD. One possible explanation for why male smokers have an increased %LAA is that even in the healthy lung, there are differences in tissue density between men and women. Dransfield's study (9) lends some support to this hypothesis. Men in GOLD Stage 0 had a significantly greater %LAA than women. However, the subjects in this study had a very high smoking exposure (mean for men 46$\pm$19 pack years; mean for women 37$\pm$20 pack years) so although this group had normal lung function, parenchymal destruction cannot be ruled out. Conversely, in a small study (n=42) containing equal numbers of male and female lifelong non-smokers between the ages 23 and 71 years, Gevenois et al (29) found no difference in either lung density or %LAA between men and women; they did note that increasing age was associated with a increased %LAA. Another possible explanation for the increased %LAA in men is that the process which results in a progressive loss of lung density

during normal aging is accelerated in men. This question was investigated by Gillooly and Lamb (30) in a small sample (15 men, 23 women) of healthy non-smokers aged 21 to 93 years. Using histological sections, they examined the relationship between airspace surface area per unit volume of lung tissue (SA/V) and age. They found that men and women had a similar negative linear relationship between SA/V and age. However, the small sample sizes of these studies may have limited the power to detect subtle differences between men and women; sex differences in baseline lung density or rate of decline cannot be ruled out.

Increased emphysema, as reflected by the greater %LAA in men could be related to their larger airway size and/or differences in smoking behavior between the sexes. Men have larger airways than women, and it is possible that tobacco smoke particles are able to penetrate deeper into their tracheo-bronchial tree so that more reach the alveolar surface whereas there may be greater deposition of particles in the airways of women. There is some support for this hypothesis; Segal et al (31) simulated particle deposition using models of the airway dimensions from healthy individuals and subjects who have chronic bronchitis or emphysema. They found that airway deposition was greatest in the chronic bronchitis model, whereas in the absence of airway constriction, deposition of particles was predicted to occur mainly in the respiratory bronchioles and alveolar regions. However, a direct comparison of particle deposition in male versus female lungs, in healthy individuals and those with COPD, has not been conducted. Differences in smoking behavior could also lead to different COPD phenotypes. 'Pack years' is a standard measure of cigarette smoke exposure but it does not reflect the other potentially important

components of smoking behavior. These include: age of onset, intensity of smoking habit (i.e. does the exposure from 1 pack smoked per day for 40 years equal the exposure from 2 packs smoked per day for 20 years?), depth of inhalation, length of time to smoke a cigarette, and type of cigarette (including length, brand, tar level, use of filter, use of additives such as menthol). Although it has been suggested that women take more puffs per cigarette, with a shorter interval between puffs (32), gender differences in smoking behavior has not been adequately investigated.

Reduced BMI, and specifically weight, was associated with an increase in %LAA. Decreased weight is a well-recognized clinical feature of COPD in general and of severe emphysema in particular. Fujimoto et al (27) categorized a sample of 172 men and women with COPD into three groups: emphysema-dominant, emphysema plus bronchial wall thickening, and no emphysema and found that subjects in the emphysema groups had a lower BMI than in the no-emphysema group. Similarly, Makita et al (33) reported that the BMI of 45 patients who had severe emphysema and 124 who had moderate emphysema was significantly lower than the BMI of COPD patients without emphysema.

It is possible that weight affects the technical measurement of %LAA. Increased adipose tissue in the chest wall could decrease the radiation dose reaching the lungs and may affect the measurement of emphysema. However, Yuan et al (34) demonstrated that a lower lung dose of radiation (which may occur in obese individuals) causes increased noise on the HRCT, widening the distribution frequency of HU leading to an overestimate of %LAA. Therefore it seems unlikely that our finding of increased %LAA associated with lower body weight is a result of

measurement artefact in overweight individuals. Our study was not designed to determine the direction of this association; low BMI could contribute to a worsening of emphysema or be a consequence of emphysema.

Interestingly the significant association between weight and %LAA was only present in men. To our knowledge, there have been no studies in which the relationship between weight and emphysema has been compared in men and women. Indeed, most investigations into the complex relationship between weight and COPD have not addressed sex differences. There have been several proposed mechanisms for the decreased weight seen in many COPD patients. An insufficiency of the male hormone, testosterone, has been associated with cachexia in COPD (35) but it is not yet known if reduced testosterone is a cause or an effect of reduced weight, or if reduced testosterone affects men and women with COPD in a similar fashion.

Although systemic inflammation has been proposed as another possible mechanism of cachexia in COPD, more attention has been paid to the relationship between increased body fat and systemic inflammation. Sex differences in this relationship have been reported. Specifically, adiposity has been shown to be more strongly associated with biomarkers of low-grade systemic inflammation in otherwise healthy women versus men (36). Increased body fat has also been associated with asthma in women. McLachlan et al (37) measured body fat percentage, prevalence of asthma, airflow obstruction, and airway inflammation (using exhaled nitric oxide) in a birth cohort of 1000 individuals aged 32 years. They found that in women only, increased body fat was associated with an increased prevalence of

asthma and increased airflow obstruction, whereas for men, decreased body fat was associated with increased airflow obstruction and bronchodilator responsiveness. Airway inflammation was not associated with body fat in either sex, although markers of systemic inflammation were not measured. Further research is needed on sex differences in the relationship between body weight, obesity, cachexia and both emphysema or airway wall remodeling seen in COPD.

3.4.2 Sex Differences in Airway Measurement on HRCT

FEV_1 % predicted was similar in men and women yet %LAA was greater in men. Based on this finding we expected to observe increased airway wall thickness in women. However, women did not have a greater wall area percent or SQRTWA. This finding is in contrast with other studies that have suggested that women with COPD have more airway wall remodeling compared to men. For example, Martinez et al (8) hypothesized that women were more likely to have airway-dominant COPD and reported that on histology, women had a greater total airway wall area as a proportion of lumen perimeter. The increase in wall area was the result of an increase in both epithelial and adventitial layer thicknesses. Tatsumi et al (38) compared the clinical phenotypes in COPD patients who were grouped according to whether they had emphysema-dominant (%LAA > 50) or airway-dominant (%LAA<25) disease. They found that airway-dominant COPD was much less prevalent (10% of sample) than the emphysema-predominant phenotype but women made up 15% of the airway-dominant COPD group and only 7% of the emphysema-dominant COPD group. A similar proportion of women in the airway-dominant

category has been reported in another study (27). Airway dimensions were not measured using HRCT in these previous studies.

The mean lumen perimeter measured in our study was 0.789 cm, which is an airway 0.251 cm or 2.51 mm in diameter. It has been demonstrated that the functionally important site of airway narrowing in COPD is at the level of the peripheral airways <3 mm in diameter (39). Presumably the absolute dimensions of the airways in this critical zone would be different in men and women; a 3mm airway is a more central airway in women compared to men. The limited spatial resolution of CT means that there is censoring at the lower end of the distribution of airway dimensions. More of the critical airways involved in airflow limitation may be censored in women than men. In addition, it is not known whether there are differences in relative airway dimensions of peripheral versus central airways, for a given airway size. If more central airways have a relatively lower airway wall area/lumen area ratio this censoring might be expected to result in artificially lower estimates of wall area% in women. This issue can only be addressed adequately by comparing airway dimensions in men and women at anatomically matched sites within the tracheo-bronchial tree, using volumetric CT and programs which allow three-dimensional reconstruction of the tree.

Conversely, quantitative HRCT tends to overestimate airway wall area measurements, with the greatest error at the level of the smallest airways (24). Although, Nakano et al (20) demonstrated a good correlation (r^2=0.57; p<0.01) between large airway wall measurement on HRCT and small airway wall measurement on histology, due to a small sample they could not determine if sex

influences this correlation. If the peripheral airways are the site of sex differences in airway pathology and the correlation between large and small airways is not the same for women versus men, it is possible that HRCT is not sensitive enough to detect subtle differences between men and women. Indeed, in the histological study of Martinez et al (8) the mean lumen perimeter of the airways that were measured was less than 3mm, and there was only a 4% increase in the ratio of total wall area to lumen perimeter in women compared to men. While this was statistically significant its clinically significance is unknown and this difference may be too small to be detected by HRCT.

Although we did not measure increased airway wall thickness on HRCT in women, we cannot exclude the possibility that, in the absence of increased emphysema, airway wall remodeling plays a strong role in airflow limitation in women. Airway hyperresponsiveness (AHR) as a risk factor for COPD has been the topic of much debate (the so-called 'Dutch' hypothesis). This hypothesis states, in part, that "the development of obstructive lung disease is based on allergy (ie, inflammation) and bronchial hyperresponsiveness, and endogenous (host) factors determined by heredity (genes), but is modulated by exogenous (ie environmental) factors (eg allergens, infections, smoking, pollution, age, and airway geometry)"(40). If women have a greater risk for AHR women smokers may be more likely to develop the airways-dominant phenotype of COPD. Kanner et al (4) noted a higher prevalence of AHR in women with mild COPD, at either a low or high concentration of methacholine. Using logistic regression, they found that women were more likely to have AHR after adjusting for age, pack years, height and weight (relative risk

1.75; CI 1.60, 1.92). This risk was attenuated when FVC or FEV_1/FVC was entered into the model (FVC: relative risk 1.29; CI 1.16, 1.43; FEV_1/FVC: relative risk 1.31; CI 1.18, 1.46) and eliminated when the mean value of FEV_1 was entered into the model (FEV_1: relative risk 1.06; CI 0.96, 1.18). They concluded that the reduction of risk when the absolute (not % predicted) value of FEV_1 was entered into the model confirmed that airway caliber was the factor responsible for the female risk for AHR. A caveat concerning this conclusion is that the study was designed to recruit only subjects who already had mild – moderate COPD. Nevertheless, an increased prevalence of AHR in women has been reported by others (41) and postulated mechanisms have included a hormonal influence on the metabolism of cigarette smoke constituents (42) or on airway behavior over a women's lifespan (43). Based on the evidence from these previous studies, we cannot rule out the hypothesis that women with COPD are predisposed to an airway disease-predominant phenotype.

3.4.3 Dyspnea

We showed greater dyspnea in women compared to men even after controlling for airflow obstruction, severity of emphysema and airway wall thickness. This finding is in agreement with several other studies, which have reported greater dyspnea in women (44-46) for a given level of lung function. This difference remained when BMI was included in a multivariable model, but was eliminated when the model was adjusted for height and weight in place of BMI. Increased height was significantly associated with decreased dyspnea. Martinez et al (8) reported a similar finding – women had greater breathlessness which remained after adjusting

for FEV_1 % predicted and emphysema severity. They found that the difference was attenuated when the model was adjusted for the inspiratory capacity/total lung capacity ratio; they did not specifically examine the influence of height. The results from our study demonstrate that anthropometric characteristics are associated with dyspnea; further research on how height, weight and sex interact to influence dyspnea is necessary.

Physiologically, dyspnea is driven by humoral, neural and musculoskeletal factors (47) but their relative contributions may be different in men and women. de Torres et al (48) compared the influence of multiple respiratory-related factors on dyspnea in men and women with mild to severe COPD. They found that while respiratory factors explained most of the variation in dyspnea levels for men, central respiratory drive (measured as the ratio of mouth occlusion pressure to maximal inspiratory pressure) was the only respiratory factor related to dyspnea in women although it explained only 30% of the variation in dyspnea score.

Our finding that height and weight influence the relationship between sex and dyspnea reinforces the importance of physiological factors. However, dyspnea can also be influenced by behavioral and sociocultural variables. The assessment of dyspnea relies on self-report; consequently the wording of questionnaires and/or their interpretation could also influence sex differences in reports of dyspnea. We used the MRC Dyspnea Scale which describes standardized activities with yes/no responses to measure dyspnea. These activities may require a greater level of work in relation to muscle strength for women, which could account for their increased dyspnea levels. Support for this hypothesis comes from Killian et al (49) who found

that in healthy adults undergoing a maximal cycle ergometry test, increased dyspnea was independently associated with female sex and decreased height for a given power output. However, sex and height influences on dyspnea disappeared when power output was expressed as a percentage of maximal power output.

3.4.4 Limitations

There were several limitations associated with our study. First, our sample was selected based on the proband having moderate to severe COPD at a relatively young age (age 45-65), plus having at least one sibling with a smoking history willing to participate. While our analysis accounted for the potential clustering of variables within families, this population may not reflect the population of COPD as a whole. Second, the cross-sectional nature of this study does not allow us to examine sex differences in the natural history of COPD. It is possible that differences between men and women in COPD phenotypes change as the disease progresses, as smoking status changes, or as women enter or complete menopause. Third, we did not measure other risk factors for COPD that could account for the measured differences in emphysema and dyspnea. Specifically, occupational exposures, repeated respiratory infections, asthma and exposure to second hand smoke have all been implicated in the development or progression of COPD and could impact sex differences in COPD phenotypes.

3.5 CONCLUSION

Our study showed that sex differences exist in COPD phenotypes, with measured differences in the severity of emphysema and the reporting of dyspnea, in a large population of smokers with, or at risk for COPD. We also found that factors related to sex, namely height and weight, had significant independent influences on measurements of emphysema, airway walls and dyspnea. If these anthropometric factors are not accounted for there is the potential to produce false associations of COPD phenotypes with sex. Alternate measurement methods may overcome this problem. Specifically in imaging, volumetric CT scanning has the ability to measure airway wall dimensions at fixed anatomic sites in the tracheo-bronchial tree. This allows the potential to standardize airway wall measurements between men and women. Similarly, optical coherence tomography is a new imaging technique that shows promise in imaging airways < 2mm in diameter (50) and could be instrumental in determining sex differences in airway wall parameters *in vivo* at the primary site of airway remodeling. In dyspnea measurement, questions that consider the relative work of a given activity for women versus men may improve our understanding of how physical characteristics interact with the gendered nature of activity to influence dyspnea. Our study should prompt further investigations on the complex nature of sex determinants and gender influences on the development of emphysema and airway wall remodeling in COPD.

Table 3-1. Algorithm for Converting Questions on Dyspnea from the American Thoracic Society/Division of Lung Diseases Respiratory Epidemiology (ATS) Questionnaire to the Medical Research Council (MRC) Dyspnea Scale

ATS Questionnaire on Breathlessness

Question	
1	Are you disabled from walking by any condition other than heart or lung disease?
2	Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?
3	Do you ever have to walk slower than people of your own age, on level ground, because of breathlessness?
4	Do you ever have to stop for breath when walking at your own pace, on level ground?
5	Do you ever have to stop for breath after walking about 100 yards (or after a few minutes) on level ground?
6	Are you too breathless to leave the house or breathless after dressing or undressing?

MRC Dyspnea Scale

Level	Description
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 the level because of breathlessness, or has to stop for breath when walking at own pace
4	Stops for breath after about 100m or after a few minutes on the level
5	Too breathless to leave the house, or breathless when dressing or undressing

Algorithm for Translating ATS Questions on Dyspnea to MRC Dyspnea Scale Score

ATS Question 1	ATS Question 2	ATS Question 3	ATS Question 4	ATS Question 5	ATS Question 6	MRC Dyspnea Scale Score
Yes						Not measured
No	No	No	No	No	No	1
No	Yes	No	No	No	No	2
No	Yes	Yes	No	No	No	3
No	Yes	Yes	Yes	No	No	3
No	Yes	Yes	Yes	Yes	No	4
No	Yes	Yes	Yes	Yes	Yes	5

Table 3-2. Characteristics of Main Group for Lung Function Analysis (n=1931)

	Female n = 914 Mean (SD)	Male n = 1017 Mean (SD)	*p* value
Demographics			
Age (years)	56.7 (8.9)	57.7 (8.7)	0.007
Weight (kg)	69.4 (18.6)	80.9 (19.7)	<0.0001
Height (cm)	161.6 (6.8)	173.8 (8.0)	<0.0001
BMI (kg/m^2)	26.5 (6.7)	26.8 (6.3)	0.39
Pack Years	34.6 (20.8)	43.0 (27.6)	<0.0001
Currently smoking, n (%)	520 (56.9%)	473 (46.5%)	<0.0001
Post-bronchodilator Pulmonary Function			
FEV_1 (litres)	2.17 (0.77)	2.95 (1.05)	<0.0001
FEV_1 % predicted	85.8 (26.2)	81.5 (26.1)	0.0003
FVC (litres)	3.23 (0.84)	4.50 (1.18)	<0.0001
FVC % predicted	100.3 (27.3)	96.2 (26.6)	0.001
FEV_1/FVC	0.66 (0.14)	0.65 (0.14)	0.013
% with COPD (FEV_1/FVC < 0.70)	51%	57%	0.003
% with COPD (FEV_1/FVC < LLN)	49%	47%	0.29
GOLD Category n (% within gender)			
0 – normal	451 (49%)	434 (43%)	
1	165 (18%)	198 (19%)	
2	209 (23%)	259 (25%)	
3	66 (7%)	86 (8%)	
4	23 (3%)	40 (4%)	

Definition of abbreviations: SD = standard deviation; BMI = body mass index; FEV_1 = forced expiratory volume, 1st second; FVC = forced vital capacity; LLN=lower limit of normal; GOLD = Global Initiative for Obstructive Lung Disease

Table 3-3. Characteristics of CT Subgroup (n = 688)

	Female n = 332 Mean (SD)	Male n = 356 Mean (SD)	*p* value
Demographics			
Age (years)	56.8 (7.4)	58.9 (7.2)	0.0002
Weight (kg)	70.2 (19.0)	84.0 (16.9)	<0.0001
Height (cm)	162.4 (6.8)	175.2 (7.0)	<0.0001
BMI (kg/m^2)	26.6 (6.6)	27.4 (5.0)	0.07
Pack Years	37.8 (19.7)	47.8(27.4)	<0.0001
Currently smoking, n (%)	182 (55%)	146 (41%)	0.0003
Post-bronchodilator Pulmonary Function			
FEV_1 (l)	1.66 (0.87)	2.27 (1.17)	<0.0001
FEV_1 % predicted	65.5 (31.9)	62.1 (30.4)	0.16
FVC (l)	2.90 (0.87)	4.09 (1.24)	<0.0001
FVC % predicted	91.6 (25.0)	88.0 (25.8)	0.06
FEV_1/FVC	0.55 (0.17)	0.53 (0.17)	0.20
Emphysema			
% LAA	19.78 (11.3)	24.00 (12.5)	<0.0001
Fractal Value (n=634)	1.98 (0.52)	1.88 (0.45)	0.01
Airways			
Lumen Perimeter (cm)	0.759 (0.159)	0.840 (0.181)	<0.0001
SQRTWA (cm)	0.387 (0.058)	0.430 (0.064)	<0.0001
Wall Area %	80.77 (3.25)	80.83 (3.72)	0.81

Definition of abbreviations: CT = computed tomography; SD = standard deviation; BMI = body mass index; FEV_1 = forced expiratory volume, 1^{st} second; FVC = forced vital capacity; % LAA = % low attenuation area; SQRTWA = square root of airway wall area

Table 3-4. Characteristics of Subjects Removed from Analysis (due to AirVolumeCT/predicted TLC < 0.54) Versus Subjects in CT Group

	Individuals in CT Group n=688 Mean (SD)	Individuals removed n=64 Mean (SD)	*p* value
Demographics			
Female n (%)	332 (48%)	25 (39%)	NS
Age (years)	57.9 (7.3)	53.83 (9.1)	0.0009
Weight (kg)	77.4 (19.2)	89.52 (19.6)	<0.0001
Height (cm)	169.0 (9.4)	171.88 (9.0)	0.02
BMI (kg/m^2)	27.0 (5.9)	30.36 (6.4)	<0.0001
Pack Years	43.0 (29.5)	34.86 (20.8)	0.01
Currently smoking, n (%)	328 (48%)	29 (45%)	NS
Post-bronchodilator Pulmonary Function			
FEV_1 % predicted	63.7 (31.1)	78.8 (28.2)	0.0002
FVC % predicted	89.8 (25.5)	89.3 (22.4)	NS
FEV_1/FVC	0.54 (0.17)	0.69 (0.14)	<0.0001
Proband/Sibling Proportion			
% Probands	40%	22%	0.005

Definition of abbreviations: SD = standard deviation; BMI = body mass index; FEV_1 = forced expiratory volume, 1^{st} second; FVC = forced vital capacity;

Table 3-5. Multivariable Models Predicting Emphysema (%LAA) (n=688)

	Parameter Estimate	95% Confidence Interval	*p* value
Model 1			
% LAA			
Intercept	33.294	(25.952, 40.636)	<0.0001
Female Sex	-2.284	(-3.577, -0.990)	0.0006
Age (years)	0.068	(-0.030, -0.167)	0.17
Pack Years	-0.003	(-0.034, 0.028)	0.84
Current Smoker=Yes	-5.540	(-6.953, -4.127)	<0.0001
BMI (kg/m^2)	-0.199	(-0.316, -0.083)	0.0008
FEV_1 % Predicted	-0.148	(-0.171, -0.126)	<0.0001
Center			<0.0001
Model 2			
% LAA			
Intercept	24.372	(5.582, 43.163)	0.01
Female Sex	-2.379	(-4.200, -0.558)	0.01
Age (years)	0.066	(-0.033, 0.166)	0.19
Pack Years	-0.003	(-0.034, 0.028)	0.86
Current Smoker=Yes	-5.554	(-6.971, -4.136)	<0.0001
Height (cm)	0.053	(-0.052, 0.158)	0.32
Weight (kg)	-0.068	(-0.109, -0.027)	0.001
FEV_1% Predicted	-0.149	(-0.171, -0.126)	<0.0001
Center			<0.0001

Definition of abbreviations: %LAA=% low attenuation area; BMI=body mass index; FEV_1 = forced expiratory volume, 1^{st} second.

Table 3-6. Multivariable Models Predicting Fractal Value (n=634)

	Parameter Estimate	95% Confidence Interval	*p* value
Model 1 – adjust for FEV_1 % predicted			
Fractal Value			
Intercept	1.7312	0.9631, 2.4992	<0.0001
Female Sex	0.1016	0.02664, 0.1766	0.008
Age (years)	-0.00029	-0.00429, 0.003698	0.88
Pack Years	-0.00079	-0.00205, 0.000470	0.22
Current Smoker	0.1447	0.08590, 0.2035	<0.0001
Height (cm)	-0.00864	-0.01293, -0.00435	<0.0001
Weight (kg)	0.01336	0.01173, 0.01499	<0.0001
FEV_1 % predicted	0.006465	0.005558, 0.007372	<0.0001
Model 2 – adjust for % LAA			
Fractal Value			
Intercept	2.4636	1.7423, 3.1850	<0.0001
Female Sex	0.05295	-0.01761, 0.1235	0.14
Age (years)	0.000361	-0.00340, 0.004123	0.85
Pack Years	-0.00233	-0.00345, -0.00120	<0.0001
Current Smoker	0.05288	-0.00438, 0.1101	0.07
Height (cm)	-0.00707	-0.01110, -0.00304	0.0006
Weight (kg)	0.01260	0.01107, 0.01414	<0.0001
%LAA	-0.02296	-0.02552, -0.02040	<0.0001

Definition of abbreviations: FEV_1 = forced expiratory volume, 1^{st} second ; %LAA=% low attenuation area.

Table 3-7. Multivariable Models Predicting Airway Wall Area % (n=688)

	Parameter Estimate	95% Confidence Interval	*p* value
Model 1			
Wall Area %			
Intercept	92.339	(90.781, 93.897)	<0.0001
Female Sex	-1.268	(-1.530, -1.006)	<0.0001
Age (years)	-0.009	(-0.030, 0.012)	0.42
Pack Years	0.005	(-0.001, 0.012)	0.10
Current Smoker = Yes	0.521	(0.231, 0.810)	0.0004
BMI (kg/m^2)	0.134	(0.109, 0.158)	<0.0001
Lumen Perimeter (cm)	-17.056	(-17.162, -16.950)	<0.0001
FEV_1 % predicted	-0.012	(-0.016, -0.008)	<0.0001
Center			<0.0001
Model 2			
Wall Area %			
Intercept	97.423	(93.487, 101.360)	<0.0001
Female Sex	-1.137	(-1.510, -0.764)	<0.0001
Age (years)	-0.007	(-0.028, 0.014)	0.53
Pack Years	0.005	(-0.002, 0.011)	0.14
Current Smoker = Yes	0.544	(0.255, 0.834)	0.0002
Height (cm)	-0.031	(-0.053, -0.009)	0.005
Weight (kg)	0.048	(0.039, 0.056)	<0.0001
Lumen Perimeter (cm)	-17.058	(-17.164, -16.951)	<0.0001
FEV_1 % predicted	-0.01222	-0.01662, -0.00782	<0.0001
Center			<0.0001

Definition of Abbreviations: BMI = body mass index; FEV_1 = forced expiratory volume, 1^{st} second.

Table 3-8. Multivariable Models Predicting SQRTWA (n=688)

	Parameter Estimate	95% Confidence Interval	*p* value
Model 1			
SQRTWA			
Intercept	0.1789	0.1532, 0.2047	<0.0001
Female Sex	-0.022	-0.026, -0.018	<0.0001
Age (years)	-0.00002	-0.0004, 0.0003	0.91
Pack Years	0.00009	-0.000002, 0.0002	0.10
Current Smoker = Yes	0.004	-0.0010, 0.0084	0.12
BMI (kg/m^2)	0.002	0.002, 0.003	<0.0001
Lumen Perimeter (cm)	0.2233	0.222, 0.225	<0.0001
FEV_1 % Predicted	-8.0×10^{-5}	$-1.5x10^{-4}$, $-7.69x10^{-6}$	0.03
Center			<0.0001
Model 2			
SQRTWA			
Intercept	0.2723	0.207, 0.338	<0.0001
Female Sex	-0.0202	-0.026, -0.014	<0.0001
Age (years)	0.00001	-0.0003, 0.0004	0.94
Pack Years	0.00008	-0.00003, 0.00018	0.15
Current Smoker = Yes	0.004	-0.0006, 0.0088	0.08
Height (cm)	-0.0006	-0.0009, -0.0002	0.002
Weight (kg)	0.0008	0.0007. 0.0010	<0.0001
Lumen Perimeter	0.223	0.222, 0.225	<0.0001
FEV_1 % Predicted	-0.00008	-0.0002, -0.00001	0.03
Center			<0.0001

Definition of Abbreviations: SQRTWA = square root of airway wall area; BMI = body mass index; FEV_1 = forced expiratory volume, 1^{st} second.

Table 3-9. Multivariable Models Predicting Airway Wall Area % in Airways > 6MM (number of subjects = 687)

	Parameter Estimate	95% Confidence Interval	*p* value
Model 1			
Wall Area %			
Intercept	87.584	85.697, 89.471	<0.0001
Female Sex	-1.850	-2.171, -1.529	<0.0001
Age (years)	0.005	-0.020, 0.303	0.69
Pack Years	0.007	-0.0009, 0.0147	0.08
Current Smoker = Yes	0.655	0.302, 1.001	0.0003
BMI (kg/m^2)	0.182	0.152, 0.211	<0.0001
Lumen Perimeter (cm)	-14.734	-14.875, -14.593	<0.0001
FEV_1 % predicted	-0.015	-0.020, -0.00964	<0.0001
Center			<0.0001
Model 2			
Wall Area %			
Intercept	94.155	89.423, 98.888	<0.0001
Female Sex	-1.6446	-2.097, -1.192	<0.0001
Age (years)	0.008	-0.018, 0.033	0.56
Pack Years	0.006	-0.002, 0.014	0.12
Current Smoker = Yes	0.689	0.334, 1.04	0.0001
Height (cm)	-0.041	-0.067, -0.014	0.002
Weight (kg)	0.065	0.054, 0.075	<0.0001
Lumen Perimeter (cm)	-14.737	-14.877, -14.596	<0.0001
FEV_1 % Predicted	-0.01527	-0.02063, -0.00992	<0.0001
Center			<0.0001

Definition of Abbreviations: BMI = body mass index; FEV_1 = forced expiratory volume, 1^{st} second.

Table 3-10. Multivariable Models Predicting SQRTWA in Airways > 6mm (number of subjects= 687)

	Parameter Estimate	95% Confidence Interval	p value
Model 1			
SQRTWA			
Intercept	0.220	0.193, 0.247	<0.0001
Female Sex	-0.025	-0.030, -0.020	<0.0001
Age (years)	$5.749x10^{-6}$	-0.00036, -0.000376	0.98
Pack Years	0.000112	$-5.47x10^{-6}$, $2.25x10^{-4}$	0.05
Current Smoker = Yes	0.0073	0.0022, 0.0124	0.005
BMI (kg/m^2)	0.0024	0.0020, 0.0028	<0.0001
Lumen Perimeter (cm)	0.1956	0.1938, 0.1973	<0.0001
FEV_1 % Predicted	-0.00015	-0.00023, -0.0007	0.0001
Center			<0.0001
Model 2			
SQRTWA			
Intercept	0.299	0.230, 0.368	<0.0001
Female Sex	-0.022	-0.028, -0.015	<0.0001
Age (years)	0.000042	-0.0003, 0.0004	0.82
Pack Years	0.000102	-0.00001, 0.0002	0.08
Current Smoker = Yes	0.007786	0.003, 0.013	0.003
Height (cm)	-0.00049	-0.0009, -0.0001	0.01
Weight (kg)	0.000863	0.0007, 0.001	<0.0001
Lumen Perimeter (cm)	0.120	0.194, 0.197	<0.0001
FEV_1 % Predicted	-0.00016	-0.0002, -0.00008	<0.0001
Center			<0.0001

Definition of Abbreviations: SQRTWA = square root airway wall area; BMI = body mass index; FEV_1 = forced expiratory volume, 1^{st} second

Table 3-11. Multivariable Models Predicting Airway Wall Area %, Adjusting for Level of Inspiration (n=688)

	Parameter Estimate	95% Confidence Interval	*p* value
Model 1			
Wall Area %			
Intercept	92.8510	90.9450, 94.7570	<0.0001
Female Sex	-1.2557	-1.5192, -0.9922	<0.0001
Age (years)	-0.00926	-0.03054, 0.01202	0.39
Pack Years	0.005368	-0.00106, 0.01179	0.10
Current Smoker = Yes	0.5248	0.2352, 0.8145	0.0004
BMI (kg/m^2)	0.1305	0.1052, 0.1558	<0.0001
Lumen Perimeter (cm)	-17.0552	-17.1615, -16.9490	<0.0001
FEV_1 % predicted	-0.01288	-0.01763, -0.00813	<0.0001
AirVolumeCT/predicted TLC ratio	-0.4236	-1.3277, 0.4806	0.36
Center			0.0001
Model 2			
Wall Area %			
Intercept	97.7948	93.6251, 101.96	<0.0001
Female Sex	-1.1419	-1.5151, -0.7686	<0.0001
Age (years)	-0.00721	-0.02849, 0.01406	0.51
Pack Years	0.004807	-0.00162, 0.01124	0.14
Current Smoker = Yes	0.5460	0.2561, 0.8359	0.0002
Height (cm)	-0.03172	-0.05375, -0.00970	0.005
Weight (kg)	0.04696	0.03804, 0.05587	<0.0001
Lumen Perimeter (cm)	-17.0569	-17.1632, -16.9506	<0.0001
FEV_1 % predicted	-0.01270	-0.01745, -0.00796	<0.0001
AirVolumeCT/predicted TLC ratio	-0.2485	-1.1677, 0.6708	0.60
Center			<0.0001

Definition of Abbreviations: BMI = body mass index; FEV_1 = forced expiratory volume, 1^{st} second; CT=computed tomography scan; TLC= total lung capacity

Table 3-12. Multivariable Models Predicting SQRTWA, Adjusting for Level of Inspiration (n=688)

	Parameter Estimate	95% Confidence Interval	p value
Model 1			
SQRTWA			
Intercept	0.1678	0.1363, 0.1993	<0.0001
Female Sex	-0.02236	-0.02663, -0.01808	<0.0001
Age (years)	-6.51E-6	-0.00036, 0.000345	0.97
Pack Years	0.000088	-0.00002, 0.00192	0.10
Current Smoker = Yes	0.003630	-0.00107, 0.008331	0.13
BMI (kg/m^2)	0.002379	0.001967, 0.002792	<0.0001
Lumen Perimeter (cm)	0.2233	0.2220, 0.2246	<0.0001
FEV_1 % Predicted	-0.00006	-0.00014, 0.000017	0.13
AirVolumeCT/predicted TLC ratio	0.009049	-0.00569, 0.02378	0.23
Center			<0.0001
Model 2			
SQRTWA			
Intercept	0.2525	0.1834, 0.3217	<0.0001
Female Sex	-0.01992	-0.02602, -0.01381	<0.0001
Age (years)	0.000036	-0.00032, 0.000387	0.84
Pack Years	0.000076	-0.00003, 0.000181	0.15
Current Smoker = Yes	0.004047	-0.00066, 0.008752	0.09
Height (cm)	-0.00055	-0.00092, -0.00019	0.003
Weight (kg)	0.000860	0.000715, 0.001005	<0.0001
Lumen Perimeter	0.2233	0.2220, 0.2246	<0.0001
FEV_1 % Predicted	-0.00006	-0.00013, 0.000020	0.15
AirVolumeCT/predicted TLC ratio	0.01266	-0.00234, 0.02766	0.10
Center			<0.0001

Definition of Abbreviations: SQRTWA = square root of airway wall area; BMI = body mass index; FEV_1 = forced expiratory volume, 1^{st} second; CT=computed tomography scan; TLC= total lung capacity

Table 3-13. Odds Ratio for Increasing Dyspnea in Women – Impact of Height and Weight Versus BMI on Estimates

Model *	Odds Ratio of Women Reporting Increasing Dyspnea	95% Confidence Intervals	*p* value
Adjusted for BMI and Post-bronchodilator FEV1 % predicted	2.05	1.48, 2.84	<0.0001
Adjusted for BMI and SQRTWA and %LAA	1.91	1.40, 2.63	<0.0001
Adjusted for Height, Weight and Post-bronchodilator FEV_1 % predicted	1.35	0.87, 2.09	0.18
Adjusted for Height, Weight, and SQRTWA and %LAA	1.38	0.88, 2.15	0.16

* All models are adjusted for age, pack years, current smoker status, and center of recruitment

Definition of Abbreviations: BMI = body mass index; FEV_1 = forced expiratory volume, 1^{st} second; SQRTWA = square root airway wall area; %LAA=% low attenuation area

Table 3-14. Multivariable Models Predicting Increased Dyspnea – Adjusting for Post-Bronchodilator FEV_1 % Predicted (n=654)

	Parameter Estimate	95% Confidence Interval	*p* value
Model 1			
MRC Dyspnea			
Female Sex	0.7170	0.3903, 1.0438	<0.0001
Age (years)	-0.0117	-0.0349, 0.0114	0.33
Pack Years	0.0096	0.0024, 0.0168	0.01
Current Smoker = yes	-0.2225	-0.5577, 0.1127	0.20
BMI (kg/m^2)	0.0578	0.0301, 0.0855	<0.0001
Post-bronchodilator FEV_1 % predicted	-0.0657	-0.0750, -0.0564	<0.0001
Model 2			
MRC Dyspnea			
Female Sex	0.2986	-0.1399, 0.7370	0.20
Age (years)	-0.0145	-0.0379, 0.0088	0.24
Pack Years	0.0087	0.0014, 0.0161	0.02
Current Smoker = Yes	-0.2521	-0.5880, 0.0838	0.15
Height (cm)	-0.0492	-0.0752, -0.0231	0.0003
Weight (kg)	0.0193	0.0094, 0.0291	0.0002
Post-bronchodilator FEV_1 % predicted	-0.0657	-0.0751, -0.0562	<0.0001

Definition of Abbreviations: FEV_1 = forced expiratory volume, 1^{st} second; BMI = body mass index;

Table 3-15. Multivariable Models Predicting Increased Dyspnea – Adjusting for %LAA & SQRTWA (n=654)

	Parameter Estimate	95% Confidence Interval	p value
Model 1			
MRC Dyspnea			
Female Sex	0.6580	0.3351, 0.9665	<0.0001
Age (years)	-0.0071	-0.0288, 0.0146	0.52
Pack Years	0.0263	0.0185, 0.0340	<0.0001
Current Smoker = Yes	-0.3372	-0.6540, -0.0205	0.04
BMI (kg/m^2)	0.0242	-0.0039, 0.0524	0.09
%LAA	6.4493	4.8088, 8.0898	<0.0001
SQRTWA (cm)	-2.6898	-5.3761, -0.0035	0.05
Center			< 0.01
Model 2			
MRC Dyspnea			
Female Sex	0.3187	-0.1297, 0.7670	0.16
Age (years)	-0.0086	-0.0301, 0.0130	0.44
Pack Years	0.0256	0.0178, 0.0334	<0.0001
Current Smoker = Yes	-0.3515	-0.6662, -0.0368	0.03
Height (cm)	-0.0325	-0.0579, -0.0071	0.01
Weight (kg)	0.0072	-0.0031, 0.0174	0.17
% LAA	6.3352	4.7119, 7.9586	<0.0001
SQRTWA (cm)	-2.1719	-4.8288, 0.4850	0.11
Center			< 0.05

Definition of Abbreviations %LAA = % low attenuation area; SQRTWA = square root of airway wall area; BMI = body mass index

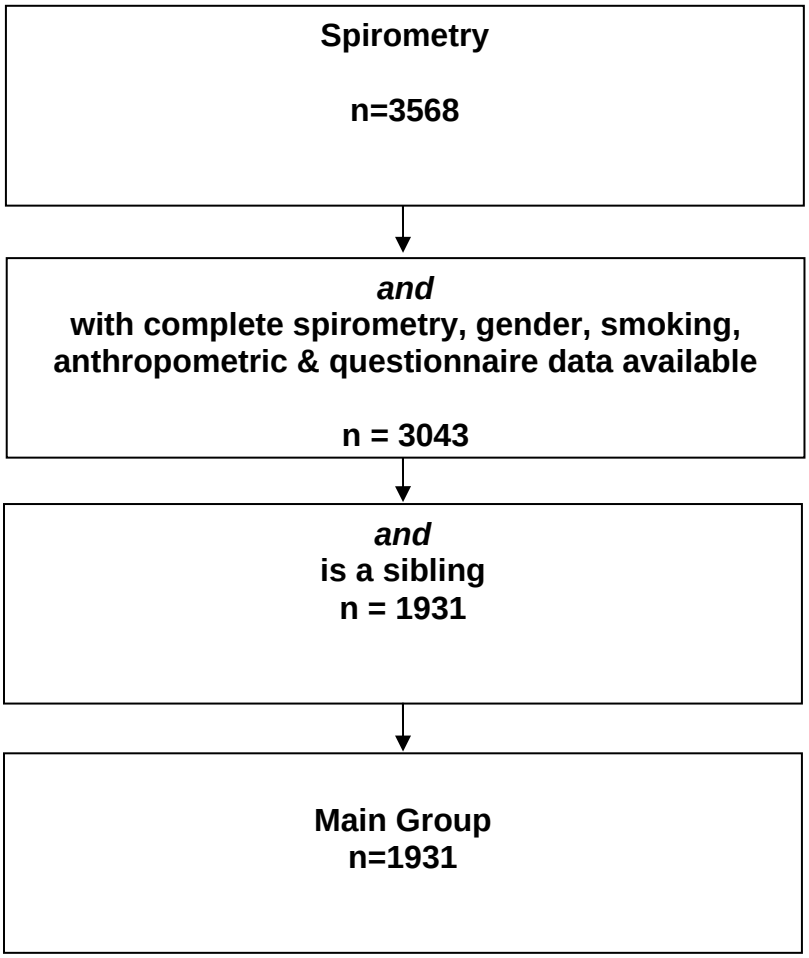

Figure 3-1a. Creation of the Main Group for Analysis (n=1931)

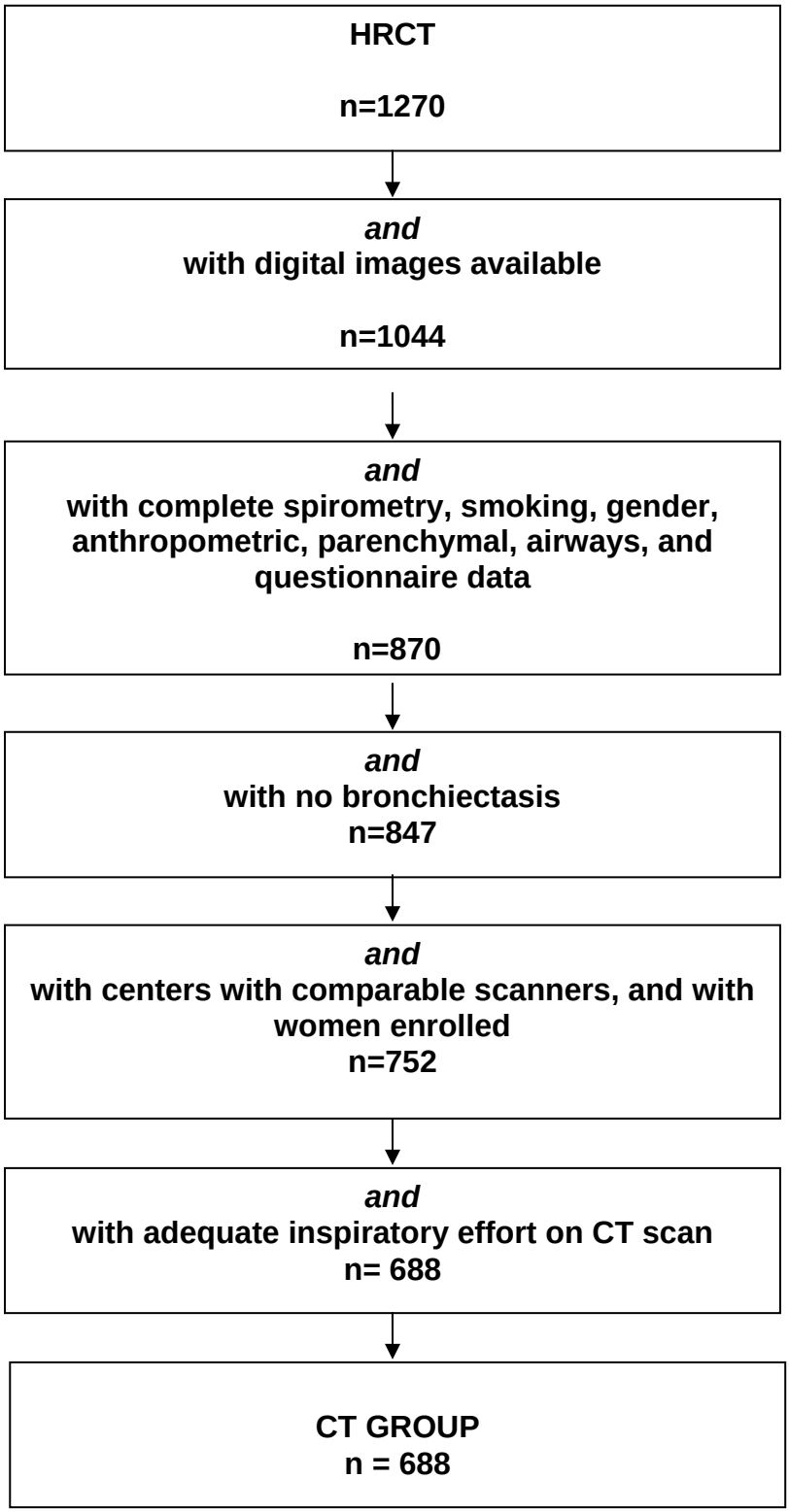

Figure 3-1b. Creation of the CT Group for analysis (n=688)

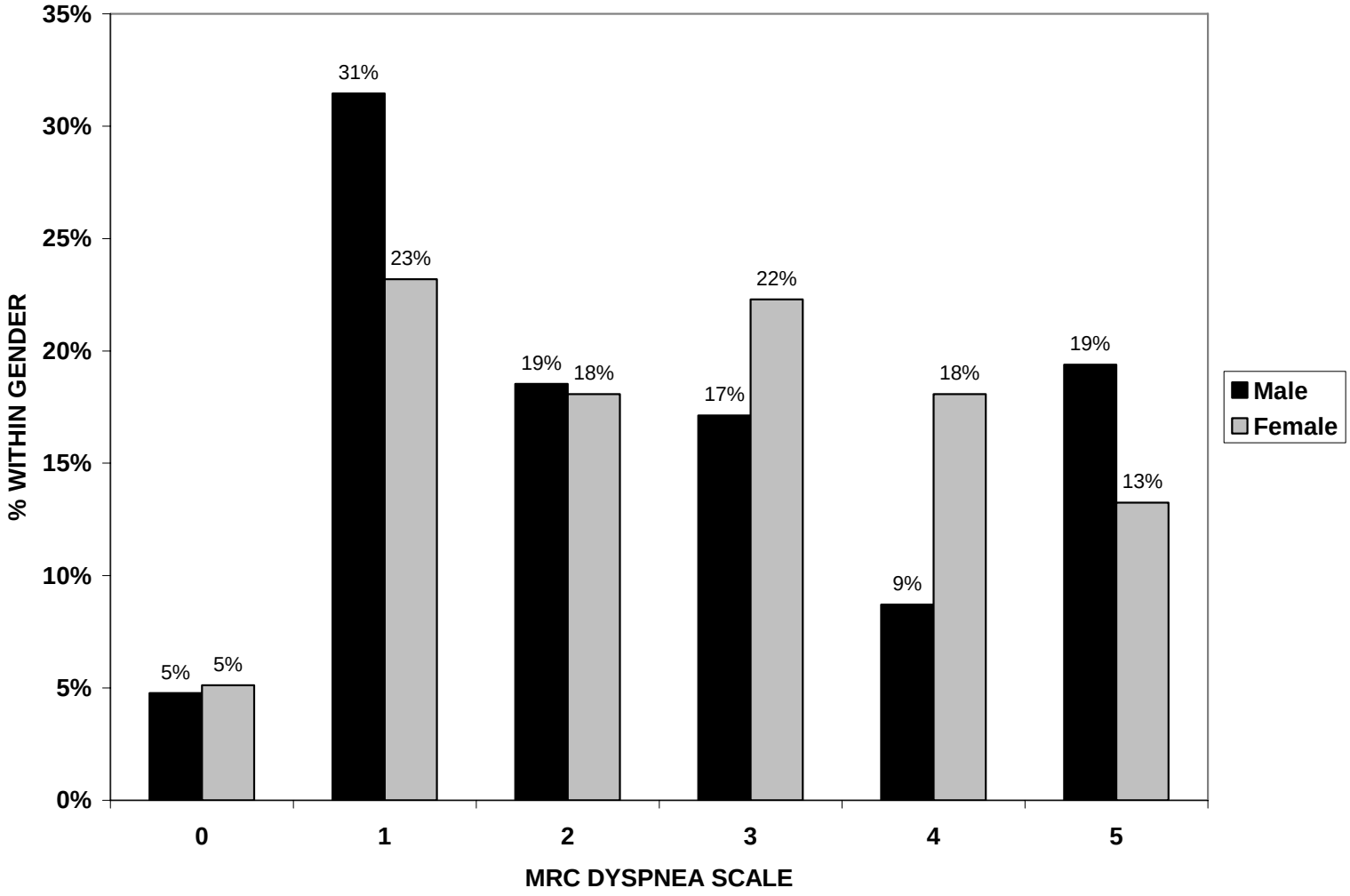

Figure 3-2. Distribution of Medical Research Council (MRC) Dyspnea Scale Scores by Gender

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CHAPTER FOUR. SUBJECTIVE AND OBJECTIVE ESTIMATES OF EMPHYSEMA: A RECEIVER OPERATING CHARACTERISTIC CURVE ANALYSIS[1]

4.1 INTRODUCTION

High resolution computed tomography (HRCT) is a sensitive method to detect changes in lung structure *in vivo,* including changes due to the parenchymal destruction which characterizes emphysema. Methods to obtain estimates of the presence and extent of emphysema from HRCT include subjective assessments by a radiologist and objective, computer-aided estimates from digital images. Subjective methods of measuring emphysema from HRCT images were developed in the mid-1980's and usually involve scoring the severity of emphysema on an ordinal scale. These scores correlate significantly with emphysema measured macroscopically and microscopically on pathological specimens (1, 2). However, there are limitations to subjective methods. Madani et al (3) noted that a subjective grading system is '…not really quantitative but is a method of ranking emphysema according to categories of severity." Subjective estimates are also time-consuming, require expert, trained radiologists, and are limited by the lack of strong inter-rater reliability (4) which restricts the ability to compare or combine emphysema scores by different readers.

Quantitative estimates of emphysema from HRCT have been more recently developed and are widely used in COPD research, although they are not yet used

[1] A version of this chapter will be submitted for publication:
Camp PG, Coxson HO, Muller NL, Pillai S, McDougall J, Silverman EK, Lomas DA, Paré PD. Subjective and objective estimates of emphysema: a receiver operating characteristic curve analysis.

routinely in the clinical arena. Quantitative methods use attenuation measurements to estimate the extent of emphysema. The 'density mask' method determines the extent of emphysema by measuring the % of voxels under a specific Hounsfield unit (HU) cutoff, or the '% low attenuation area' (%LAA). The 'lower percentile' method estimates the extent of emphysema by identifying the HU at the lower 5^{th} or 15^{th} percentile of the HU frequency distribution curve. The HU value at the lower 5^{th} percentile correlates with microscopic measurements of emphysema (5). However, as the 'lower percentile' method could underestimate emphysema if the lung has areas of abnormally high lung attenuation values, the 'density mask' method is recommended (3). Density mask estimates of emphysema correlate with measurements of macroscopic and microscopic emphysema (6-8) but are not able to characterize the heterogeneity of the emphysematous spaces.

Fractal analysis of the lung has extended the 'density mask' analysis of emphysema to include further information on how areas of low lung density are organized. They rely on the fact that the lung structure is fractal, i.e. a shape composed of smaller shapes, that, when analysed closely, resemble the whole shape. Using complex metrics, Mishima et al (9) characterized the emphysematous spaces in the lung by measuring the size of the contiguous voxels under a HU cut-off. An emphysematous space can be one voxel, or be a cluster of two to many thousands of contiguous voxels under a specific attenuation cut-off. The slope of the regression line of the log-log plot of the cumulative frequency of the number of voxels versus the size of the clusters yields the fractal value, an estimate of the relative size of the emphysematous spaces. Individuals who have larger

emphysematous spaces have a decreased slope and a lower fractal value. This approach has been used to predict the outcome in COPD patients undergoing lung volume reduction surgery (10).

Although estimating the size of the emphysematous spaces may be an improvement over the global estimate of low lung attenuation area provided by the density mask method, previous studies using the fractal analysis approach to estimate emphysema have had small samples sizes (<40) or have not directly compared the fractal value estimates of emphysema with subjective or %LAA estimates. In addition, previous studies of the fractal value have not reported the number of women in their sample or have not included women at all.

Different measurement tools may lead to different emphysema estimates in men and women. This could be the result of true sex differences in emphysema; an example of this occurs if features of emphysema are different in men and women and are better detected with one measure versus another. In addition, gender bias may exist with these measures. With respect to radiologist scores, a reader is able to differentiate between male and female scans due to the presence of breast shadows. There may be gender bias in the subjective measurement of emphysema if emphysema is considered to be more likely a 'man's disease' by the reader (11). There is also the potential of gender bias in the objective measurement of emphysema. In Chapter Three, we reported that BMI and weight were independently associated with %LAA, and weight and height were independently related to fractal value. These measures are usually different in men and women. Failure to consider how the different measures compare in subgroups of men and

women based on anthropometric characteristics could lead to conclusions of differences in measures based on sex, when in fact differences may be due to size.

Therefore, the purpose of this study is to compare the ability of the fractal value, radiologists' subjective rating, and % LAA to differentiate COPD from non-COPD subjects in a sample (n=634) of men and women. We also compared the three measures of emphysema in men and women grouped into categories of weight, height, BMI and age.

4.2 METHODS

4.2.1 Subject Selection

We analyzed data from the participants in the GlaxoSmithKline International COPD Genetics Network (12), a multi-centre study designed to investigate genetic susceptibility for COPD. This study recruited individuals (probands) with relatively early-onset severe COPD (defined as post-bronchodilator FEV_1 < 60% predicted, FEV_1/VC (vital capacity) < 90% predicted, and age 45-65 years) and a minimum 5 pack-year smoking history. Siblings of these COPD patients who had a minimum 5 pack-year smoking history were also recruited, regardless of lung function. We excluded individuals with alpha-1 antitrypsin deficiency and other chronic pulmonary diseases such as tuberculosis. Ten sites participated in this study (four in North American, two in Great Britain, and four in Continental Europe). Three thousand and forty-three individuals were recruited into the genetics study of COPD. The sample for this study consisted of 634 individuals who had complete lung function,

anthropometric, demographic, and emphysema data. Creation of the sample for analysis is illustrated in Figure 4-1. All subjects provided written, informed consent and the study was approved by the ethics review board at each study centre.

4.2.2 Classification of Disease

Although pathological examination is the gold standard for diagnosing and quantifying emphysema, this method is not feasible in studies of living subjects. Instead, we used spirometric measures of lung function to classify subjects with or without COPD. As per the Global Initiative for Obstructive Lung Disease (GOLD) criteria, we used the ratio of the post-bronchodilator forced expiratory volume in 1 second (FEV_1) to the forced vital capacity (FVC) less than 0.70 as the spirometric criteria for defining COPD (Appendix 1). Since clinically important COPD may not occur until the disease has progressed past Gold Stage 1, we repeated the analysis using a second indicator of COPD: GOLD Stage 2 or greater, defined as a post-bronchodilator $FEV_1 < 80\%$ predicted and $FEV_1/FVC < 0.70$. Both COPD variables were dichotomized.

4.2.3 Pulmonary Function

Spirometry was conducted pre- and post-bronchodilator (salbutamol 180 µg administered via an Aerochamber® spacer) using a SurveyTach™ portable spirometer (WE Collins, Braintree, MD) by trained personnel in accordance with American Thoracic Society standards (13). A minimum of three recordings were

made and the higher of the FEV_1 and forced VC (FVC), were expressed as a percentage of predicted values (14).

4.2.4 HRCT Scans

All subjects were asked if they were willing to receive a HRCT scan as part of the study. Creation of the sample for analysis is illustrated in Figure 4-1. Subjects were not excluded from the overall study if they refused the scan and were under no obligation to participate in this aspect of the study. If there was a scan that was acquired for other reasons within the last 2 years these scans were obtained for analysis. The scans were acquired at suspended full inspiration (apex to base) using 1 or 1.25 mm slice thickness, a 20 mm gap and the smallest field of view that included both lungs. Scans were performed on General Electric or Siemens scanners in order to provide comparable data for analysis. Six sites had General Electric or Siemens scanners and suitable numbers of men and women to allow for statistical comparisons. The images were reconstructed using a high spatial frequency reconstruction algorithm and saved in the DICOM 3.0 format. The images were then archived onto optical media and transferred to the James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research (Vancouver General Hospital site, Vancouver, Canada). Scans were analyzed using a custom software package (Emphylx-J, James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research, Vancouver, Canada).

Emphysema measurements are based on estimates of lung density, which are affected by the amount of air in the lungs. A poor maximal inspiratory effort may

underestimate emphysema on HRCT. In addition, a maximal inspiratory effort is needed to ensure full airway opening and accurate airway measurement. Although all sites followed a standardized scanning protocol, it is possible that some subjects did not follow instructions precisely. To exclude individuals who obviously did not take an adequate inspiration during HRCT scanning we excluded scans for analysis where the air volume on HRCT was less than 54% of the predicted total lung capacity (TLC) for that subject (AirVolumeHRCT/predicted TLC). Predicted values for TLC were based on recommended reference equations from the European Respiratory Society and American Thoracic Society (15). Fifty-four percent is the average value for predicted functional residual capacity as a percent of predicted total lung capacity.

The objective analysis of the lung parenchyma was performed using a previously described technique (16, 17). Briefly, the lung parenchyma was segmented from the chest wall and large central blood vessels using a contour-following algorithm. %LAA was measured using a 'density mask' cut-off of -950 Hounsfield units (HU), which is appropriate for this CT acquisition technique (8). The fractal value was calculated by summing the number of connected pixels below the density mask cutoff of -950 HU. An emphysematous lesion can be very large, consisting of thousands of connected pixels, or as small as one pixel. The number of lesions of all sizes was counted and the cumulative number of these lesions larger than a given size was plotted against that lesion size on a log-log plot. The inverse slope of this relationship is the fractal value.

In addition to the two quantitative measurements of emphysema, two radiologists independently reviewed each scan. Emphysema was scored on a 6-point scale (0 – no emphysema; 1 – trivial, less than 5% of the lung with emphysema; 2 – mild, 5-25% of the lung with emphysema; 3 – moderate, 25-50% of the lung with emphysema; 4 – severe; 50-75% of the lung with emphysema; and 5 – very severe, greater than 75% of the lung with emphysema). If the radiologists' scores differed by 1, the average of the two scores was taken. If the radiologists' score differed by more than 1, the radiologists met and determined a consensus score.

4.2.5 Data Analysis

We used a receiver-operating characteristic (ROC) curve analysis to compare the relationships between each of the three estimates of emphysema and the presence or absence of COPD. Independent t-tests and simple linear regression were used to describe the data. Logistic regression models (PROC LOGISTIC and PROCSURVEYLOGISTIC, SAS Version 9.1, SAS Institute, Cary, North Carolina) were used to create the ROC graphs and calculate the area under the ROC curve (AUC). Models were adjusted for the clustering of data within family and center. To test which of the curves had the greatest AUC, we used a bootstrap analysis. This was done with the entire sample of men and women. In the bootstrap procedure, repeated samples were selected with replacement from the original set of observations. Each bootstrap imputation randomly selected a sample of 207 families with the same proportion of families per center as in the original dataset.

The imputation procedure was then repeated 500 times to generate an overall estimate of the difference between the AUC of each of the three estimates.

In order to determine if the three emphysema estimates could predict COPD similarly in the entire sample of men and women, we repeated the analysis with an interaction term for gender X emphysema in the model. We also separated men and women in groups based on weight, height, BMI, and age. We calculated the mean values of height, weight and BMI within each sex and separated the men and women into low and high groups according to these mean values. We also calculated the mean age for the entire sample and separated men and women into low and high groups based on this value. Due to the small sample sizes of these subgroups, we focused our analysis on the graphical comparisons of the ROC curves of the three emphysema estimates, within each subgroup.

4.3 RESULTS

Six hundred thirty-four men and women were recruited from six sites and had complete spirometry, radiology assessment, %LAA and fractal value estimates of emphysema. Creation of the sample for analysis is illustrated in Figure 4-1. The prevalence of COPD varied depending on the criteria used for definition (Table 4-1). The proportions of men and women were similar in both groups. Using $FEV_1/FVC < 0.70$ as the definition of COPD, the characteristics of those with and without COPD are shown in Table 4-2. Those with COPD were older and had more pack years of smoking, and had lower weight and BMI than those without COPD. Individuals with

COPD also had more emphysema as estimated by the radiologist, a greater %LAA, and a significantly smaller fractal value indicating larger emphysematous spaces compared to the non-COPD group. Unadjusted univariate linear regression analysis demonstrated that all three estimates of emphysema were significantly associated with post-bronchodilator FEV_1 % predicted (Figure 4-2a to 4-2c).

Using the definition of COPD as $FEV_1/FVC < 0.70$, the radiologist estimate of emphysema had the best ROC curve (Figure 4-3) and largest AUC (AUC=0.847) followed by the fractal value (AUC=0.786) and %LAA (AUC=0.674). Using the more stringent definition of COPD ($FEV_1/FVC < 0.70$; FEV_1 % predicted < 80%), the radiologist estimate of emphysema continued to have the largest AUC, followed by the fractal value and the % LAA (0.816, 0.767, and 0.652, respectively). Changing the threshold of emphysema for the fractal value and the % LAA to -910 HU did not change the results (fractal value AUC = 0.769, % LAA AUC = 0.639). The bootstrap analysis confirmed that the radiologist rating of emphysema was a significantly better predictor of COPD than either the fractal value or the % LAA, using either definition of COPD. The fractal value was a significantly better predictor of COPD than %LAA ($p<0.05$). Adding % LAA to the fractal value in the statistical model did not significantly increase the AUC above that achieved using the fractal value alone.

The ROC curves for the three estimates of emphysema were similar for men and women (Figure 4-4 to 4-6), although by visual inspection the ROC curves for the radiologist rating and the %LAA for women appear greater than for men. The interaction terms for sex and each emphysema estimate were not significant, showing that in the sample as a whole, the relationships between each of the

emphysema estimates and COPD ($FEV_1/FVC < 0.70$) were statistically similar for both men and women. These results did not change when the second definition for COPD was used or when the threshold for emphysema was changed to -910 HU.

The distribution of COPD was similar for men and women within each subgroup. For each group, the radiologist rating of emphysema consistently had the best ROC curve and the highest values for AUC (Figure 4-7 to Figure 4-22; Table 4-3). However, weight, height, BMI and age did affect the relationship between the curves in each subgroup. For example, the curve for the fractal value approached that of the radiologist rating in several subgroups. This was most apparent in the female low height group, where the curves for all estimates were similar. In the female low weight group, the ROC curve for %LAA was similar to the ROC curve for the fractal value. For women with high weight, and for men in either weight group, the ROC curve for %LAA was worse than the curve measured in the sample as a whole. This was especially apparent in the male high weight and high BMI group, where the ROC curve for %LAA was similar to the line of identity, signifying a minimal ability of %LAA to differentiate COPD in this group.

In general the AUC values for men and women for all the estimates were greater in the low versus the high weight, height and BMI groups. In addition, the AUC values were greater for women than for men for any of the measures, in any of the subgroups.

For men, age also strongly affected the AUC values and ROC curves for %LAA. While men of low age and women of any age had AUC values that were similar to those generated for the sample as a whole, the %LAA for men in the old

age group corresponded with the worse ROC curve and lowest values for AUC, showing that in older men, %LAA had no ability to differentiate individuals with COPD from those with no obstruction.

We previously reported in Chapter Three that height and/or weight influenced whether women would be more likely to have an FEV_1/FVC less than the lower limit of normal (LLN). We repeated the subgroup analysis with two other definitions for COPD: GOLD Stage 2; and the $FEV_1/FVC < LLN$. Using these different definitions of COPD slightly altered the AUC values compared to the COPD definition of $FEV_1/FVC < 0.70$, but the relationships between the three estimates, for all the subgroups, generally remained the same (Table 4-3).

4.4 DISCUSSION

This ROC analysis of a large cohort of male and female smokers was designed to test if objective measures of emphysema, specifically %LAA and the fractal value, could detect individuals with COPD as well as or better than subjective, radiologist-determined emphysema scores. We found that for both men and women, the radiologist subjective score had the best predictive value as evidenced by the significantly larger AUC than either the % LAA or the fractal value, although there were some exceptions when the sample was divided into subgroups. We reasoned that since the fractal value and the % LAA are independent measures of emphysema their combination would be superior to either alone, however an

additive model did not significantly improve the AUC beyond that of the fractal value alone.

We used FEV_1/FVC as the indicator of disease in the analysis. In COPD, reductions in FEV_1/FVC are due to a combination of parenchymal destruction and small airway inflammation and remodeling. It could be argued that an emphysema-specific lung function parameter, such as diffusing capacity, is a more appropriate outcome measure. However, Nakano et al (18) reported that %LAA was similarly correlated with FEV_1/FVC and diffusing capacity. In addition, the large values for AUC observed in this study suggest that emphysema estimates can differentiate COPD patients from non-COPD patients.

We found the radiologists' ratings of emphysema had the best ROC curve and could differentiate COPD from non-COPD better than either or both of the computer-generated, objective measurements. This finding was generally consistent in men and women and within subgroups of weight, height, BMI and age. Subjective ratings of emphysema have evolved from scoring fixed pathological specimens obtained at autopsy, to estimating the severity of emphysema on an ordinal scale based on the examination of HRCT slices of the chest in living patients. Although subjective scores are moderately to strongly correlated with macroscopic or microscopic lung sections (r=0.44 and 0.91, respectively) (4, 19) this method has limitations. First, although one investigator reported good to excellent intra-rater reliability for subjective estimates of emphysema (κ=0.738 to 0.936), inter-rater reliability was only moderate (κ=0.431 to 0.589) (4). In the research setting moderate inter-rater reliability could limit the interpretation of results from multi-

center studies with multiple readers. Second, research studies which utilize subjective measures of emphysema require highly-trained readers and are time-consuming to conduct. These limitations have led to the increasing use of objective measures in the hope that these are comparable and more reproducible than subjective measures. The results of this study raise serious concerns regarding this trend. Our results suggest that the advantages of reproducibility afforded by computer-assisted algorithms may be negated by inaccuracy.

Why the radiologist estimate of emphysema best predicted COPD is not clear, but it is possible that the radiologist subjective rating is capturing information from the CT scan not detected by the computer program. This additional information may include signs of hyperinflation, bronchial wall thickening, and the nature and distribution of the emphysematous spaces. Although this additional information is not included in the emphysema score, it may influence the radiologists' decision-making process. In addition, in smokers with COPD centrilobular emphysema with large lesion sizes is the predominant emphysema phenotype, as opposed to panacinar emphysema which is characterized by small areas of low lung density homogeneously distributed throughout the lung. These large emphysematous spaces which characterize smoke-induced COPD may be best detected visually by expert readers.

Our findings are in contrast to those reported by Bankier et al (4). In their study, they compared macroscopic assessments of emphysema (from lung sections obtained after lung resection or lung transplantation) with subjective estimates of emphysema from HRCT, and with %LAA. The macroscopic assessment of

emphysema was considered the gold standard. The investigators found that the correlation between the subjective score and the gold standard was weaker than the correlation between %LAA and the gold standard, although they did not statistically compare the correlations. In addition, they found that the subjective measurements overestimated the severity of emphysema, whereas the %LAA did not. However, they did not relate their radiological or pathological measurements of emphysema to lung function; their subjects were individuals who underwent lung surgery for cancer, and lung function and previous diagnosis of COPD were not reported. It is possible that the radiologists' estimate of emphysema correlates more closely with functionally significant emphysema than do the objective measures. Alternatively the superior performance of the radiologists in the present study may relate to their expertise or to the inclusion in their 'score" of some additional unreported features that are suggestive of airflow obstruction as discussed above.

Of the two computer-generated, objective estimates of emphysema, the fractal value was significantly better at differentiating COPD from non-COPD patients in the overall sample and consistently within the groups divided based on weight, height, BMI or age. This is an important finding. Currently, %LAA is the more commonly-used objective method of estimating the severity of emphysema in research populations. %LAA provides an estimate of the extent of decreased lung density, which has been shown to be associated with macroscopic and microscopic measurements of emphysema (4, 6, 8) . Although %LAA can be used to estimate emphysema throughout the entire lung, or can be applied separately to specific regions, such as upper middle and lower lung, or into core and rind estimates, it

does not provide information as to the nature of the emphysematous spaces. The fractal value gives an indication as to how emphysematous spaces are organized. The smaller the fractal value, the larger the relative size of the emphysematous spaces. Similar to the radiologist reading, the fractal value may be better than %LAA at differentiating COPD from non-COPD in this sample of smokers because it is detecting the large emphysematous spaces characteristic of centrilobular emphysema. Our finding is in contrast with those reported by Mishima et al (9). In their study, neither %LAA nor the fractal value was significantly correlated with FEV_1/FVC. However, their COPD patients had severe airflow obstruction (mean $FEV_1/FVC = 0.35 \pm 0.12$), and their overall sample size was small (COPD patients = 73; normal subjects = 30) with only men enrolled, which may have limited their ability to detect a relationship between the fractal value and airflow obstruction. However, they did report stronger correlations between the fractal value and diffusing capacity than between %LAA and diffusing capacity.

Although overall the radiologist estimate of emphysema best predicted COPD and the fractal value was the better of the two measurements, examining the ROC curves by sex and subgroup did illustrate some important findings. We found that the curve for the fractal value approached that of the radiologist rating in several subgroups. This was most apparent in the female low height group, where in fact the curves for all estimates, including %LAA, were similar. In contrast, the %LAA performed much worse in the male high weight, high BMI, and high age groups. It would appear that in heavy men, measurements of low lung density do not predict the presence or absence of airflow obstruction. It is not known if this is a deficiency

of %LAA to detect functionally important emphysema in heavier men, or if it is related to the measurement of lung function in this group. However, as we also reported in Chapter Three that weight was independently associated with %LAA in men but not women, sex differences in the impact of weight on measurements of emphysema need to be addressed.

Similarly, the AUC value for %LAA measurement in older men was the lowest of any of the subgroups. In men, the %LAA estimate may be too sensitive to the decrease in lung density normally associated with age and is not able to differentiate low lung density relative to disease compared to low lung density associated with the aging process.

There were some limitations to this study. First, we did not validate any of the emphysema measurements against the recognized gold standard, a pathologic diagnosis of emphysema. However, obtaining pathologic specimens is usually only possible in individuals undergoing surgery or autopsy. As such the available subjects are few in number and do not usually represent the full spectrum of COPD severity. Second, although the sex X emphysema estimate interaction term was not statistically significant, we did see important differences between men and women when the data was analyzed by subgroup. This suggests that important interactions do exist. Further examination of the influence of age, anthropometric measurements and sex in larger samples is warranted. Third, our study was conducted in a group of male and female smokers recruited for a previous genetics study of COPD. As such the results of this study are best applied to research populations. However, %LAA is used to measure emphysema severity in biomarker studies of COPD, and

COPD treatment trials also require the accurate identification of emphysema patients in order to develop phenotype-specific interventions. Therefore it is important to determine which of the available measures should be used to identify emphysema and measure the extent of severity in COPD research populations.

4.5 CONCLUSION

Based on the results from this study, the radiologist estimate of emphysema is the best method to differentiate COPD from non-COPD patients. However, based on previous reports of only moderate inter-rater reliability, it alone may not be enough to fully identify and characterize emphysema patients. Objective computer-aided estimates of emphysema do not suffer limitations in inter- and intra-rater reliability provided the same reconstruction algorithms and measurement methodology are used. Of the two objective measures tested in this study, the fractal value best identifies clinically important emphysema overall and within most of the subgroups. Although %LAA may give a global and regional measurement of low lung density, this metric alone does not appear to adequately capture the characteristics of emphysema that are related to reduced lung function as compared with the fractal value and the radiologists' estimates. This was especially apparent in heavier or older men. Since the fractal value provides information on the distribution of the lesion size, but not on the extent or severity of emphysema overall, future studies should focus on the further development and validation of the fractal value as an emphysema measurement tool.

Table 4-1. Prevalence of COPD in Sample (n=634)

COPD Definition	COPD Female n (%)	COPD Male n (%)	Non-COPD Female n (%)	Non-COPD Male n (%)
$FEV_1/FVC < 0.70$	219 (45.3)	264 (54.7)	82 (54.3)	69 (45.7)
FEV_1 % predicted < 0.80 and $FEV_1/FVC < 0.70$ (GOLD Stage 2)	184 (44.7)	228 (55.3)	117 (52.7)	105 (47.3)

Definition of Abbreviations*:* FEV_1/FVC = forced expiratory volume, 1^{st} second / forced vital capacity ratio; GOLD = Global Initiative for Obstructive Lung Disease

Table 4-2. Characteristics of Subjects with and without COPD

	COPD n = 483 Mean (SD)	non-COPD n = 151 Mean (SD)	*p* value
Demographics			
% Female	45.3%	54.3%	0.05
Age (years)	58.7 (6.8)	55.7 (7.8)	0.0002
Weight (kg)	76.0 (18.6)	82.3 (20.9)	0.0004
Height (cm)	169.0 (9.4)	169.0 (8.8)	0.89
BMI (kg/m^2)	26.5 (5.6)	28.9 (6.7)	0.0001
Pack Years	47.3 (24.1)	30.2 (22.4)	<0.0001
Currently smoking, n (%)	47.4%	46.4%	0.82
Post-bronchodilator Pulmonary Function			
FEV_1 (l)	1.61 (0.85)	3.17 (0.89)	<0.0001
FEV_1 % predicted	52.3 (24.5)	102.1 (19.4)	<0.0001
FVC (l)	3.34 (1.20)	4.14 (1.15)	<0.0001
FVC % predicted	85.85 (24.9)	104.27 (24.34)	<0.0001
FEV_1/FVC	0.47 (0.14)	0.77 (0.04)	<0.0001
Emphysema			
Radiologist Score (0-5)	2.23 (1.29)	0.66 (0.64)	<0.0001
% Low Attenuation Area	23.90 (12.67)	16.35 (9.70)	<0.0001
Fractal value	1.82 (0.45)	2.30 (0.41)	<0.0001

Definition of abbreviations: SD = standard deviation; BMI = body mass index; FEV_1 = forced expiratory volume, 1^{st} second; FVC = forced vital capacity

Table 4-3. AUC Values for Women and Men – Weight, Height, BMI and Age Subgroups

	WOMEN			MEN		
	COPD = FEV_1/FVC < 0.70	COPD = GOLD Stage 2	COPD= FEV_1/FVC < LLN	COPD = FEV_1/FVC < 0.70	COPD = GOLD Stage 2	COPD= FEV_1/FVC < LLN
Weight						
Low Weight – Radiologist	0.867	0.840	0.879	0.871	0.853	0.871
Low Weight - %LAA	0.768	0.712	0.764	0.648	0.662	0.660
Low Weight – Fractal	0.772	0.782	0.768	0.796	0.782	0.791
High Weight – Radiologist	0.843	0.795	0.847	0.780	0.758	0.757
High Weight - %LAA	0.640	0.626	0.621	0.613	0.569	0.565
High Weight – Fractal	0.805	0.792	0.777	0.762	0.731	0.761
Height						
Low Height – Radiologist	0.849	0.792	0.858	0.867	0.821	0.814
Low Height - %LAA	0.800	0.704	0.785	0.638	0.628	0.614
Low Height – Fractal	0.794	0.756	0.780	0.797	0.742	0.747
High Height – Radiologist	0.879	0.856	0.881	0.798	0.796	0.819
High Height - %LAA	0.652	0.671	0.634	0.627	0.619	0.628
High Height – Fractal	0.784	0.802	0.764	0.759	0.753	0.773
BMI						
Low BMI – Radiologist	0.867	0.842	0.866	0.866	0.863	0.861
Low BMI - %LAA	0.754	0.705	0.757	0.652	0.663	0.652
Low BMI – Fractal	0.777	0.790	0.771	0.790	0.768	0.773
High BMI – Radiologist	0.846	0.789	0.858	0.790	0.762	0.770
High BMI - %LAA	0.669	0.640	0.640	0.608	0.578	0.579
High BMI – Fractal	0.792	0.769	0.751	0.772	0.768	0.772

Table 4-3 continued.

	Women			Men		
	COPD = FEV_1/FVC < 0.70	**COPD = GOLD Stage 2**	**COPD= FEV_1/FVC < LLN**	**COPD = FEV_1/FVC < 0.70**	**COPD = GOLD Stage 2**	**COPD= FEV_1/FVC < LLN**
Age						
Low Age – Radiologist	0.848	0.808	0.847	0.819	0.840	0.833
Low Age - %LAA	0.735	0.678	0.727	0.666	0.648	0.674
Low Age – Fractal	0.801	0.784	0.784	0.763	0.791	0.770
High Age – Radiologist	0.881	0.844	0.895	0.841	0.776	0.804
High Age - %LAA	0.683	0.670	0.682	0.563	0.574	0.556
High Age - Fractal	0.765	0.771	0.756	0.784	0.696	0.752

Definition of Abbreviations: AUC = area under the curve; BMI = body mass index; FEV_1 = forced expiratory volume, 1^{st} second; FVC=forced expiratory volume; GOLD=Global Initiative for Obstructive Lung Disease; LLN=lower limit of normal; %LAA=% low attenuation area

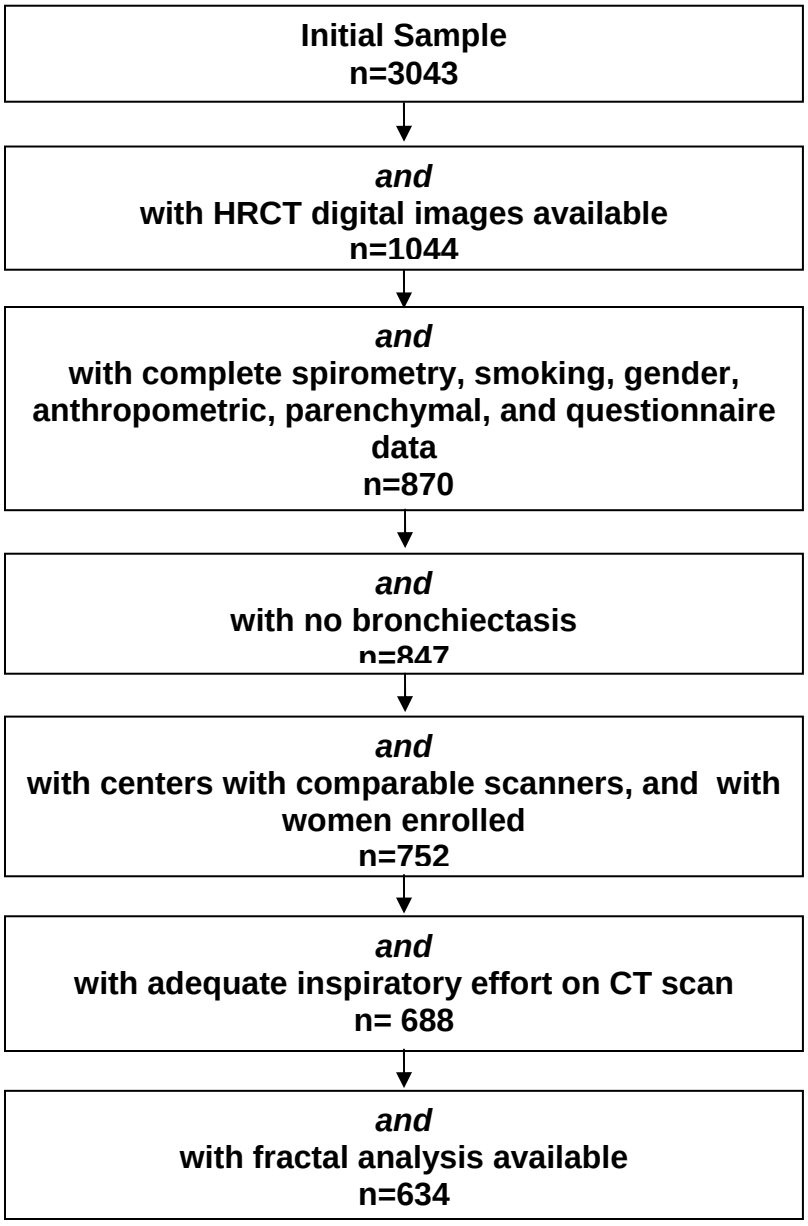

Figure 4-1. Creation of Study Sample (n=634)

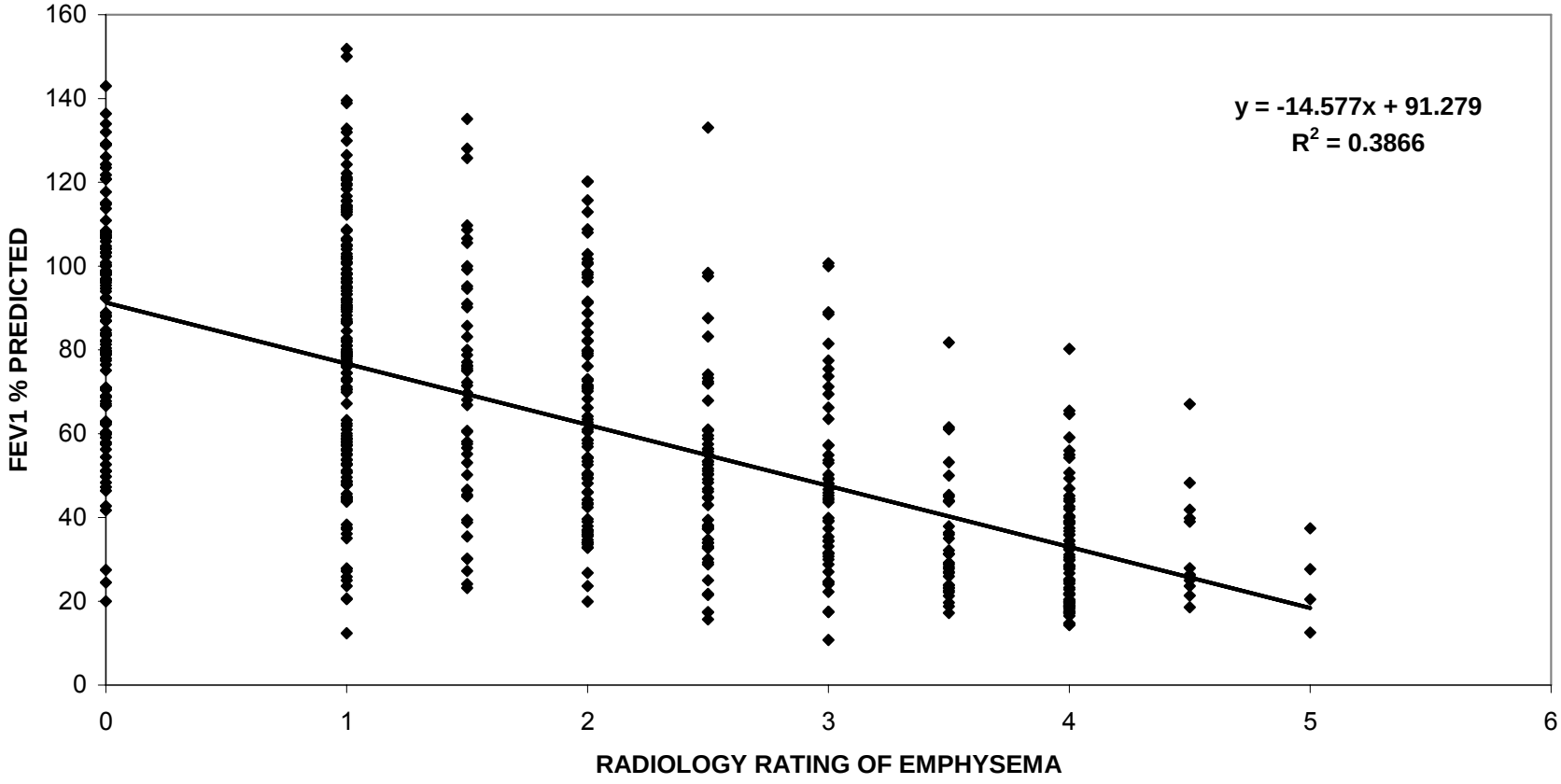

Figure 4-2a. Relationship of Radiologist Rating of Emphysema with Post-Bronchodilator FEV_1 % predicted

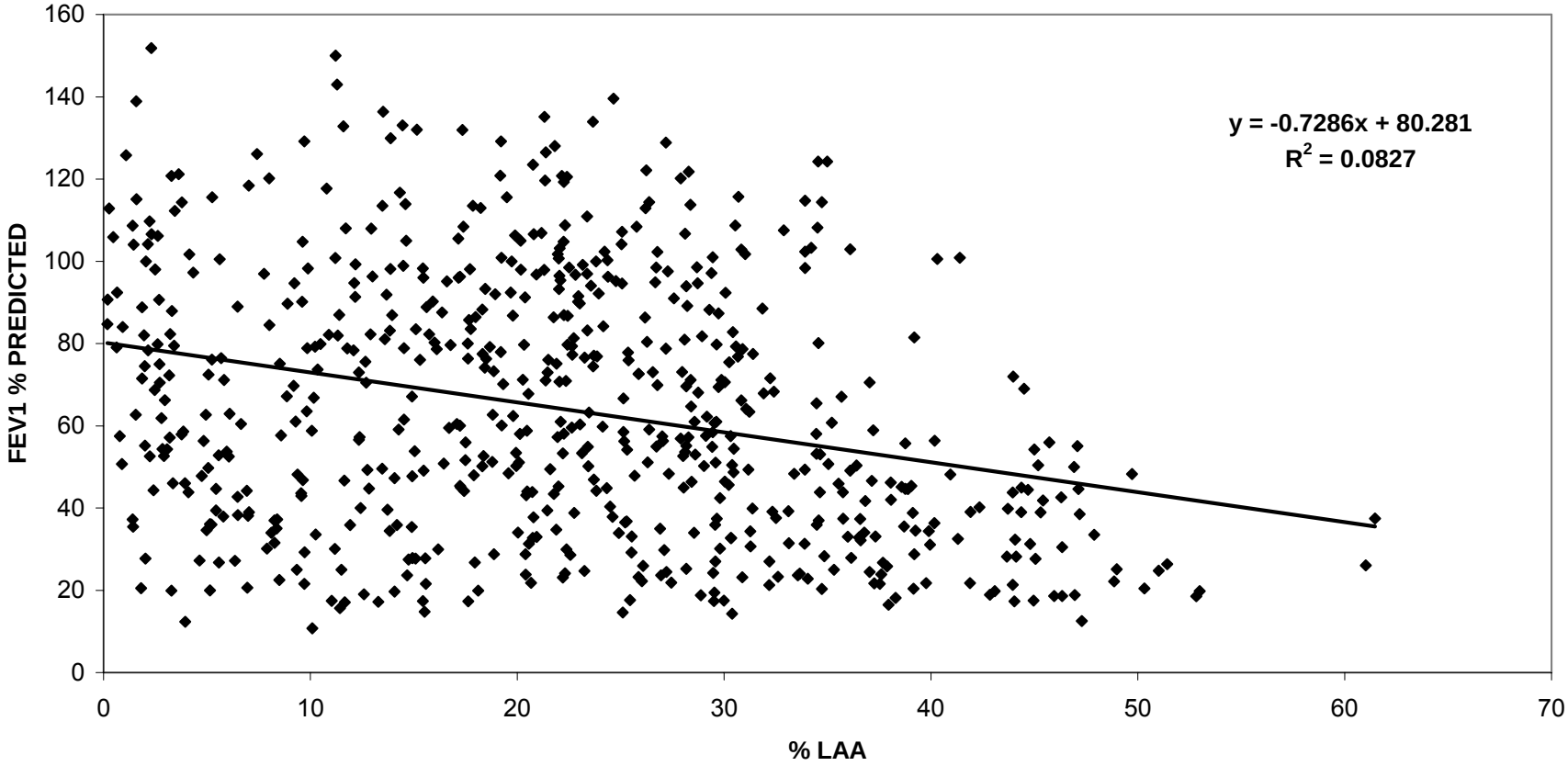

Figure 4-2b. Relationship of %LAA with Post-Bronchodilator FEV_1 % predicted

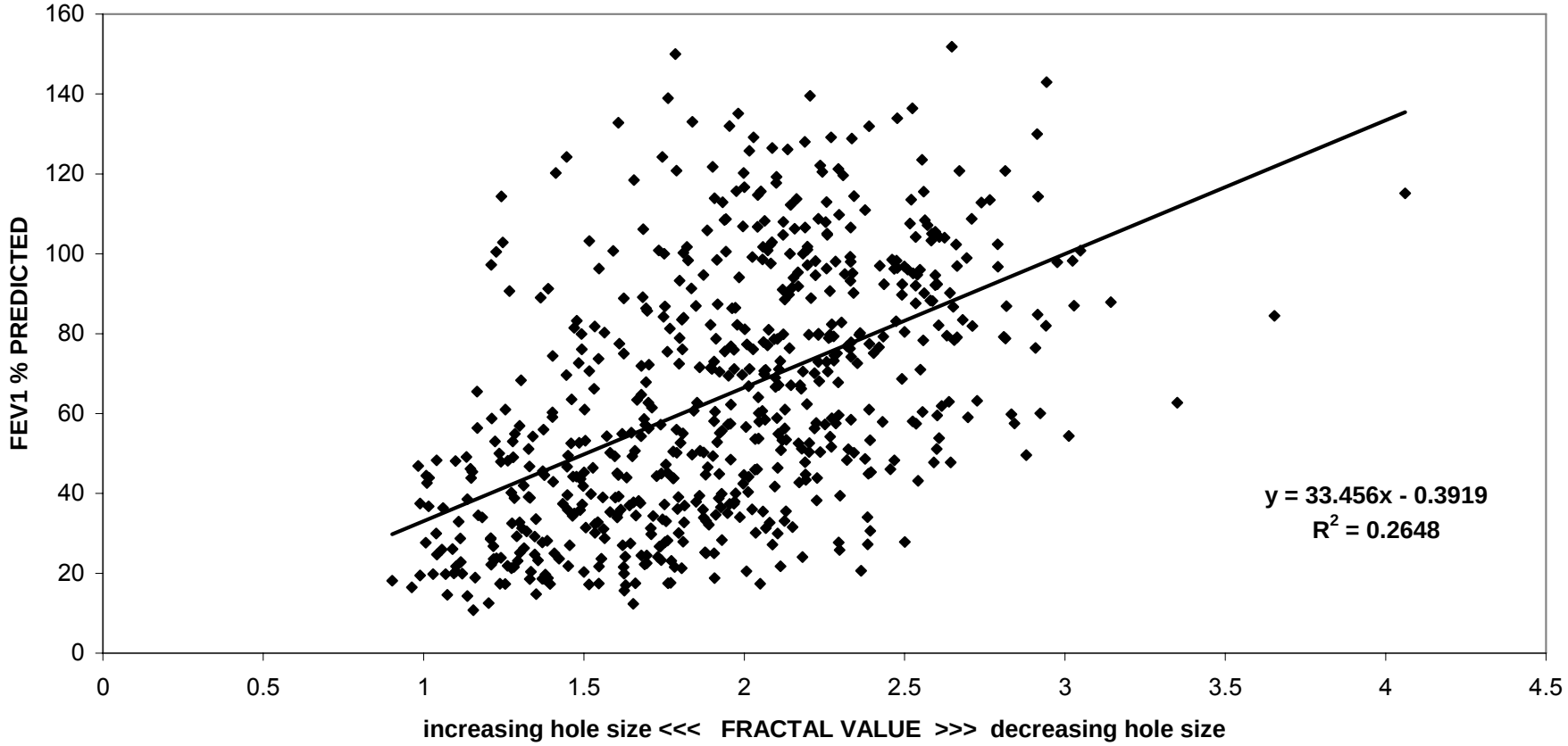

Figure 4-2c. Relationship of Fractal Value with Post-Bronchodilator FEV_1 % predicted

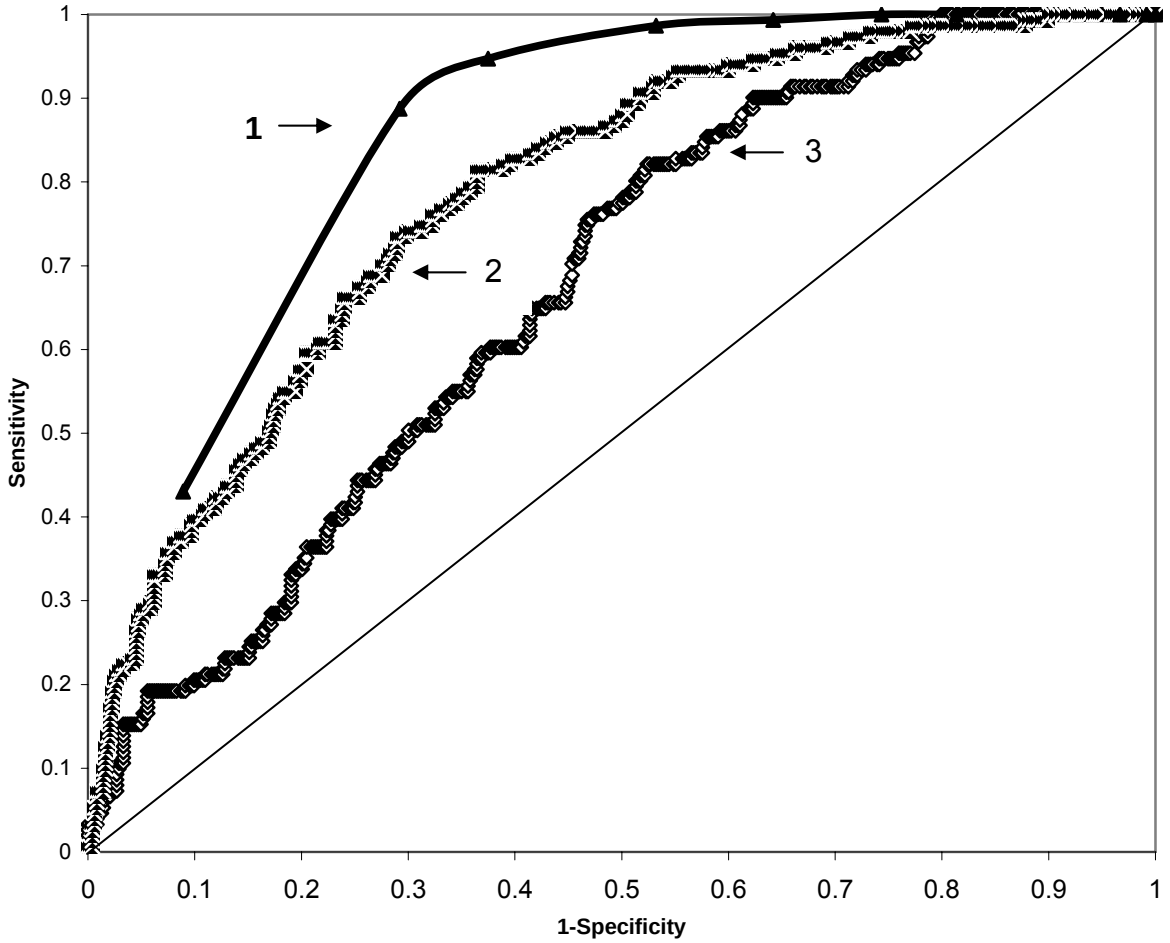

Figure 4-3. ROC Curves for Radiologist Rating (1) , Fractal Value (2) and % LAA (3) Estimates of Emphysema (COPD = $FEV_1/FVC < 0.70$)

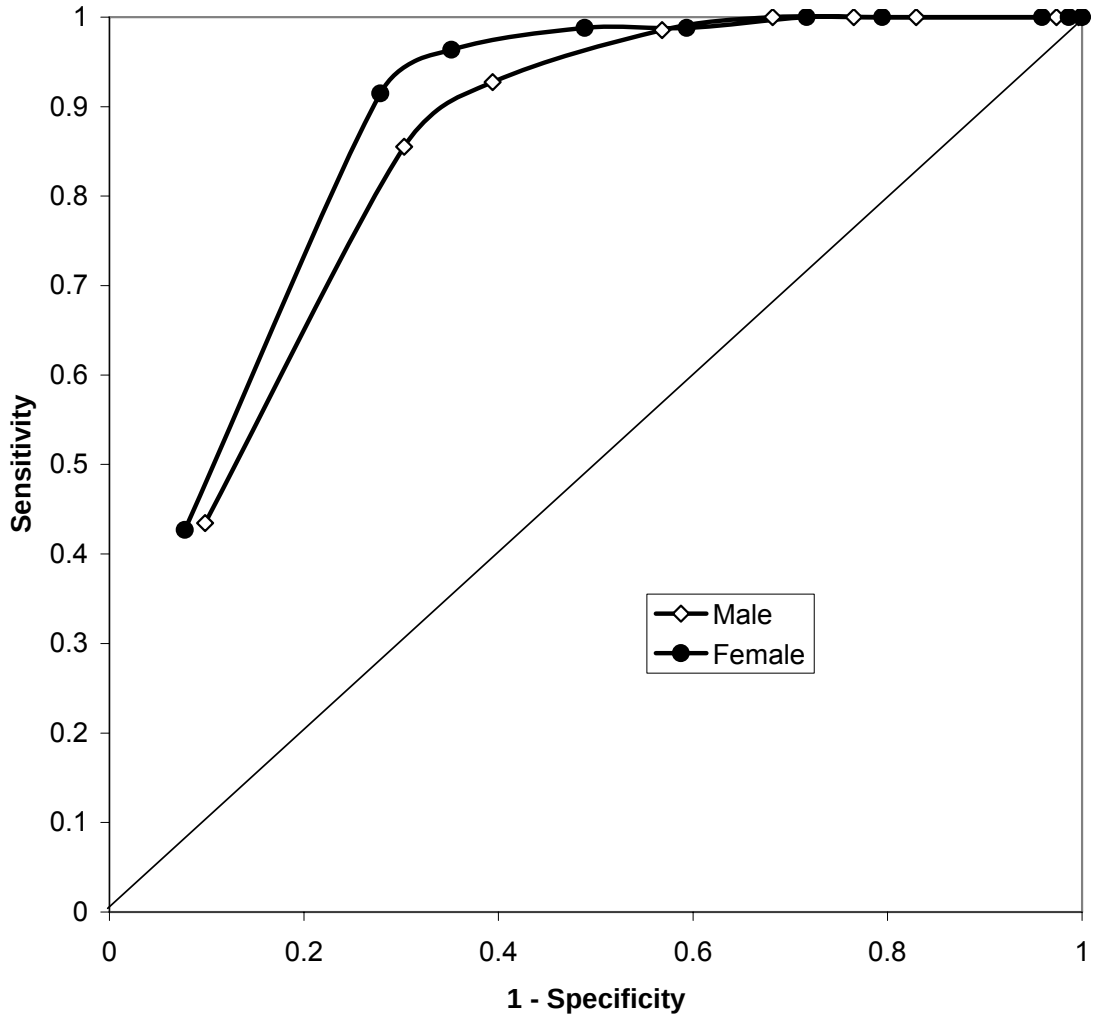

Figure 4-4. ROC Curves for Radiologist Score, by Sex (COPD=FEV_1/FVC < 0.70)

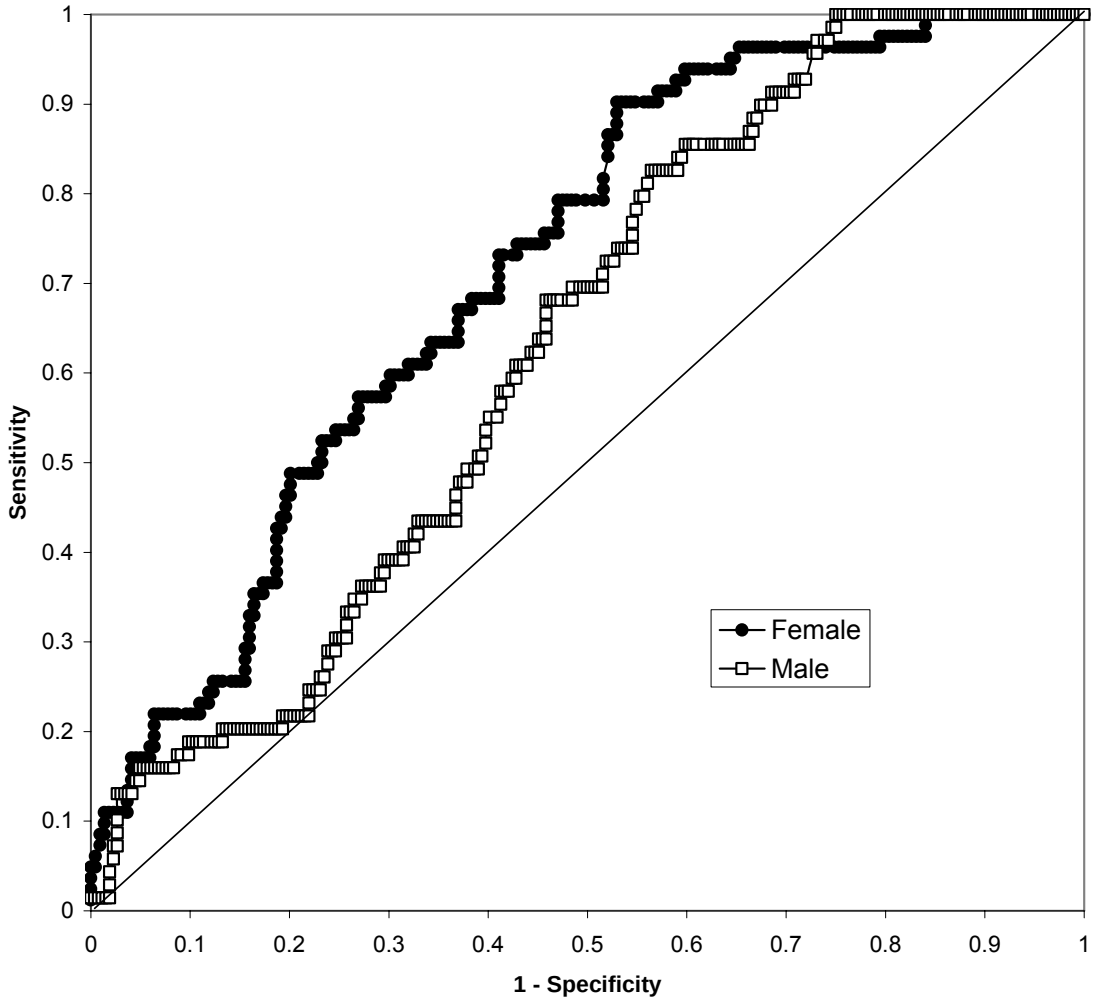

Figure 4-5 ROC Curves for %LAA, by Sex (COPD=FEV_1/FVC < 0.70)

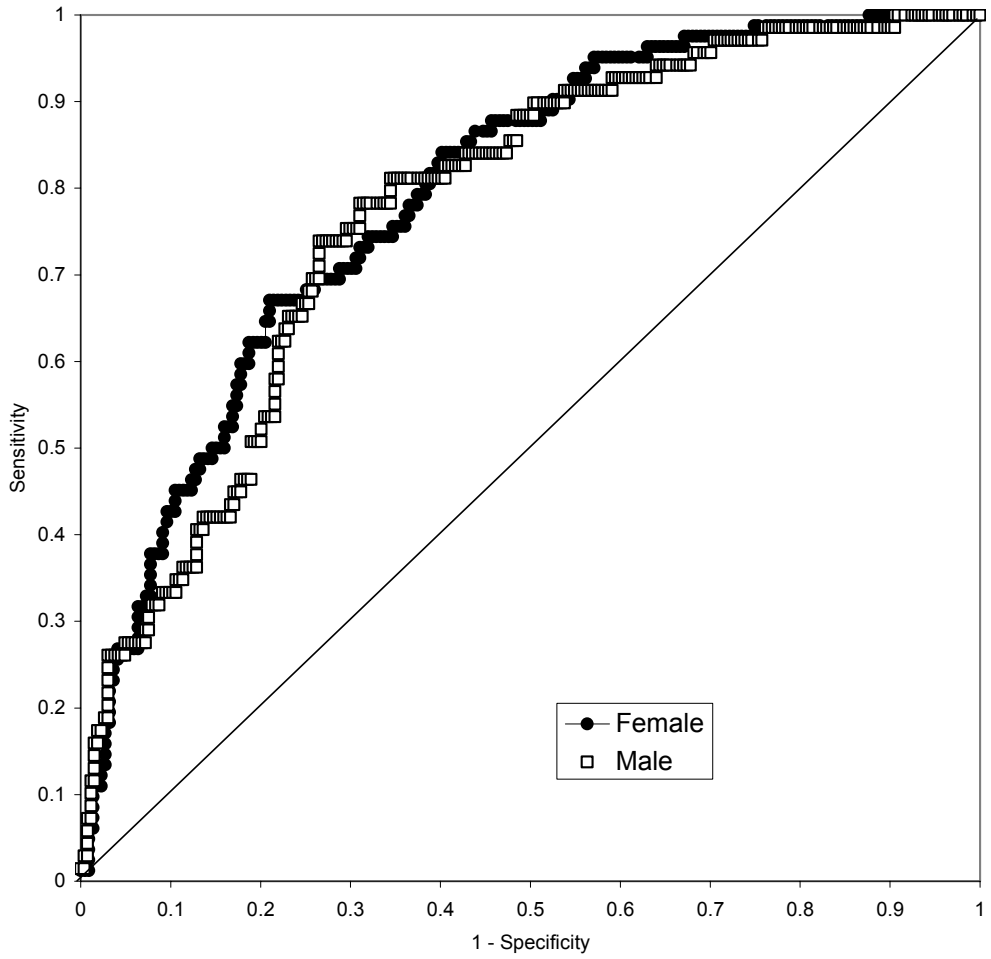

Figure 4-6. ROC Curves for Fractal Value, by Sex (COPD=FEV_1/FVC < 0.70)

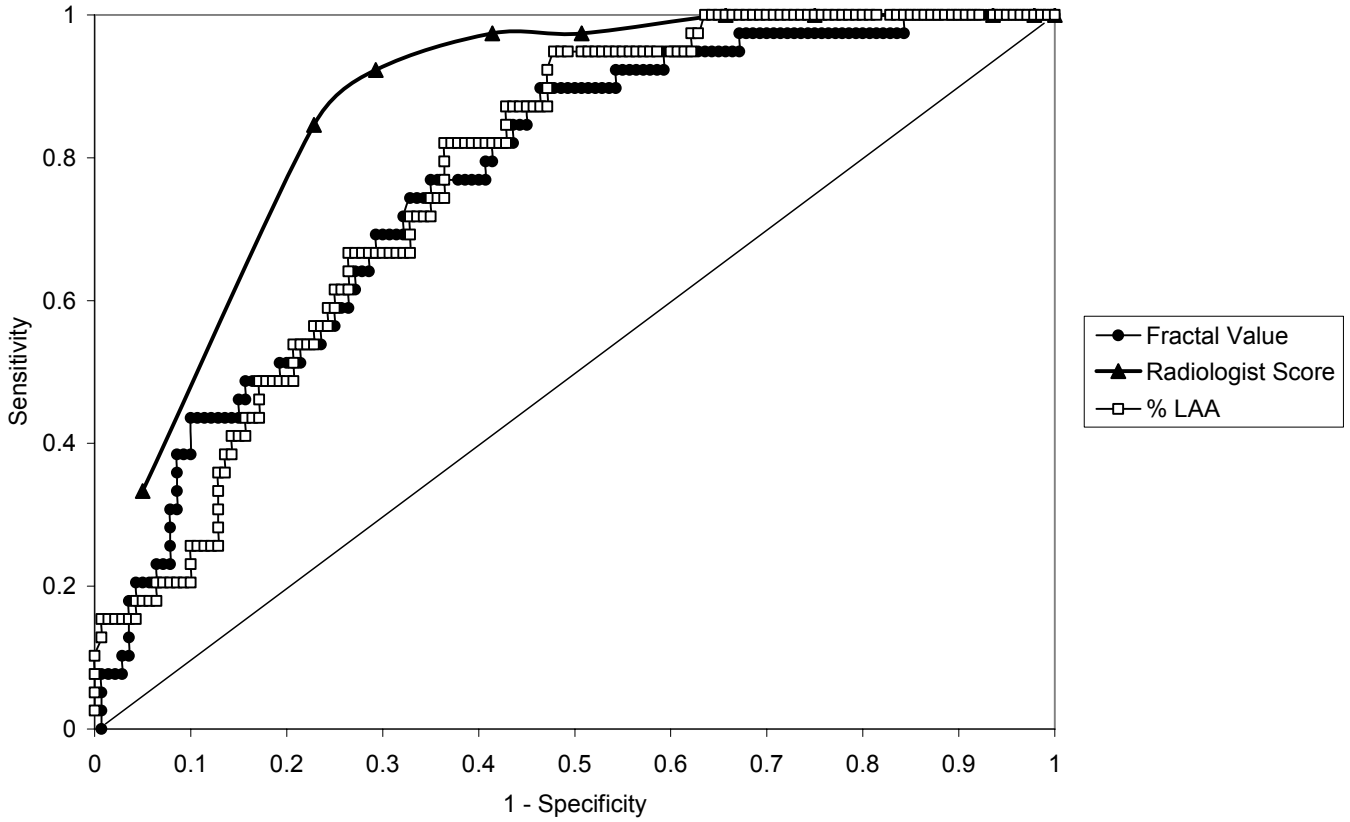

Figure 4-7. ROC Curves for Women – Low Weight

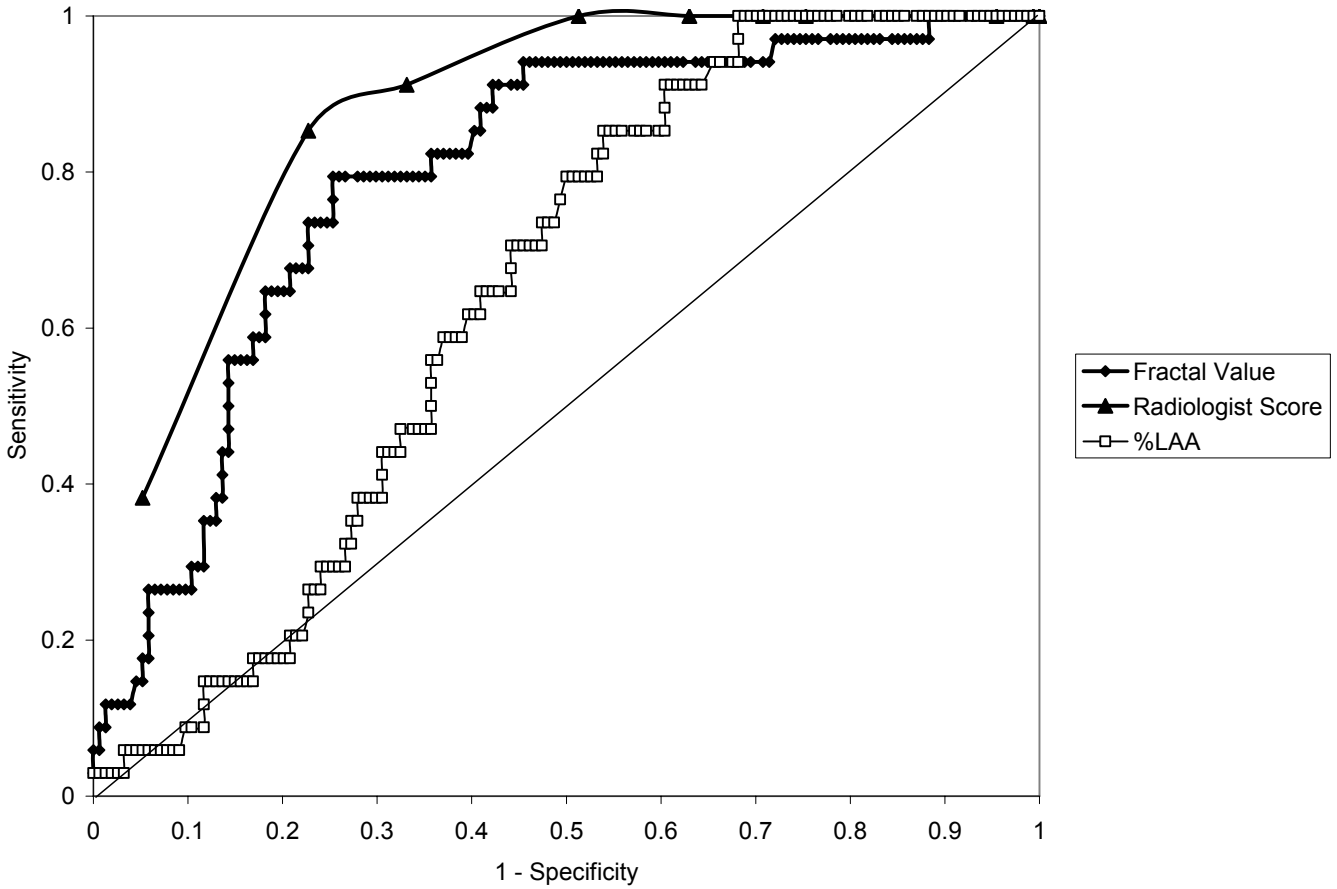

Figure 4-8. ROC Curves for Men – Low Weight

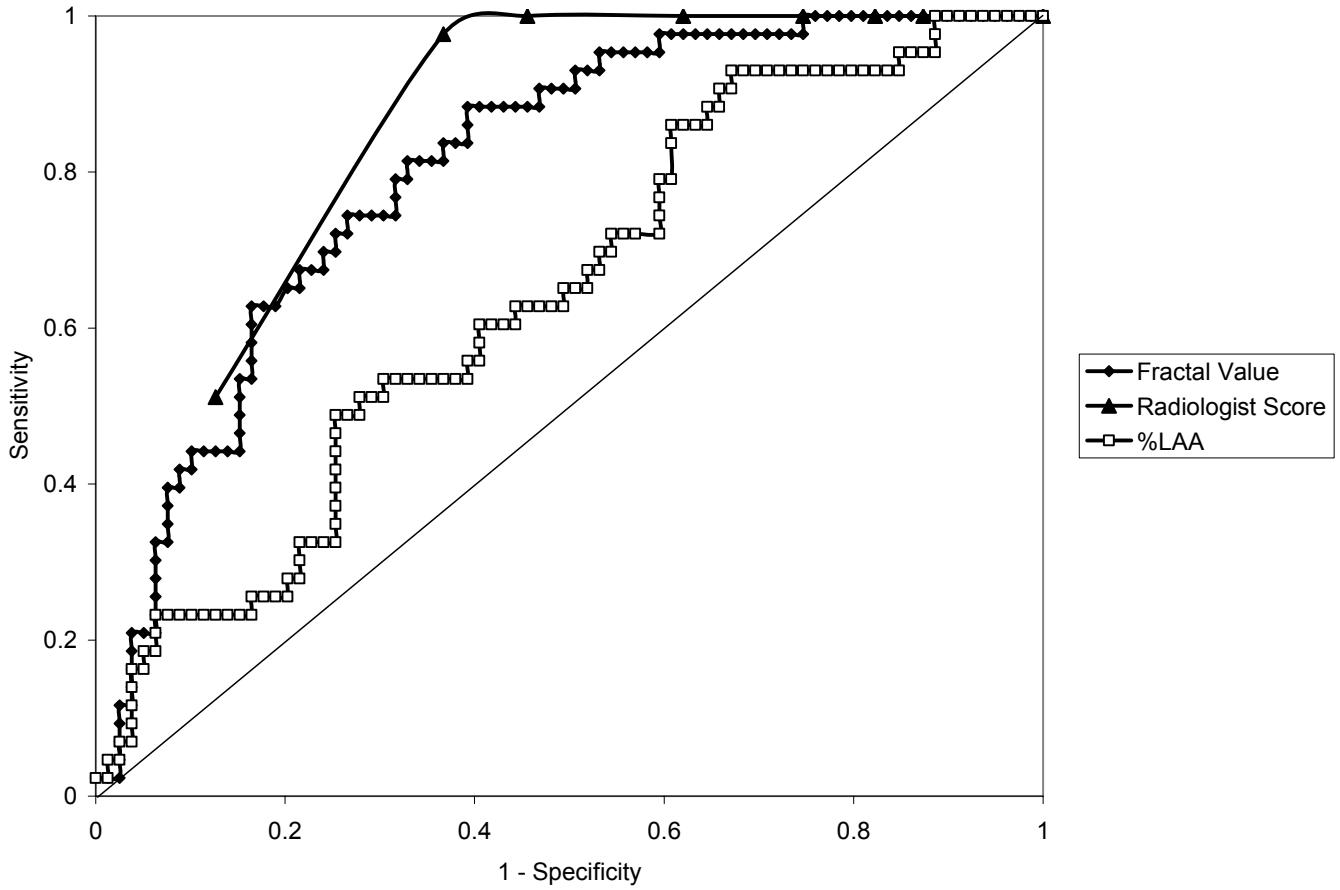

Figure 4-9. ROC Curves for Women – High Weight

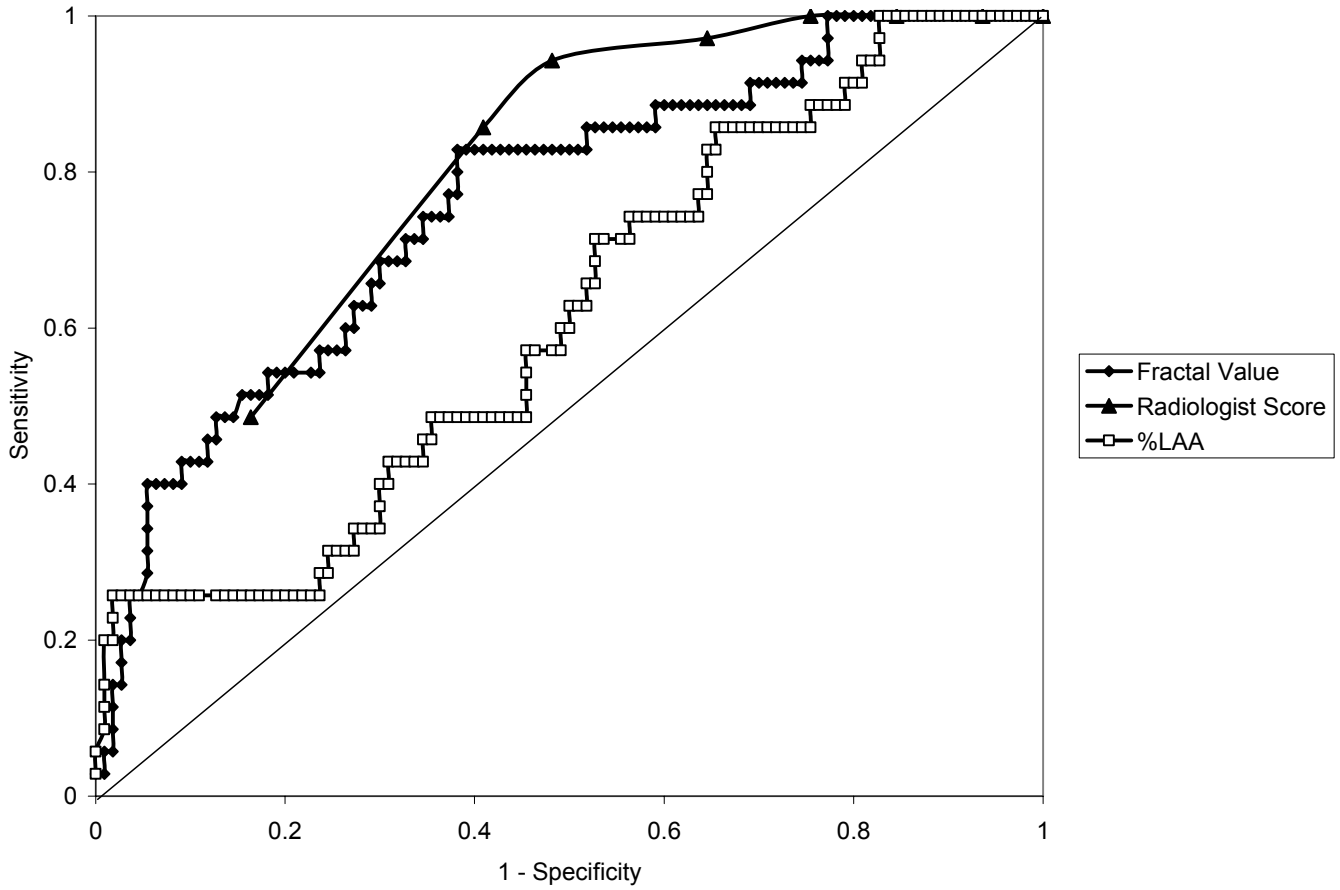

Figure 4-10. ROC Curves for Men – High Weight

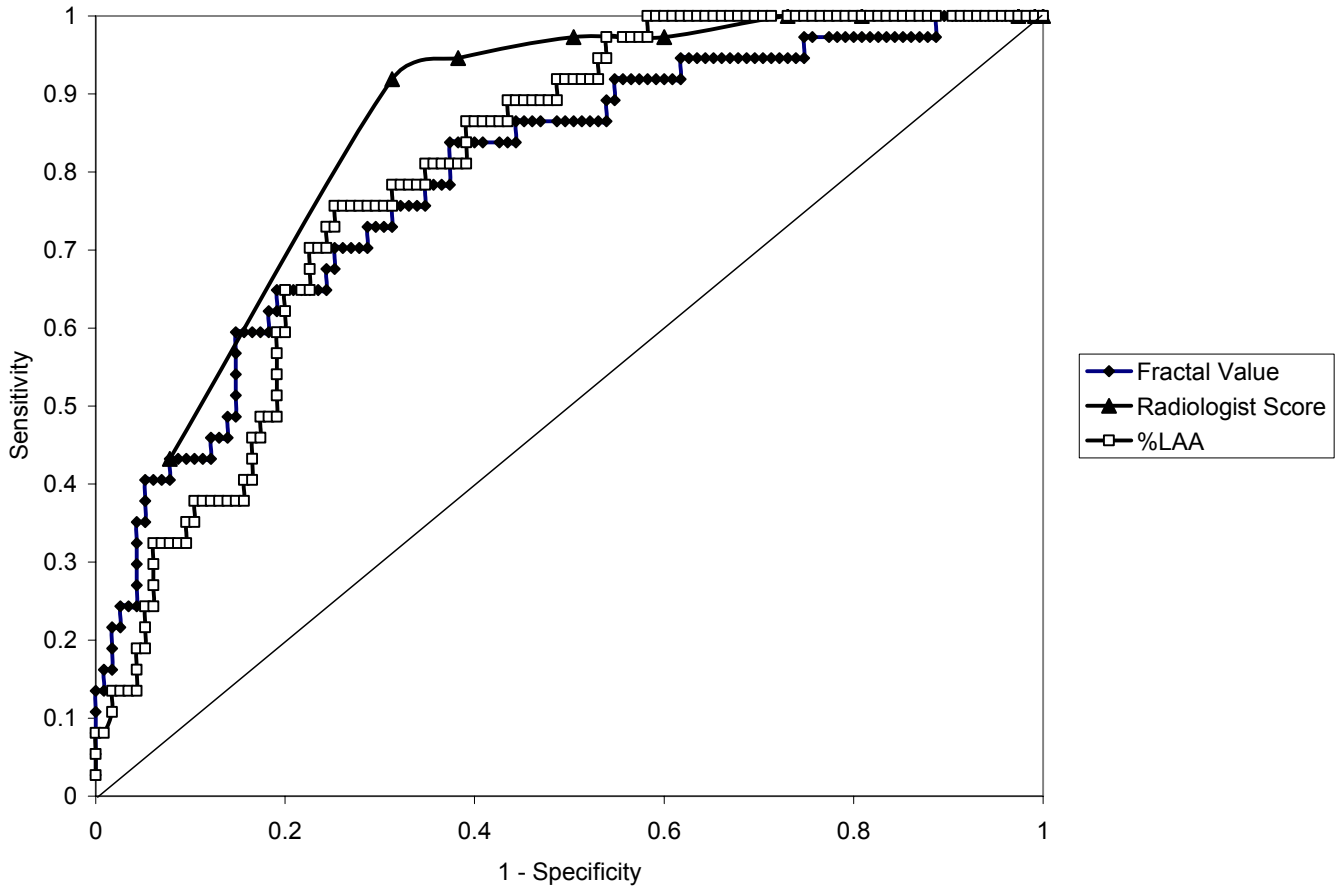

Figure 4-11. ROC Curves for Women – Low Height

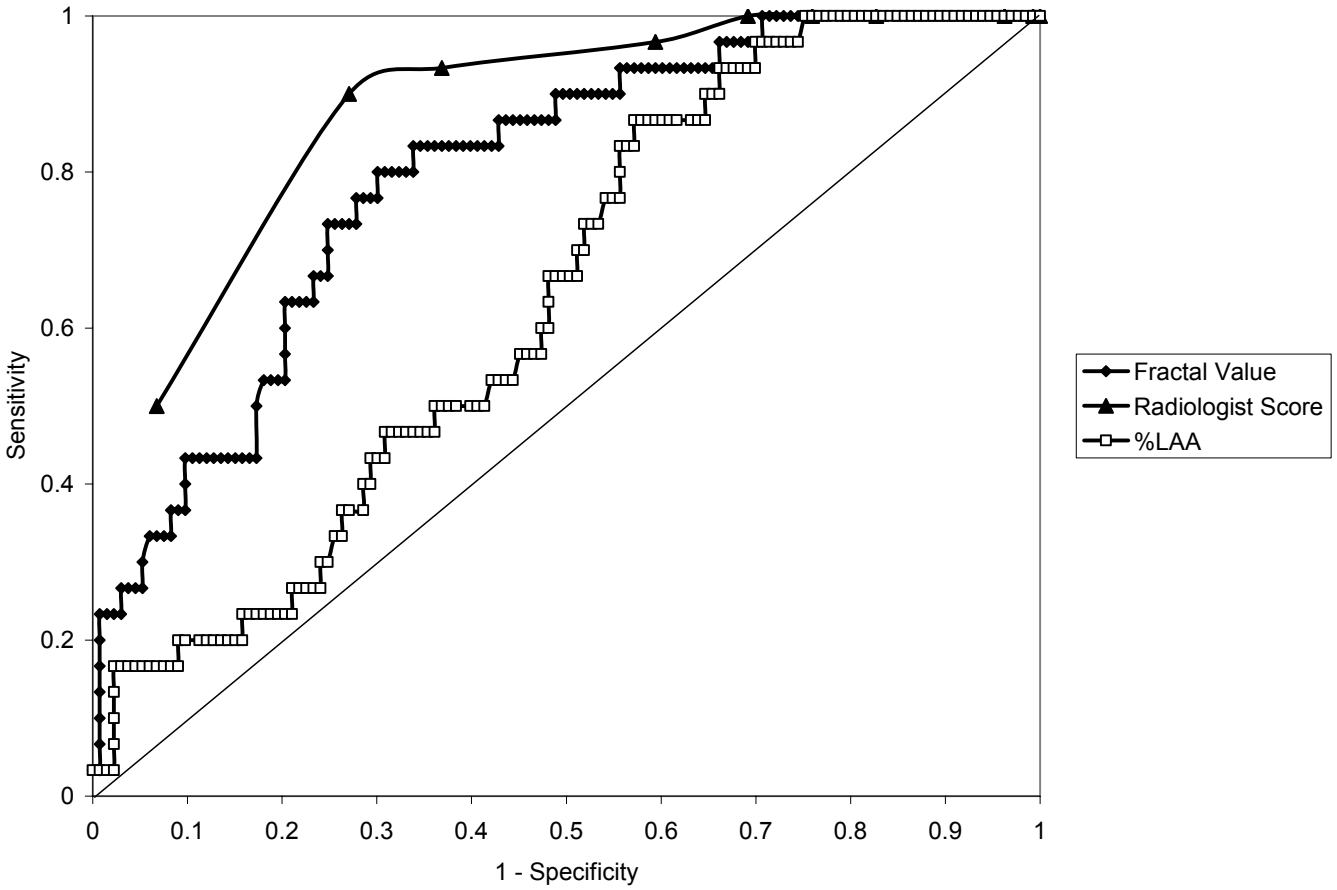

Figure 4-12. ROC Curves for Men – Low Height

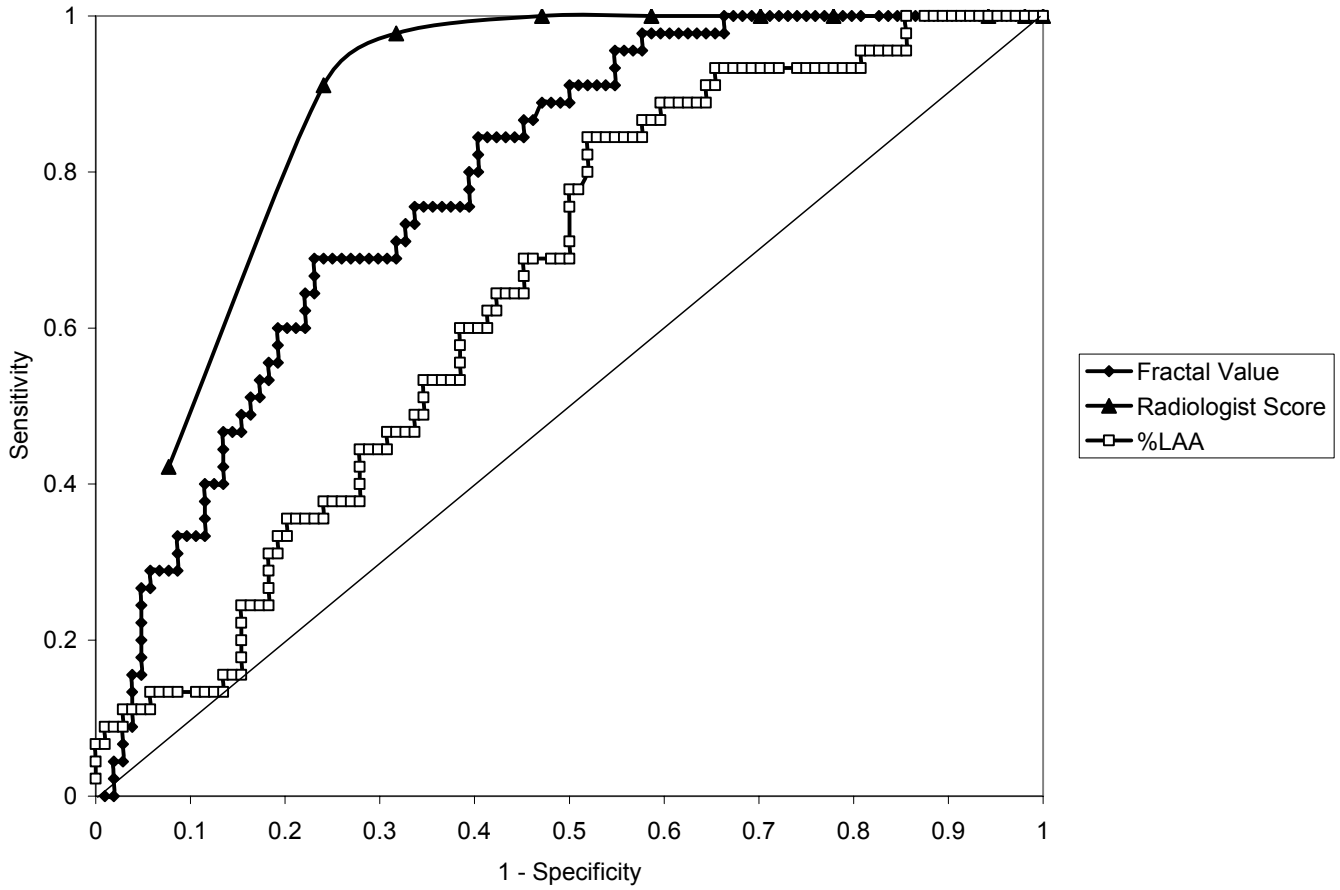

Figure 4-13. ROC Curves for Women – High Height

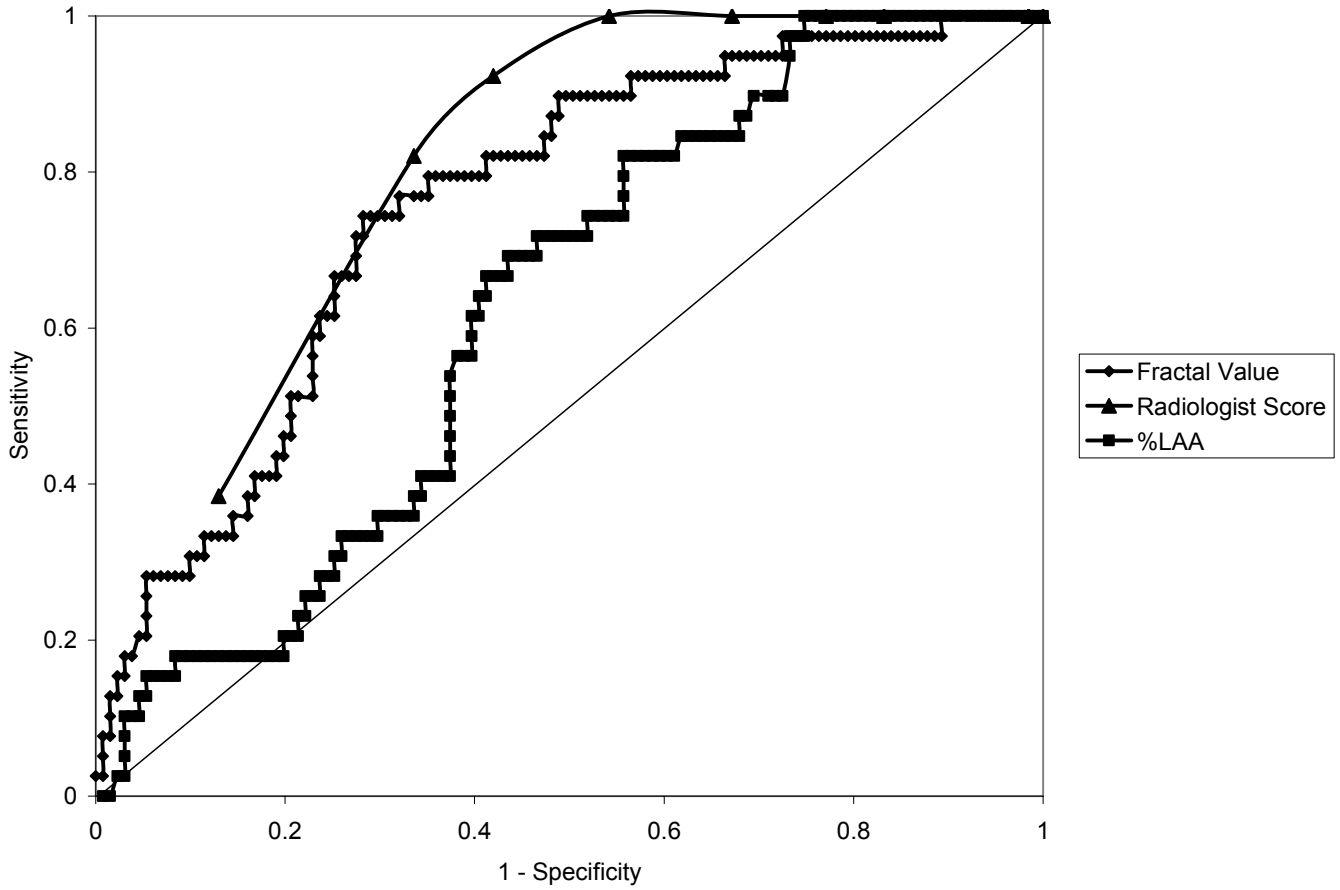

Figure 4-14. ROC Curves for Men – High Height

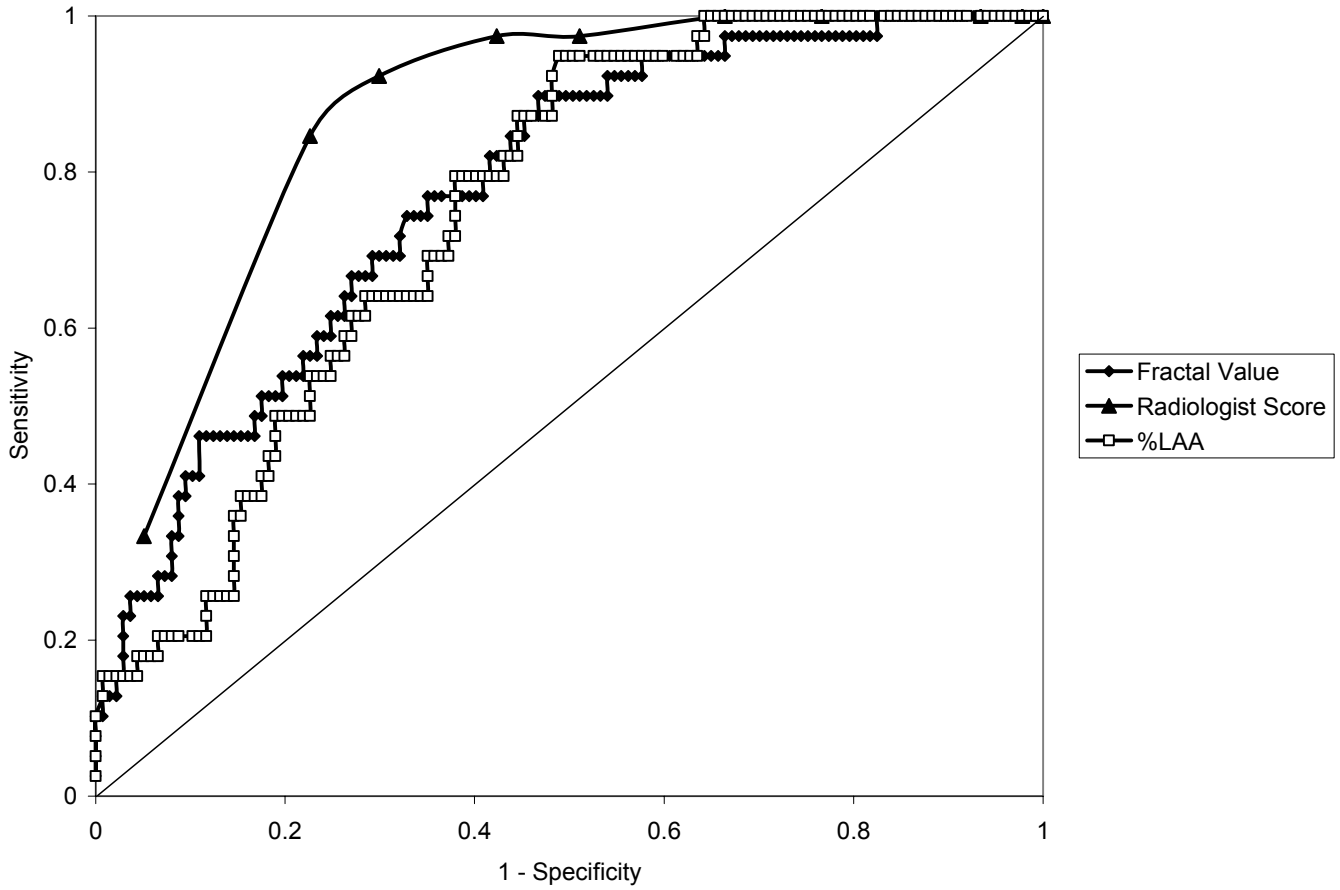

Figure 4-15. ROC Curves for Women – Low BMI

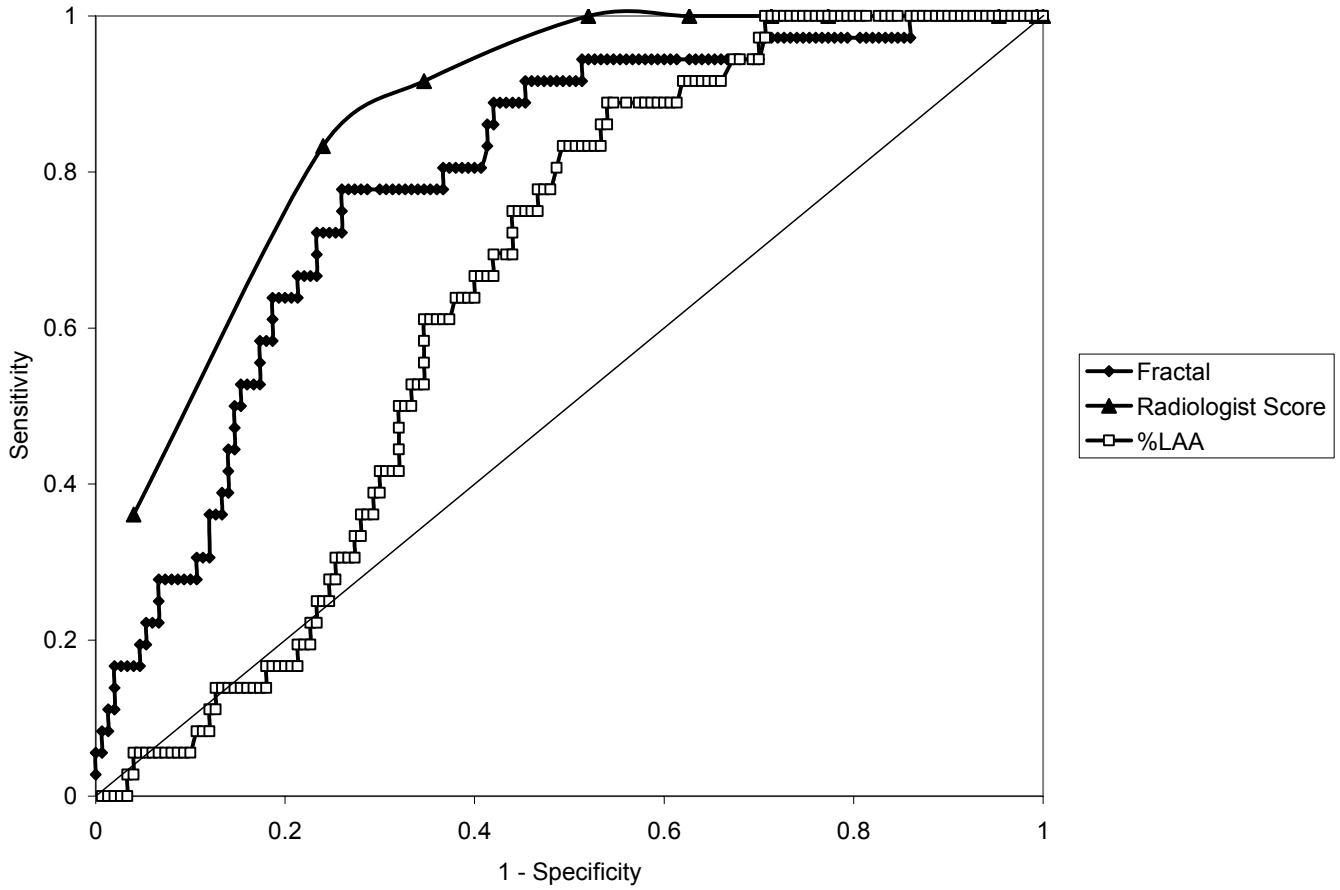

Figure 4-16. ROC Curves for Men – Low BMI

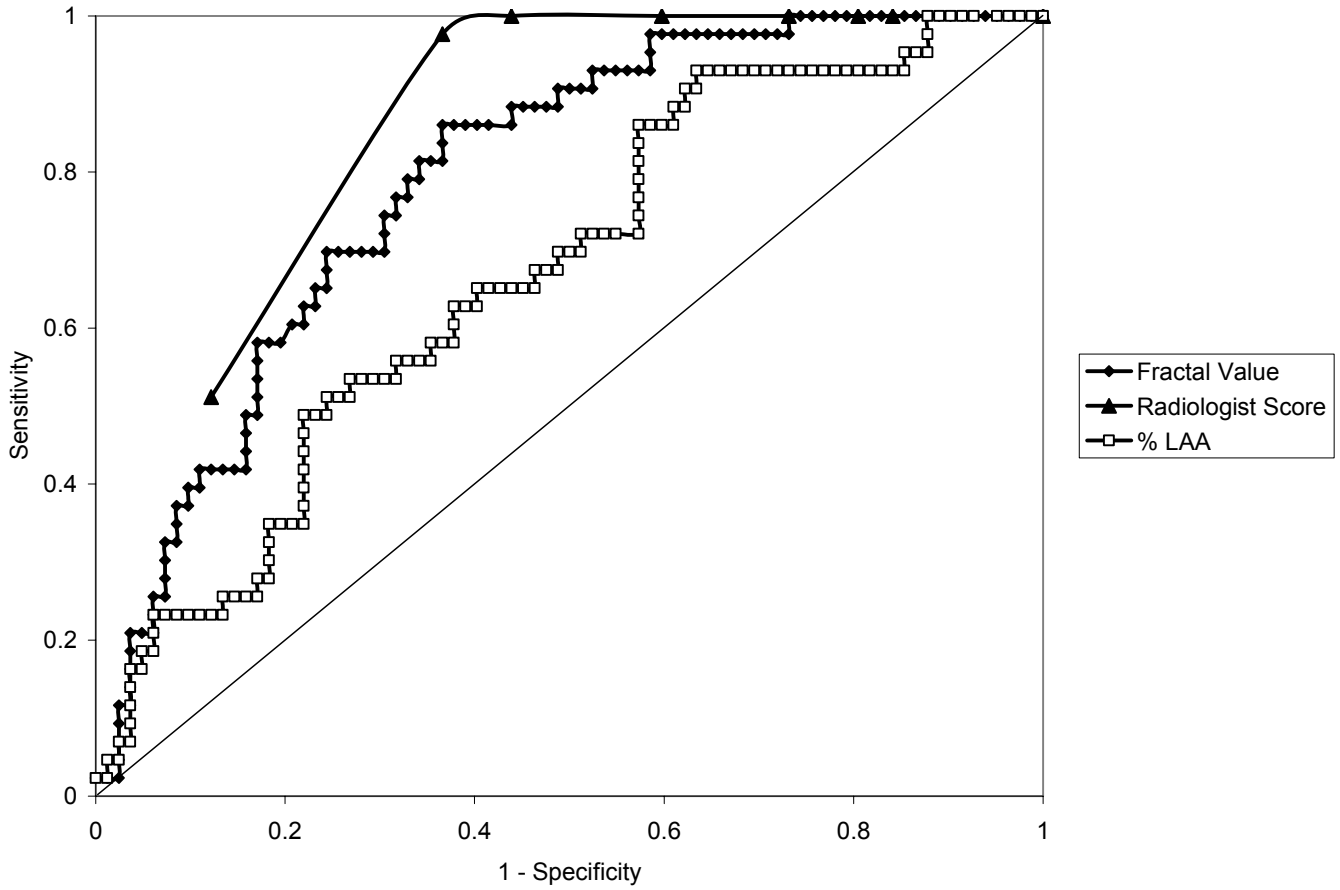

Figure 4-17. ROC Curves for Women – High BMI

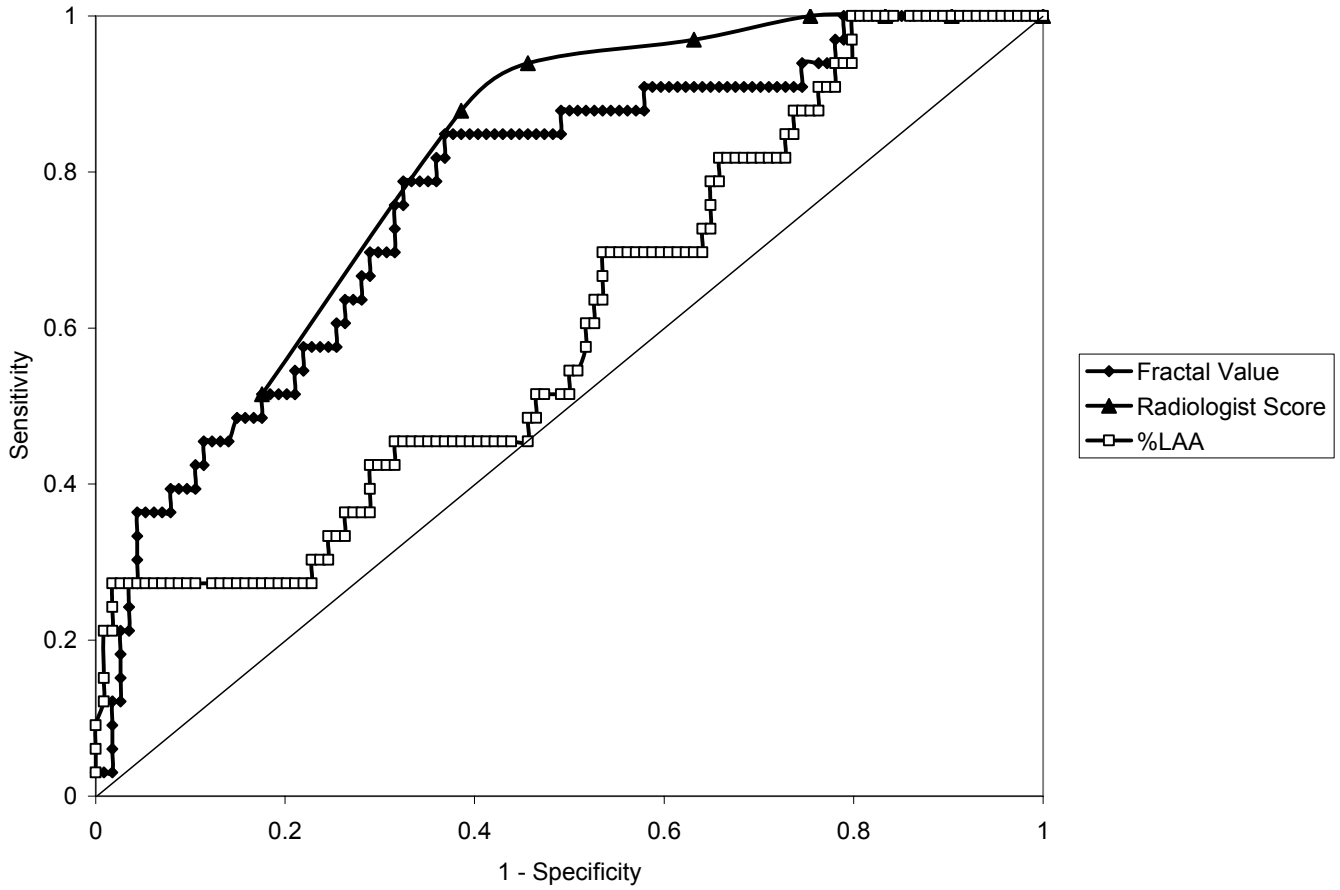

Figure 4-18. ROC Curves for Men – High BMI

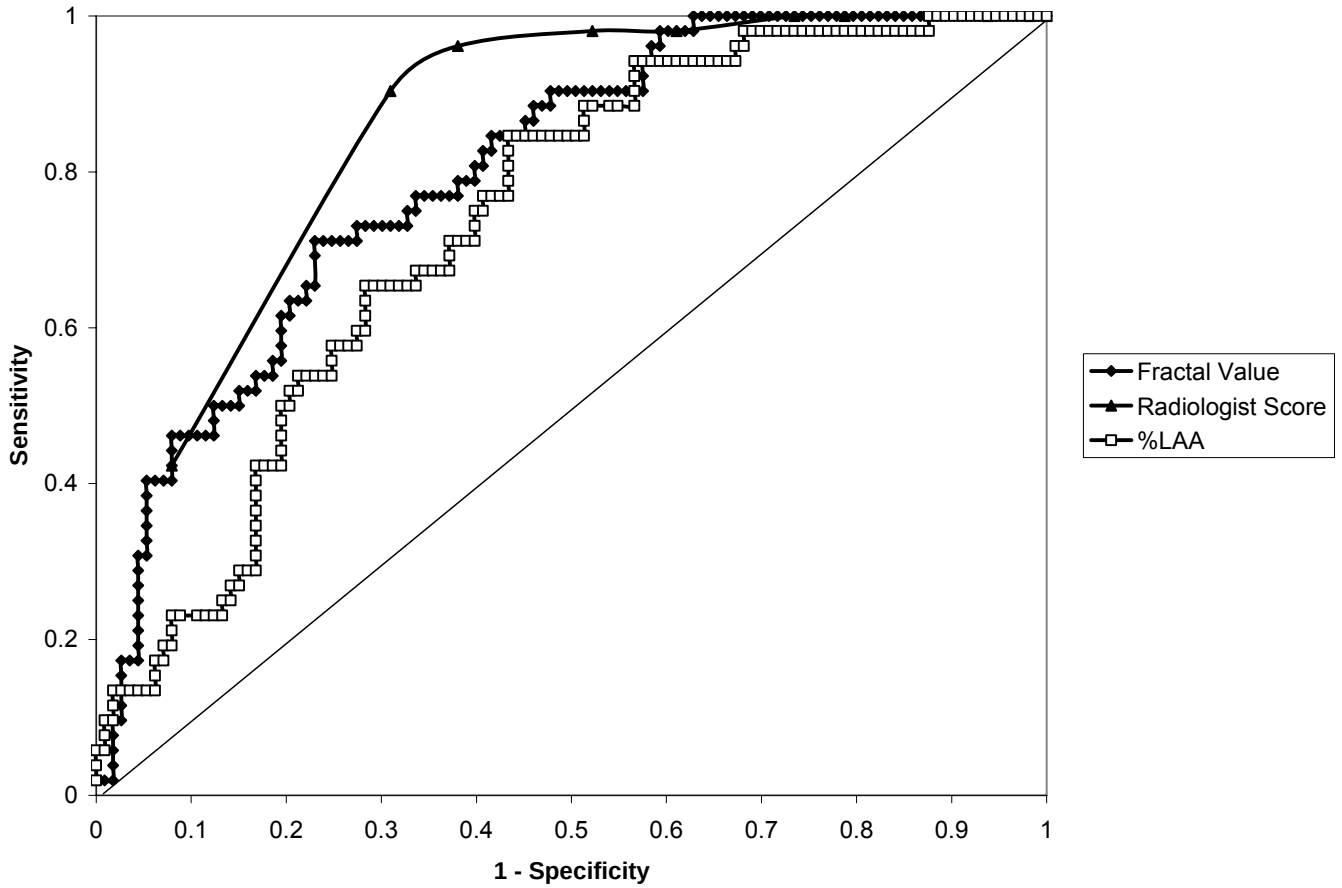

Figure 4-19. ROC Curves for Women – Low Age

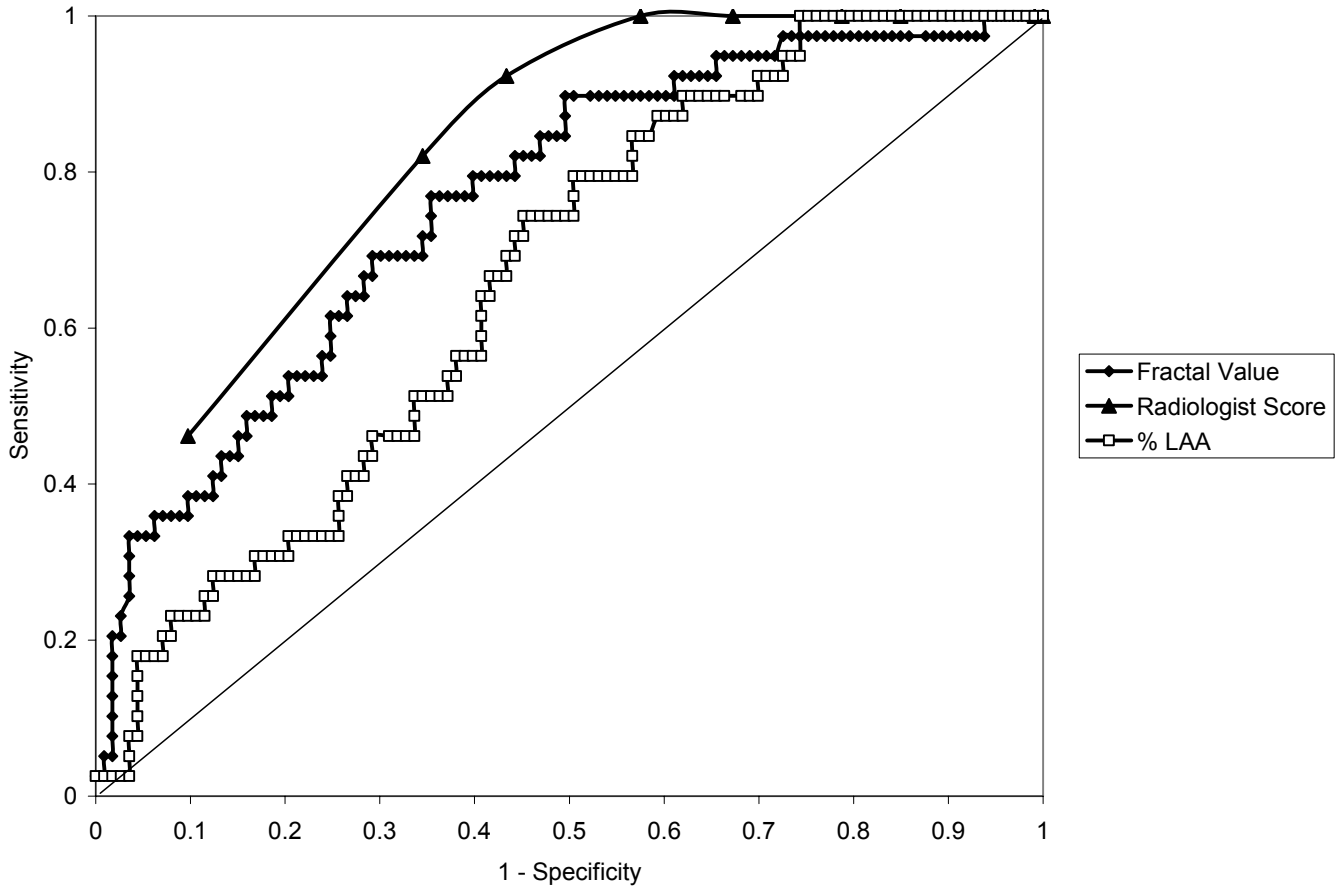

Figure 4-20. ROC Curves for Men – Low Age

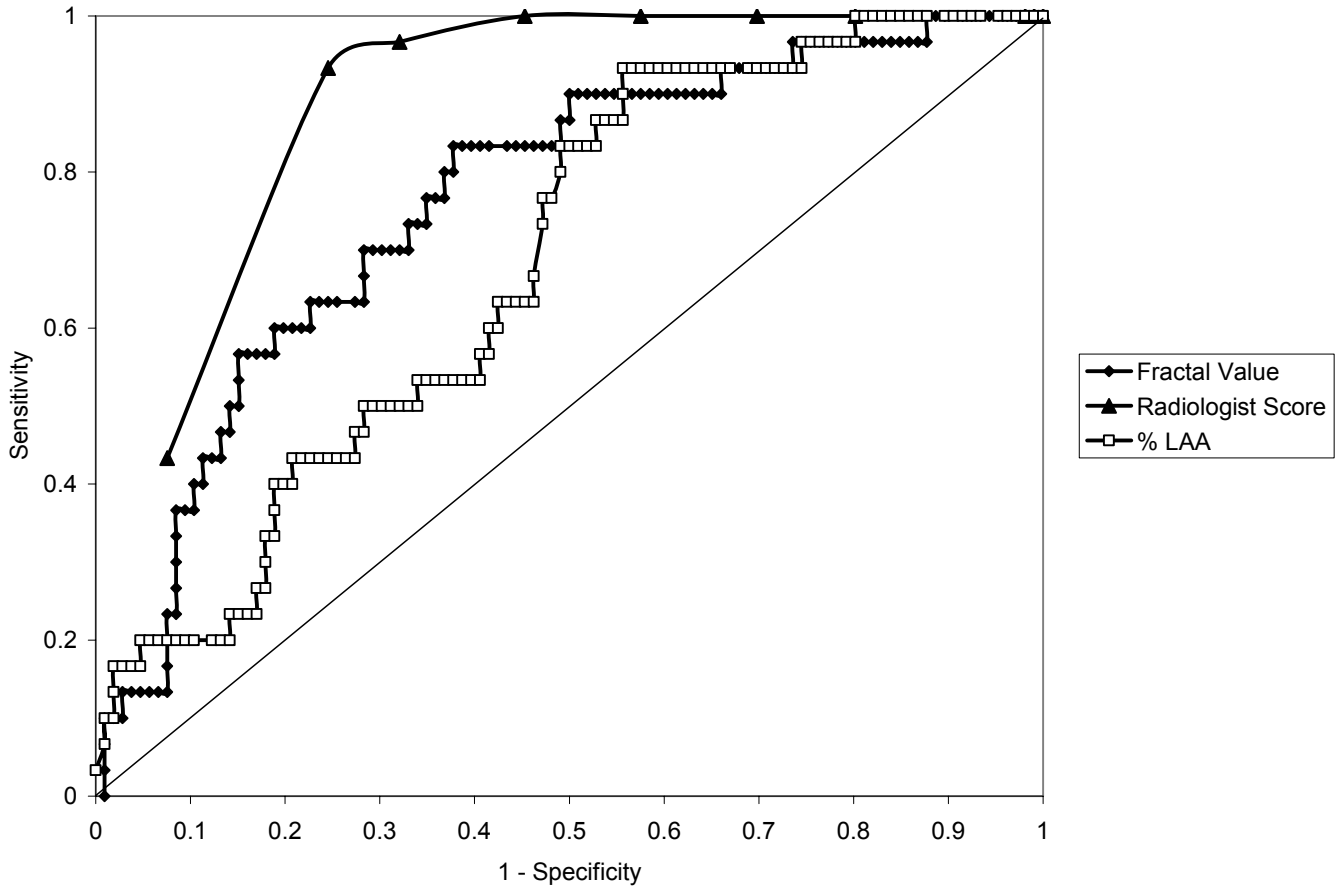

Figure 4-21. ROC Curves for Women – High Age

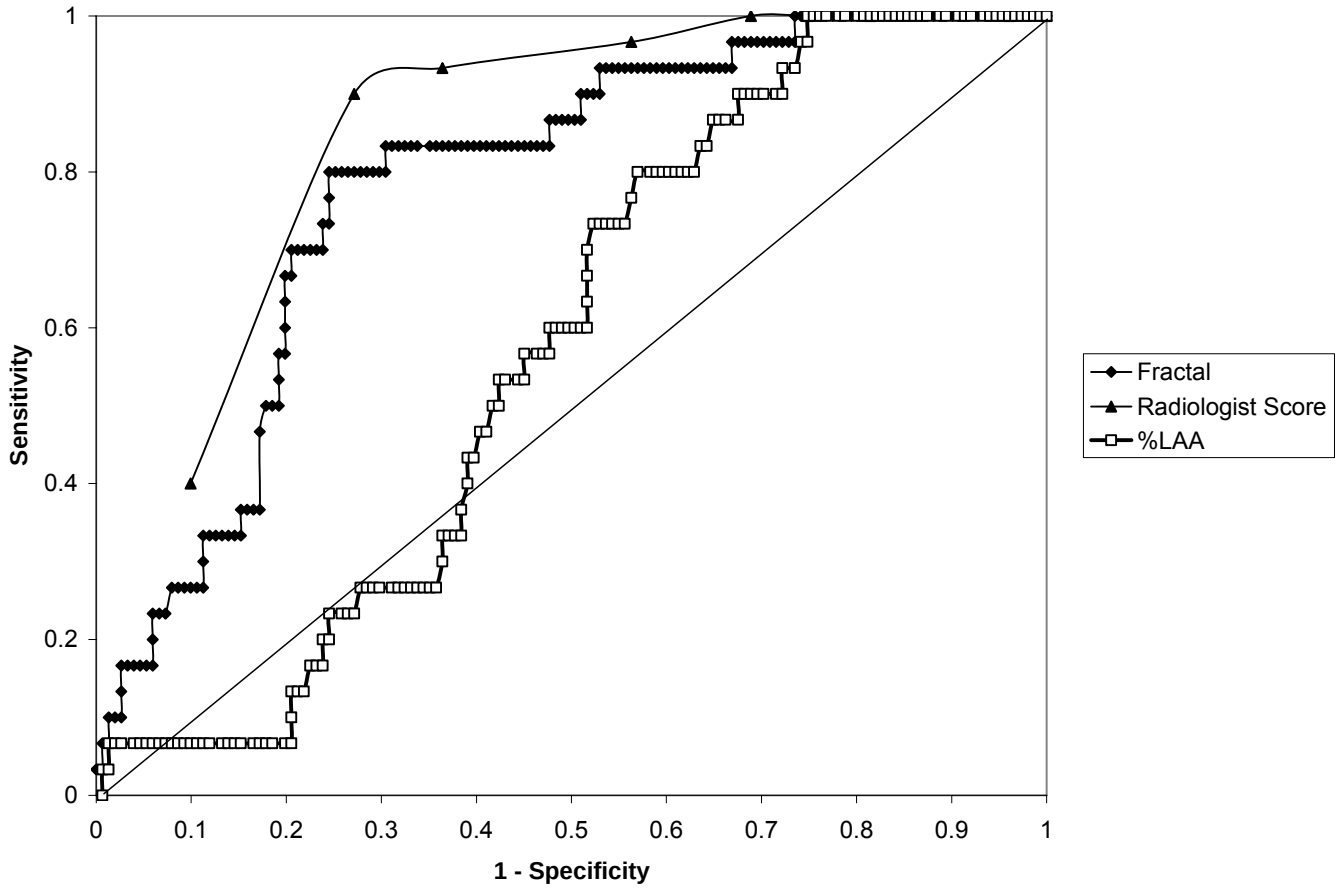

Figure 4-22. ROC Curves for Men – High Age

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CHAPTER FIVE. STRUCTURAL AND FUNCTIONAL DIFFERENCES BETWEEN TOBACCO SMOKE- AND BIOMASS SMOKE-INDUCED CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN MEXICAN WOMEN[1]

5.1 INTRODUCTION

Indoor air pollution from biomass burning has been implicated as a risk factor for the development of chronic bronchitis and chronic obstructive pulmonary disease (COPD), especially in developing countries (1-6). Biomass smoke exposure is important since approximately 50% of the world's population use biomass fuels as primary sources of energy for cooking, light, and heat (7) and they are often used in dwellings where ventilation is poor.

The clinical characteristics of COPD associated with exposure to biomass smoke and its prognostic factors have recently been well described. Ramirez-Venegas et al (8) reported that COPD patients exposed to biomass smoke were more likely to be women and despite less severe airflow obstruction than tobacco smokers with COPD they had similar symptoms, exercise capacity, quality of life and use of health services and supplementary oxygen.

Emphysema, as evidenced by an increase in low attenuation areas on lung computed tomography (CT) scans, as well as airway wall thickening are well-recognized features of COPD due to tobacco smoke. Whether these features are similar in biomass smoke-induced COPD is not known, since the pathological

[1] A version of this chapter will be submitted for publication:
Camp PG, Ramirez-Venegas A, Sansores R, McDougall J, Sin DD, Paré PD, Müller NL, Silva CIS, Rojas CE, Coxson HO. Structural and functional differences between tobacco smoke- and biomass smoke-induced chronic obstructive pulmonary disease in Mexican women.

processes which lead to COPD following biomass smoke exposure are poorly understood. There is some evidence that small airway disease may be the predominant lesion in biomass smoke-induced COPD. In a study of lung tissue obtained at autopsy Rivera et al (9) compared the morphological and morphometrical characteristics in those who had prolonged exposure to wood smoke with those exposed to tobacco smoke. Lungs exposed to wood smoke showed more significant and severe bronchiolitis and less emphysema compared to lungs exposed to tobacco smoke.

High resolution computed tomography (HRCT) and multi-detector computed tomography (MDCT) scans allow visualization of airways and parenchyma in much greater detail than conventional computed tomography scans and have made possible the investigation of the site, magnitude, and distribution of parenchymal destruction, gas trapping and airway narrowing *in vivo*. There have been no studies directly comparing the parenchymal and airway features of COPD in patients exposed to biomass smoke versus tobacco smoke using MDCT. We compared MDCT scans of women with COPD due to biomass smoke exposure matched with women with COPD due to tobacco smoke exposure. We hypothesized that biomass smoke exposure would result in an airway-predominant phenotype of COPD, with increased airway wall thickness and air-trapping.

5.2 METHODS

5.2.1 Subject Selection

We conducted a cross-sectional study to compare MDCT scans in twelve Méxican women who had COPD due to biomass smoke with twelve women whose COPD was due to tobacco smoke.

Subject recruitment, lung function and questionnaire testing was carried out in México City at the COPD Clinic of the National Institute of Respiratory Diseases, a referral hospital which provides health care services to the economically-deprived population of México. The MDCT scans were performed in the Médica Sur Hospital in México City and the quantitative and qualitative measurements of emphysema and airway dimensions were done at the James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research (Vancouver General Hospital site) in Vancouver, Canada.

We recruited women with a diagnosis of COPD based on the GOLD criteria (10). The level of exposure to biomass or tobacco smoke was determined by a clinical interview and a standardized Spanish version of the American Thoracic Society (ATS) questionnaire (11) with the additional questions referring to cooking fuels. Women with biomass smoke exposure were considered eligible for the study if they had been exposed to biomass smoke (predominantly while cooking) on a daily basis for at least 6 months. Cumulative exposure was expressed as hour-years, the product of the number of years cooking with wood stoves by the average number of hours spent daily in the kitchen. Women with tobacco smoke exposure were

considered eligible if they had accumulated a minimum of ten pack-years of cigarette smoke exposure. If subjects fulfilled the inclusion criteria, they were invited to participate in the study after reading and signing an informed consent. Subjects were matched one-to-one by age (plus or minus 5 years) and % predicted forced expiratory volume in 1 second (FEV_1 % predicted) (plus or minus 10%). We excluded subjects who had both biomass smoke and tobacco smoke exposure or had a history of other chronic pulmonary diseases such as asthma, tuberculosis or bronchiectasis. The study was reviewed by the ethical review boards at the National Institute of Respiratory Diseases, Médica Sur, and the University of British Columbia (St. Paul's Hospital).

5.2.2 Lung Function and Questionnaire Testing

Subjects underwent post-bronchodilator spirometry, plethysmography, six minute walk test (6MWT), and MDCT. Subjects also completed the Medical Research Council (MRC) Dyspnea Scale (12), the St. George's Respiratory Questionnaire (SGRQ) (13) and the Chronic Respiratory Questionnaire (CRQ) (14) translated into Spanish. Evaluation was made when subjects had been free of exacerbations for a minimum of one month. Post-bronchodilator spirometry was done using a dry rolling-seal volume spirometer (Sensormedics; Yorbalinda, California) following the procedures recommended by the ATS (15) and using Mexican standard reference equations (16). These reference equations are similar to the National Health and Nutrition Examination Survey III values for Mexican-Americans (17). The 6MWT was done according to ATS guidelines (18) using

distance walked during the second test for the analysis. Plethysmographic lung volumes were following the procedures recommended by ATS and using ATS reference equations (19).

5.2.3 CT Scan Acquisition

MDCT scans of the thorax were obtained at suspended full inspiration and expiration using a Siemens Sensation 16 multi-detector CT scanner (Siemens SA, Mexico City, Mexico). Contiguous CT images were reconstructed using a 1mm slice thickness and both a low (b35f) spatial frequency reconstruction algorithm for emphysema measurements, and a high (b65f) spatial frequency reconstruction algorithm for airway measurements.

Measurement of Emphysema. A quantitative assessment of emphysema was performed using a 'density mask' analysis, with a threshold for defining emphysema of -950 Hounsfield units (20). This analysis provides a % low attenuation area (% LAA) with increasing values indicating more severe emphysema. We also calculated the fractal value which is the inverse slope of the log-log relationship of the size of the low attenuation spaces versus the number of spaces. Individuals who have diffuse emphysema and smaller LAA spaces will have a larger fractal value than individuals with larger emphysematous spaces (21).

In addition to the quantitative measurements of emphysema, two radiologists blinded to the hypotheses and exposure groups independently reviewed each scan. Emphysema was scored on a 6-point scale (0 – no emphysema; 1 – trivial, less than 5% of the lung with emphysema; 2 – mild, 5-25% of the lung with emphysema;

3 – moderate, 25-50% of the lung with emphysema; 4 – severe; 50-75% of the lung with emphysema; and 5 – very severe, greater than 75% of the lung with emphysema). After independently scoring the scans, the radiologists met and determined a consensus score for scans where their original scores differed.

Airways and Air Trapping. All airways cut in a reasonable cross section (long/short internal diameter 2.2 or less) were analyzed. Every 10th slice was used to avoid the possibility of airway overlap. Airway dimensions were measured using custom software (Emphylx-J, James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research, Vancouver, B.C.). A region of interest was selected by clicking in the general area where the airway was located; this causes the program to magnify that region. A seed point was placed in the airway lumen and 64 rays were projected 360 degrees around the airway. The x-ray attenuation values were measured along each ray and the airway wall was defined using the full-width-at-half-maximum principle (22). The airway lumen perimeter (Pi) and outer airway wall perimeter (Po) were measured by connecting the end points of each of the rays through the airway wall using a spline function. Manual editing of projection rays was used to remove rays that project beyond the airway wall into neighboring dense structures such as pulmonary arteries**.** The lumen area (Ai) was defined as the area inside the internal perimeter. The total area of the airway (Ao) was defined as the area inside the outer perimeter. The airway wall area (Aaw) was defined as the area between these two perimeters and the percent of the airway that was wall (WA%) was Ao-Ai/Ao x 100.

Wall area and wall area percent are directly related to the size of the airway. Wall area is greater in larger airways, while the wall area percent decreases as airway size increases. There are various methods to estimate airway wall thickness. By plotting the Pi of each airway against the square root of wall area for each individual subject, a linear regression equation can be derived (23). Using this equation, the square root of the wall area at a standard Pi (usually 10mm) can be calculated for each subject. Calculating the square root of the wall area at Pi of 10mm (SQRTWA@Pi10) allows for the comparison of overall airway wall thickness between subjects while accounting for the different airway sizes measured in each subject. One limitation of this method is that all the airway measurements are condensed into one summary measure of wall thickness. Individuals with heterogeneous airway disease and more variation in SQRTWA for a given Pi may have a less accurate estimate of SQRTWA@Pi10 than individuals with a stronger linear relationship between SQRTWA and Pi. An alternate method is to compare the SQRTWA and the wall area % between the two exposure groups using all the airways measured, yet statistically adjust for the intrasubject variability (24). We utilized the latter method for this study.

Although previous studies (25) have reported errors in measuring small airways with a lumen perimeter less than 6mm on CT scan, women have a substantial proportion of their airways below this cutoff. In our sample, 52% of the airways in the biomass group and 47% of the airways in the tobacco group had a lumen perimeter < 6mm. All airways were included in the analysis since excluding the smallest airways could bias the data against women in the biomass group.

Air trapping was scored qualitatively in a similar fashion to the emphysema scoring. By comparing the inspiratory and expiratory scans, the radiologists independently scored each scan on a six point scale (0 – no air trapping; 1 – trivial, < less than 5% air trapping; 2 – mild, 5-25% air trapping; 3 – moderate, 25-50% air trapping, 4 – severe, 50-75% air trapping; 5 – very severe, greater than 75% air trapping). Since mild air trapping can occur in healthy individuals (26) a score of 3 or more was considered 'abnormal' air trapping. As with the emphysema scoring, the radiologists met and determined a consensus score when their original scores differed.

Using both inspiratory and expiratory scans, we also calculated a quantitative air trapping measurement. CT quantitative measures of air trapping are strongly correlated with airway neutrophils and are considered a sensitive indicator of airway wall disease (27, 28). We calculated the ratio of the measured lung air volume on the expiratory scan to the measured lung air volume on the inspiratory scan. (i.e. a radiographic RV/TLC ratio). In individuals with air trapping, we would expect this ratio to be higher.

5.2.4 Data Analysis

Subjects were first compared according to exposure using a paired t-test. Due to the small sample size we summarized the qualitative scores of emphysema and air-trapping into two dichotomous variables. For emphysema, we considered scores 0-2 (none to mild) to indicate no emphysema, and scores 3-5 (moderate to very severe) to indicate emphysema. Similarly, for air trapping we considered scores 0-2 (none to mild) to indicate no air trapping, and scores 3-5 (moderate to

very severe) to indicate air trapping. We calculated the crude odds ratio and confidence intervals of having either emphysema or air trapping between exposure groups.

To test for differences between exposure groups for parenchymal and airway continuous variables we used PROC MIXED in SAS 9.1 (SAS Institute, Cary, North Carolina). PROC MIXED is a mixed model which allows for both random and fixed effects. Since each biomass smoke subject was paired with a tobacco smoke subject, we included a variable which accounted for the matching based on age and FEV_1 % predicted (29). For the airway analysis we used measurements made from airways of multiple sizes within each individual (24 subjects = 1004 airways); therefore, 'individual' was also considered a random effect in the airway analysis to account for the potential clustering of airway measurements within individuals.

5.3 RESULTS

Twelve subjects in each exposure group were recruited. Two of the subjects in the biomass group did not perform an acceptable expiratory MDCT scan. One subject in the biomass group and one in the tobacco group did not complete the plethysmography test. Individuals who did not complete the test and their corresponding matches were removed from air trapping analysis. There were no differences between the two groups in age, post-bronchodilator forced expiratory volume in the 1st second (FEV_1) and the forced vital capacity (FVC) % predicted, and FEV_1/FVC (Table 5-1). The mean cumulative exposure to wood smoke was 260 ± 80

hour-years for the biomass group whereas the mean pack-years for the tobacco smoke group was 30 ± 12 pack-years. Women in the biomass group were shorter than those in the tobacco group; however, the BMI was similar. Exercise capacity was moderately reduced in both groups and the MRC Dyspnea Scale was also similar. Although the total score for the SGRQ and the CRQ was similar in both groups, there was a significant clinical and statistical difference in the Activities domain of the SGRQ, with the biomass group having a worse health status in this domain.

5.3.1 Emphysema

The radiologists' rating of emphysema showed a clear division between the two groups (Figure 5-1), with only one woman in the biomass group having emphysema. The tobacco group was 11 times more likely (95% confidence interval 1.06, 114.09) to have an emphysema rating 3 or above, indicating moderate to severe emphysema. Although the groups had similar severity of % LAA (26 $\pm$ 7% in the biomass group; 29 $\pm$ 7% in the tobacco group; p = non-significant) (Table 5-2), the fractal value was significantly smaller in the tobacco group, indicating larger emphysematous spaces. This difference remained when adjusted for weight, BMI or dyspnea but was attenuated when adjusted for height (p=0.12) (Table 5-3). However, height was not significantly related to the fractal value within each diagnostic group (biomass group, p=0.35, tobacco group, p=0.59).

5.3.2 Airway Disease

The biomass group showed evidence of greater airway remodeling compared to the tobacco group. Women in the biomass group had a smaller mean lumen perimeter and lumen area (Table 5-2). Women exposed to biomass smoke also had thicker airway walls; their SQRTWA and WA % was significantly greater than the women exposed to tobacco smoke. This difference remained after adjusting for height, but was eliminated after the model was adjusted for weight or BMI. Within-group analysis revealed that weight was related to SQRTWA and WA% in the biomass group ($p=0.06$ and $p=0.05$, respectively); this relationship was not significant in the tobacco exposed group.

There was also evidence for air trapping in the biomass group (Figure 5-2). Seven of ten women in the biomass group had evidence of air trapping as rated by the radiologist. The biomass group was 5.4 times more likely to have radiologist-rated abnormal air trapping than the tobacco group but this association did not quite reach statistical significance (95% confidence interval 0.80, 36.87, $p=0.07$). Women in the biomass group also had a significantly greater RV/TLC ratio ($p=0.005$) (Table 5-5). This difference remained after adjusting for height, weight, BMI, or level of dyspnea. Although women in the biomass group had a greater MDCT expiratory air volume/inspiratory air volume ratio this difference was not significant in the mixed model analyses.

5.4 DISCUSSION

5.4.1 Emphysema and Airway Disease in COPD

In this study we measured differences in COPD phenotypes in 12 biomass smoke-exposed women compared with 12 tobacco-smoke exposed women. Specifically, on MDCT women with biomass smoke exposure had evidence of more airway remodeling, with thicker airway walls and radiologist-rated air trapping, while women with tobacco smoke exposure were more likely to have radiologist-rated emphysema with larger emphysematous spaces. To our knowledge, this study represents the first direct comparison of COPD phenotypes in individuals exposed to biomass versus tobacco smoke, using both quantitative MDCT and radiologists' assessments of emphysema and airway remodeling.

In this small sample, we did find that height, weight, and BMI impacted the relationships between exposure and measurements of fractal value and airway wall thickness. This finding is consistent with those reported in Chapters Three and Four – anthropometric characteristics can influence the objective measurements of emphysema and airway wall thickness obtained from HRCT. Future research which uses HRCT to compare groups must either control for these measurements or match groups on anthropometric characteristics as well as lung function or age. In addition, further within-group exploration of the relationship between height, weight and HRCT measures of pulmonary characteristics in large sample sizes is warranted.

Much of our knowledge of COPD today results from extensive research on

the effects of tobacco smoke on the pulmonary system. Tobacco smoke exposure leads to decreases in expiratory flow and COPD by two distinct pathophysiological processes -- emphysematous destruction of the lung parenchyma, and/or remodeling and narrowing of the small, peripheral airways. Less is known about the pathophysiology of COPD due to other risk factors, such as occupational exposures, or biomass smoke. The results from this study point to an airway disease-predominant phenotype in individuals exposed to biomass smoke.

Our finding that biomass smoke-induced COPD is related to changes in airway walls is supported by earlier epidemiological studies on the effects of biomass smoke. Perez-Padilla et al (6) recruited women with chronic bronchitis, chronic airflow obstruction, or both and compared them with other lung disease patients and healthy individuals. They found that after adjustment for confounders, the group of women with chronic bronchitis and airflow obstruction were over 14 times more likely to have been exposed to wood-smoke compared to the healthy individuals. Regalado et al (30) found that women cooking with biomass-fueled stoves reported more phlegm and cough than women using gas stoves.

There is a lack of information on the morphological characteristics of individuals exposed to biomass smoke. Arslan et al (31) assessed the effects of biomass smoke on the respiratory system in 21 women from Turkey. They found that compared to healthy, non-smoking controls, on HRCT female non-smokers exposed to biomass were 7 times more likely to have fibrotic bands, 5 times more likely to have peribronchovascular thickening, 7 times more likely to have nodular radio-opacities, and 16 times more likely to have curvilinear densities. A second

Turkish study by Kara et al (32) also found that on HRCT those exposed to biomass had evidence of pulmonary fibrosis, including an increased prevalence of ground-glass appearance and fibrotic bands. Radiological evidence for COPD was not reported in either study.

Using an animal model, Fidan et al (33) measured several indicators of lung damage in rabbits exposed to tobacco smoke, biomass smoke (dried dung) and a control group (air). Although the biomass and tobacco smoke-exposed rabbits had similar levels of emphysema, the histopathological score for respiratory epithelial proliferation in the biomass-smoked rabbits was twice that for the tobacco-smoked rabbits. However, statistical comparisons were not made between the two smoke-exposed groups.

Why biomass smoke would lead to more severe airways disease whereas tobacco smoke is more closely associated with emphysema is not known. Several mechanisms may be responsible. First, the composition of biomass smoke is not identical to that of tobacco smoke. Over 4000 identified constituents are present in tobacco smoke, including nicotine, carbon monoxide, polynuclear aromatic hydrocarbons, tar, and benzo(a)pyrene. Biomass smoke has many of the same constituents (7) but the exact composition would differ depending on the source of fuel (wood, animal dung, coal), the efficiency of combustion, and other physical factors such as relative humidity. Differences in chemical composition could lead to different pathophysiological processes.

Second, differences in particle size between biomass and tobacco smoke could lead to different spatial patterns of pulmonary deposition and an airway or

parenchymal-predominant phenotype. Fine particles, with diameters less than 10μm, are considered the best indicator of the health effects of most combustion sources (34). Interestingly, despite differences in combustion mode, particle size in biomass smoke from wood sources is similar in size to tobacco smoke particles. Naeher et al (34) reviewed papers on the health effects of wood smoke and found wood smoke particle size ranged from 0.15 to 0.4 μm. An earlier review from Bernstein et al (35) on tobacco particles reported a similar range of sizes, from 0.18 to 0.34. Naeher et al (34) also noted that there was no persuasive evidence that wood smoke particles were more dangerous than particles of a similar size from other combustion sources. These data suggest that particle size is not likely to be an important determinant of differences in COPD phenotypes between biomass and tobacco smoke.

Third, the age of onset for biomass smoke exposure is different than that for tobacco smoke exposure. Individuals who live in rural villages where biomass is the predominant fuel source are exposed at a very early age, and continue to be exposed throughout their lives. Women and girls receive the largest cumulative exposures since they are usually responsible for cooking. Biomass exposure is associated with multiple acute respiratory infections in children (7). These respiratory infections may alter the structure and function of the airway walls beginning at an early age, and may predispose individuals to an airways-predominant COPD phenotype as adults.

Fourth, there are possible differences in the inhalation pattern of those exposed to biomass versus tobacco smoke. Individuals inhaling biomass smoke

likely engage in a consistent tidal volume breathing pattern. Conversely, cigarette smokers usually smoke in a two-phase pattern – first the smoke is drawn into the mouth without direct inhalation into the lungs, then there is pause, and finally the smoke is inhaled into the lungs with an additional volume of air (35). Average inhalation volumes have been measured at approximately 25% of vital capacity, which is twice that of tidal volume (35). This increase in inhalation volume in cigarette smokers compared to those exposed to biomass smoke may draw smoke more deeply into the lungs and may increase the deposition of the tobacco smoke particles in the lung parenchyma, leading to an emphysema-predominant COPD phenotype.

Finally, the presence of pulmonary fibrosis could impact the expression of COPD phenotypes. Pulmonary fibrosis is characterized by an abnormal and excessive deposition of fibrotic tissue in the lung parenchyma and has been associated with biomass exposure (31, 32). Whether this process is protective of lung destruction due to the pathophysiological process of emphysema is not known.

5.4.2 Limitations

One important limitation of this study is the small sample size. Although we found significant differences between the biomass and tobacco groups in emphysema and airway wall changes, it is likely our small sample size prevented us from detecting changes in all parameters. Therefore, in many respects, our results should be considered as hypothesis-generating. Larger sample sizes and ongoing follow-up of the two exposure groups should provide important information on the

different pathophysiologic pathways that lead to COPD.

We cannot rule out the possibility that ethnicity contributed to our observations of increased airway disease in the biomass smoke group and increased emphysema in the tobacco smoke group. In México, women in rural communities are likely to be of indigenous descent whereas women born in urban communities are likely to have Spanish ancestry. Therefore the predisposition to one or the other COPD phenotype could be the result of different genetic susceptibilities, not different smoke exposures. In addition, rural versus urban women would have differing exposures to other factors, including ambient outdoor air pollution, nutrition, and preventive health care, all of which could affect the development of COPD later in life. Although it may not be possible to separate the interaction of exposure and ethnicity, Albalak et al (1) provided evidence for increased risk of airways' dysfunction in biomass smoke-exposed individuals, after controlling for ethnicity. In their study, two Bolivian villages which were virtually identical in terms of ethnic ancestry, socioeconomic status, altitude, geography, diet, home construction and access to health care, were recruited. In one village, it had been decided over 60 years ago to build an outdoor cooking area, as exposure to wood smoke was making several adults sick. Cooking has continued to be an outdoor activity ever since, while in the second village, cooking was done indoors with no ventilation. The investigators found that concentrations of particulate matter were 4 times higher in homes with indoor cooking, and outdoor cooking was associated with a 60% reduced risk for chronic bronchitis. Although airflow obstruction or emphysema was not measured, there was evidence that the

association between biomass smoke and airways disease is not solely due to different ethnic backgrounds.

5.5 CONCLUSION

In this study we detected an airway-predominant phenotype in women previously exposed to biomass smoke, and an emphysema-predominant phenotype in female ex-cigarette smokers. To our knowledge, this is the first such study that has directly compared the phenotypical expression of airway remodeling and emphysema in biomass- versus tobacco smoke-exposed individuals, using both objective and subjective, expert evaluation of MDCT. The increase in cigarette smoking in the developing world, coupled with the continued use of biofuels, could contribute to a growing epidemic of COPD worldwide. Results from this study should motivate further investigations in the complex interaction between different smoke exposures and the pathophysiology of COPD.

Table 5-1. Baseline Demographic, Exposure, Pulmonary Function, Functional Ability and Health Status by Exposure

Variable	Biomass Group Mean (SD) n=12	Tobacco Group Mean (SD) n=12	Mean Difference Biomass - Cigarette	t-statistic	p
Demographics					
Age (years)	68.9 (6.9)	69.3 (5.4)	-1.08	-0.768	0.46
Height (cm)	147.0 (5.6)	153.5 (6.3)	-6.42	-2.287	0.04
Weight (kg)	58.0 (10.8)	59.1 (9.9)	-1.09	-0.218	0.83
BMI (kg/m^2)	27.0 (5.8)	25.0 (3.2)	1.95	0.979	0.35
Smoke Exposure					
Biomass Smoke Exposure (hour-years)	260.3 (80.3)	0	na	na	Na
Cigarette Smoke Exposure (pack-years)	0	30.4 (12.0)			
Post-bronchodilator Pulmonary Function					
FEV_1 % predicted	50.9 (13.9)	56.1 (10.8)	-5.16	-1.615	0.13
FVC % predicted	75.9 (19.9)	84.4 (13.2)	-8.55	-1.429	0.18
FEV_1/FVC	0.53 (12.51)	0.52 (9.13)	0.01	0.330	0.75
Functional Ability and Dyspnea					
6MWT	315 (119.66)	356 (142.3)	-40.83	-0.834	0.42
MRC Dyspnea Scale	1.17 (1.03)	1.00 (0.85)	0.17	0.616	0.55

Table 5-1. continued

Variable	Biomass Group Mean (SD) n=12	Tobacco Group Mean (SD) n=12	Mean Difference Biomass - Cigarette	t-statistic	P
Health Status					
St. George's Respiratory Questionnaire					
Symptoms	46.4 (27.4)	26.1 (17.2)	20.29	2.028	0.07
Activities	56.0 (19.9)	41.7 (18.9)	20.81	2.385	0.04
Impacts	31.0 (18.2)	22.4 (13.8)	8.59	1.039	0.32
Total	40.6 (17.6)	31.6 (14.8)	8.96	1.400	0.19
Chronic Respiratory Questionnaire					
Dyspnea	13.1 (9.5)	14.3 (7.7)	-1.67	-0.393	0.70
Emotion	34.3 (8.6)	37.8 (8.1)	-3.58	-0.910	0.38
Fatigue	17.4 (4.8)	19.6 (4.9)	-2.17	-0.986	0.35
Mastery	19.2 (4.1)	22.8 (4.3)	-3.67	-1.976	0.07
Total	83.9 (15.2)	94.5 (14.6)	-10.58	-1.552	0.15

List of Abbreviations: SD = standard deviation; BMI = body mass index; FEV_1 = forced expiratory volume, 1^{st} second; FVC = forced vital capacity; 6MWT = six minute walk test; MRC = Medical Research Council;

Table 5-2. Baseline Emphysema, Airway and Air Trapping Characteristics by Exposure Group

Variable	Biomass Smoke Exposure n = 12 Mean (SD)	Cigarette Smoke Exposure n = 12 Mean (SD)	Mean Difference (BIOMASS – CIGARETTE)	t-statistic	p
Emphysema					
% LAA	26.38 (6.91)	29.04 (7.36)	-2.657	-1.286	0.23
Fractal Value	2.314 (0.393)	2.008 (0.232)	0.307	2.640	0.02
Airway					
Lumen Perimeter (cm)	0.65 (0.08)	0.71 (0.08)	-0.065	-2.142	0.06
Lumen Area (cm^2)	0.036 (0.010)	0.044 (0.010)	-0.007	-2.123	0.06
Wall Perimeter (cm)	1.55 (0.09)	1.61 (0.04)	-0.065	-1.333	0.21
Wall Area (cm^2)	0.146 (0.013)	0.154 (0.023)	-0.007	-0.946	0.36
SQRTWA (cm)	0.369 (0.018)	0.377 (0.029)	-0.008	-0.800	0.44
Wall Area %	84.11 (2.417)	82.483 (2.051)	1.632	2.117	0.06
Air Trapping (10 in each group)					
RV/TLC	0.677 (0.072)	0.597 (0.080)	0.080	4.586	0.001
MDCT Expiratory Air Volume / Inspiratory Air Volume	0.810 (0.144)	0.679 (0.136)	0.113	1.649	0.13

List of Abbreviations: SD = standard deviation; % LAA = % low attenuation area; SQRTWA = square root airway wall area; RV/TLC = plethymographic residual volume / total lung capacity

Table 5-3. Multivariable Linear Regression Mixed Models Predicting Parenchymal Outcomes

	Parameter Estimate	95% CI	p
% LAA			
Biomass Group	-2.66	-7.21, 1.89	0.23
Biomass Group Height	-1.50 0.18	-6.84, 3.84 -0.27, 0.63	0.55 0.39
Biomass Group Weight	-2.50 0.14	-6.98, 1.97 -0.11, 0.39	0.24 0.24
Biomass Group BMI	-3.11 0.23	-7.93, 1.71 -0.39, 0.85	0.18 0.43
Biomass Group Dyspnea	-2.84 1.07	-7.69, 2.02 -2.57, 4.72	0.22 0.53
Fractal Value			
Biomass Group	0.31	0.05, 0.56	0.02
Biomass Group Height	0.22 -0.014	-0.07, 0.51 -0.037, 0.009	0.12 0.21
Biomass Group Weight	0.31 0.005	0.042, 0.58 -0.009, 0.019	0.03 0.44
Biomass Group BMI	0.26 0.022	0.003, 0.525 -0.009, 0.052	0.05 0.14
Biomass Group Dyspnea	0.3436 -0.2225	0.1384, 0.5489 -0.3565, -0.08856	0.004 0.004

Definition of Abbreviations: %LAA = % low attenuation area, CI = confidence interval

Table 5-4. Multivariable Linear Regression Mixed Models Predicting Airway Wall Thickness

	Parameter Estimate	95% CI	p
SQRTWA * (cm)			
Biomass Group	0.005	-0.00065, 0.01069	0.08
Biomass Group	0.009	0.002, 0.015	0.01
Height	0.0006	0.00004, 0.0012	0.04
Biomass Group	0.004	-0.0014, 0.0099	0.14
Weight	0.0007	0.0003, 0.0010	0.0001
Biomass Group	0.0009	-0.00525, 0.0070	0.78
BMI	0.0015	0.0006, 0.0023	0.0007
Biomass Group	0.005	-0.0007, 0.0107	0.08
MRC Dyspnea Scale	-0.0005	-0.00578, 0.0047	0.84
Wall Area % *			
Biomass Group	0.3260	-0.1396, 0.7915	0.17
Biomass Group	0.7420	0.1899, 1.2947	0.01
Height	0.06762	0.02156, 0.1137	0.004
Biomass Group	0.2394	-0.2308, 0.7096	0.32
Weight	0.0705	0.0426, 0.0984	<0.0001
Biomass Group	-0.0839	-0.5890, 0.4211	0.74
BMI	0.1416	0.07302, 0.2102	<0.0001
Biomass Group	0.3250	-0.1443, 0.7942	0.17
MRC Dyspnea Scale	-0.3309	-0.7538, 0.0921	0.12

* Adjusted for Lumen Perimeter

Definition of Abbreviations: %LAA = % low attenuation area, CI = confidence interval

Table 5-5. Multivariable Linear Regression Mixed Models Predicting Air Trapping Outcomes

	Parameter Estimate	95% Confidence Interval	p
Plethysmographic RV/TLC			
Biomass Group	0.08048	0.04078, 0.1202	0.001
Biomass Group Height	0.08117 0.000118	-0.03953, 1.1971 -0.00398, 0.004219	0.005 0.95
Biomass Group Weight	0.07884 -0.00070	0.4931, 0.7821 -0.00304, 0.003637	0.003 0.41
Biomass Group BMI	0.08294 -0.00219	0.03979, 0.1261 -0.00802, 0.003637	0.002 0.41
Biomass Group MRC Dyspnea	0.07819 0.02288	0.03661, 0.1198 -0.01324, 0.05901	0.003 0.18
MDCT Expiratory Air Volume / Inspiratory Air Volume			
Biomass Group	0.1130	-0.02864, 0.2546	0.10
Biomass Group Height	-0.01379 -0.01864	-0.1500, 0.1225 -0.03031, -0.00697	0.82 0.006
Biomass Group Weight	0.1134 -0.00044	-0.03531, 0.2621 -0.00885, 0.007979	0.117 0.91
Biomass Group BMI	0.09247 0.006909	-0.05941, 0.2444 -0.00901, 0.02283	0.20 0.35
Biomass Group MRC Dyspnea	0.1061 0.03433	-0.03900, 0.2512 -0.04391, 0.1126	0.13 0.34

List of Abbreviations: RV/TLC = residual volume / total lung capacity; MDCT = multidetector computer tomography scan; BMI = body mass index; MRC = Medical Research Council

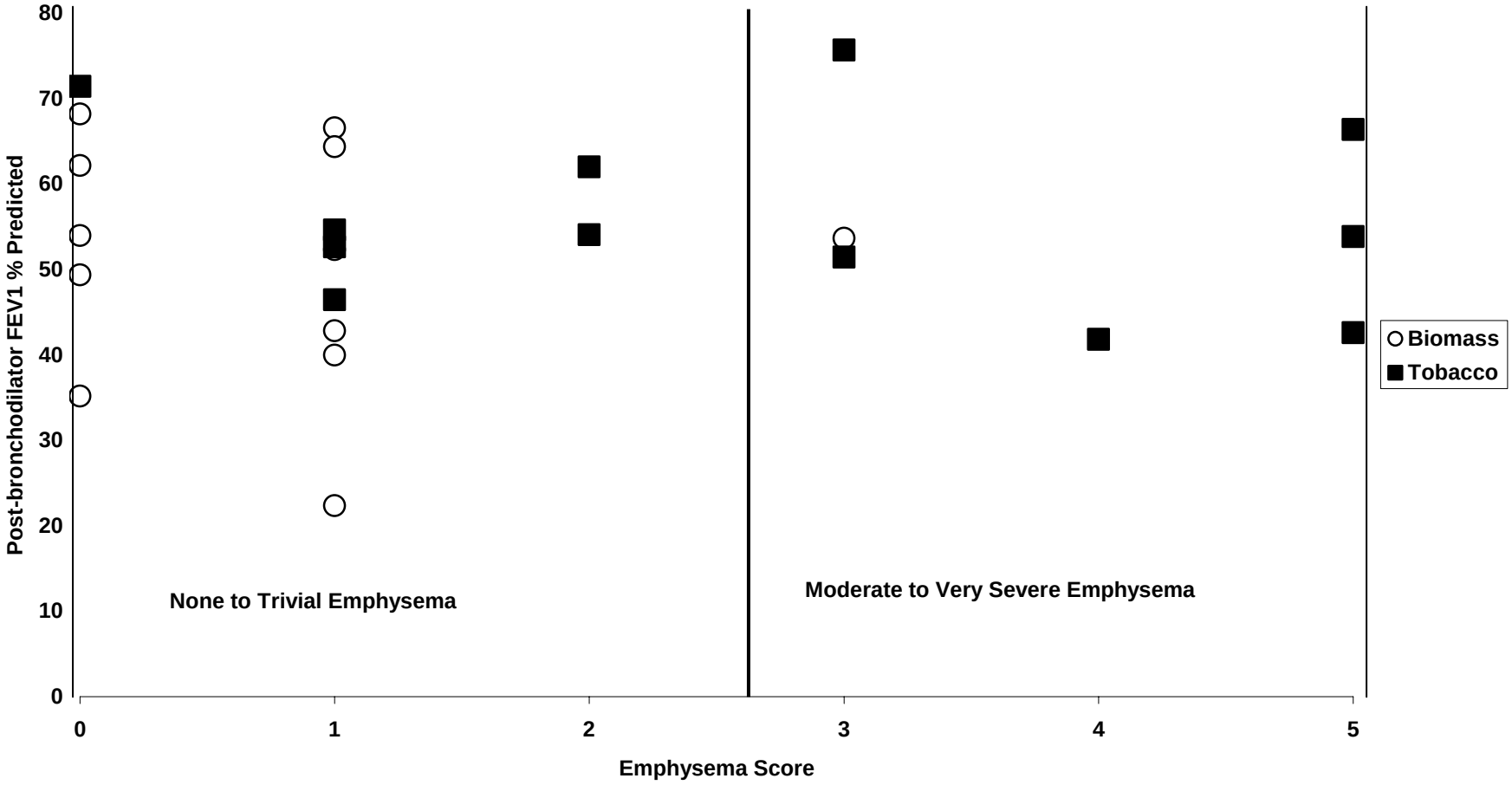

Figure 5-1. Relationship of Emphysema Scores with Post-Bronchodilator FEV_1 % Predicted, by Exposure Group

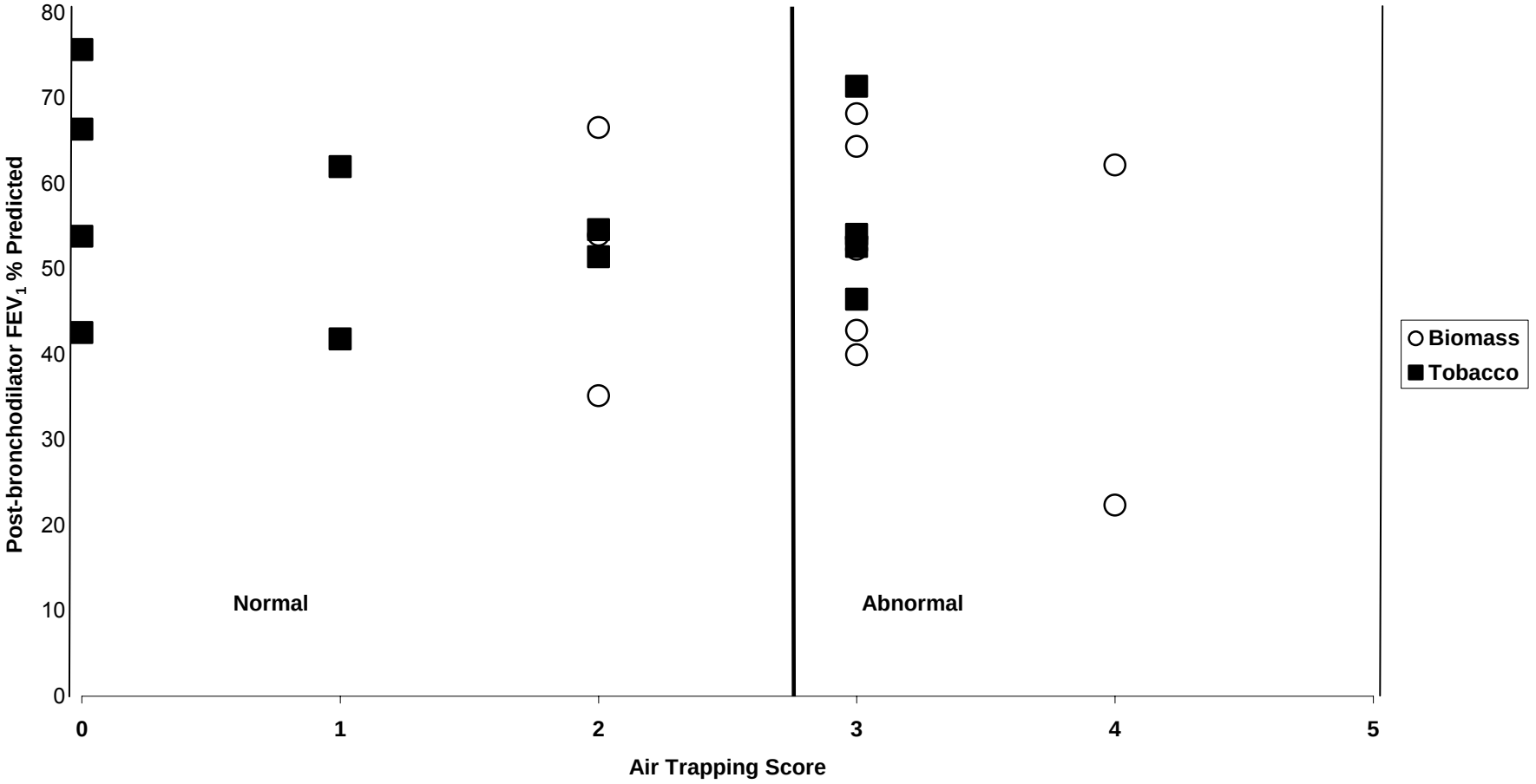

Figure 5-2. Relationship of Air Trapping Scores with Post-Bronchodilator FEV_1 % Predicted

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CHAPTER SIX. GENERAL DISCUSSION AND CONCLUSION

6.1 GENERAL DISCUSSION

There is increased interest in identifying sex and gender differences in COPD and calls for further research (1). In this dissertation we describe a detailed examination of how sex and gender influence COPD in the specific areas of epidemiology, pathophysiology, measurement and unique risk factors. We used administrative health services, respiratory questionnaire, lung function and imaging data to characterize COPD in men and women and tested for differences in specific parameters. We also found that the choice of measurement tools may have influenced our results, and compared characteristics of COPD between two groups of women exposed to different risk factors for COPD. In this chapter we discuss the key findings from each study and provide recommendations for future research.

6.1.1 The Gender Factor: Epidemiology and Management of COPD in British Columbia

Summary of findings and contributions to the fiel. In 2001 and 2007 Health Canada reported that, based on self-report, there is greater prevalence of COPD in women compared to men (2, 3). They also predicted that COPD mortality rates in women will rise exponentially and will soon surpass that of men. In this study we used administrative health services data to compare the prevalence, mortality, medication use and lung function testing in men and women coded for COPD.

Using a case definition to identify individuals with COPD, we found that, in contrast to the Health Canada Reports, the male cumulative prevalence of COPD in British Columbia (BC) was greater than the female cumulative prevalence, with approximately 4.7% of men and 4.0% of women coded for COPD by the 2003/2004 fiscal year. We did not find evidence of increasing mortality rates for women with COPD.

Including ICD-9 490 (bronchitis, not specified as acute or chronic) doubled the prevalence estimates for COPD with important gender and age differences. In the younger age groups, women had a higher prevalence of COPD than men if ICD-9 490 was included in the case definition. Whether these younger women who have repeated episodes of bronchitis (at least 2 doctor's visits for bronchitis within 1 year) represent the beginning of the 'female COPD epidemic' is unknown. Individuals coded with ICD-9 490 may not have COPD at all, since spirometry and medication use in this group was much lower than in the COPD population coded with ICD-9 491, 492, and/or 496.

Contributions to the Field. Results from this study lead to an important question -- Why would self-report data find a higher prevalence for COPD in women, while administrative data show a higher prevalence in men? Although it is possible that epidemiological trends for COPD are different in BC than for Canada overall, it is more likely that the differences are due to the methods of measurement. There are two possible scenarios which warrant further scrutiny. First, the administrative data is correct, and the increased prevalence in self-reported COPD in women is spurious due to gender differences in reporting. It is possible that women over-

report physician-diagnosed COPD on health surveys, or that men under-report. However, there are no studies describing gender differences in interpreting and answering pulmonary questions on the Canadian Community Health Survey. Second, the self-report data is correct, and the increased prevalence in men seen in the administrative data is due to a gender bias in diagnosing or coding COPD. Although women are reporting on survey that they have received a diagnosis of chronic bronchitis or emphysema from their doctor, it is possible that doctors are coding these women with ICD-9 codes other than those used for COPD, such as ICD-9 493 (asthma), ICD-9 466 (acute bronchitis) or ICD-9 490 (bronchitis, not specified as acute or chronic). Since ICD-9 490 is used in the case definition for COPD (3-5) in many studies and surveillance strategies our finding emphasizes the importance of considering how measurement tools may influence conclusions related to gender differences in epidemiology.

6.1.2 Sex Differences in Emphysema and Airway Disease in Smokers

Summary of Findings. Recent reports suggest that women may be more susceptible to cigarette smoke and to an airway-predominant rather than an emphysema-predominant COPD subtype. To further investigate these issues, we analyzed emphysema and airway wall measurements obtained from HRCT scans in a large sample of male and female smokers with a wide range of disease severity (healthy smokers, and Global Obstructive Lung Disease (GOLD) (6) classification levels 1-4). We hypothesized that on HRCT, male smokers would exhibit more emphysema and female smokers would have thicker airway walls after adjusting for

confounders. In addition we expected that women would report greater dyspnea after adjusting for lung function, emphysema and airway measurements. We found that for a given age, smoking history and smoking status, FEV_1 % predicted and anthropometric measures, men were more likely to have CT features of emphysema, whereas women were more likely to report dyspnea. We did not detect an increase in airway wall dimensions in women, but we did see a strong influence of weight and height on wall area percent and SQRTWA.

Contributions to the Field. Similar to the results of Chapter Two, we found that gender bias in measurement may have affected our results. As mentioned, we did not detect an increase in airway wall thickness in women after adjusting for covariates. This was in contrast to our expectations, as men and women had similar lung function, but men had more emphysema. The ability to accurately measure minute differences in airway wall thickness may be a factor. As per established methodology, we selected airways for analysis that were cut in reasonable cross-section on CT scan. This method does not distinguish where in the tracheo-bronchial tree the airway is located. The limited spatial resolution of CT means that there is censoring at the lower end of the distribution of airway dimensions. More of the critical airways involved in airflow limitation may be censored in women than men. In addition, it is not known whether there are differences in relative airway dimensions of peripheral versus central airways, for a given airway size. If more central airways have a relatively lower airway wall area/lumen area ratio this censoring might be expected to result in low estimates of wall area% in women. In the research setting, CT scans are routinely used to estimate emphysema and

airway wall thickening in COPD but this measurement tool has not undergone a rigorous gender- and sex-based analysis. Based on the evidence from this study, HRCT may not be the appropriate method to detect differences between men and women in airway wall thickness. While it is possible that there are truly no differences between men and women in airway wall remodeling, previous studies have reported small but significant sex differences in wall area for a given airway size (7). This issue can only be addressed adequately by comparing airway dimensions in men and women at anatomically matched sites within the tracheo-bronchial tree, using volumetric CT or optical coherence tomography and programs which allow three-dimensional reconstruction of the tree.

We found that women report more dyspnea than men, but this difference was attenuated by including height and weight in the model. This is a novel finding. Previous studies have reported gender differences in dyspnea reporting but few have controlled for anthropometric measures (8-10). In separate analyses by sex, de Torres et al (11) found that BMI predicted dyspnea in men only, but did not look at the separate effects of height and weight. Although it is not clear *why* height and weight affect dyspnea reporting, it is important to include in any sex or gender-based analysis covariates that are known to be different between men and women. As previously quoted, "…there is a risk of overemphasizing sex differences in relation to other anatomical and physiological contributions to population variation . . . the relevant source of variation may be size difference, not the sex difference, and may not apply to small men or large women. It is undeniably easier to record sex rather than measure the relevant body dimensions, but it may not be as good a predictor"

(12). Within-sex investigation on the predictors of dyspnea would help to separate the physiological from the psychosocial factors which may be different in women versus men.

In addition to the influence of physical factors, we also speculate in the discussion how the dyspnea items in the questionnaire may have contributed to the findings, and highlighted the importance of considering methods of measurement in studies of gender differences in symptom reporting. The American Thoracic Society Respiratory Epidemiology Questionnaire and the Medical Research Council Dyspnea Scale are frequently-used survey tools yet little investigation has been done on how symptom questions are interpreted by men and women. Using qualitative interviews to understand gender differences in the interpretation of items on the ATS questionnaire, Alley et al (13) found that gender differences exist in the interpretation and reporting of phlegm symptoms but did not find differences in the reporting of dyspnea symptoms. However, her sample consisted of young men and women employed in the marine industry, not individuals with COPD. Further research in this area is warranted. In addition, the questionnaire items may not be measuring the same construct. The ATS questionnaire uses pre-selected activities and asks the level of dyspnea experienced with each activity. These activities may require different expenditure of energy and subsequently elicit different levels of dyspnea for women versus men or for smaller versus larger individuals regardless of sex. Our findings highlight the importance of considering both physical factors related to sex and psychosocial factors related to gender in the measurement of dyspnea.

6.1.3 Subjective and Objective Estimates of Emphysema: A Receiver Operating Curve Analysis

Summary of Findings. High resolution computed tomography (HRCT) is a sensitive method to detect changes in lung structure *in vivo,* including changes due to the parenchymal destruction which characterizes emphysema. Methods to obtain estimates of emphysema from HRCT include subjective assessments by a radiologist and objective, computer-aided estimates of digital images. Although these methods have shown moderate to good correlation with measurements of emphysema from pathologic specimens, each method has limitations for use in clinical research settings. Radiologists' subjective methods do not have strong inter-rater reliability and may not be suitable for multi-center research studies with multiple readers. %LAA provides a reliable measure of low lung density but provides little information about how emphysematous spaces are organized. The fractal value has not been widely-used and has not been subject to rigorous evaluation. Therefore, the purpose of the study detailed in Chapter Four was to compare the fractal dimension, radiologists' subjective rating, and % LAA to differentiate COPD from non-COPD subjects in a large sample (n=634) of men and women. We found that for both men and women, the radiologist subjective score had the best ROC curve and a significantly larger AUC than either the % LAA or the fractal value. Combining the fractal value with the % LAA in an additive model did not significantly improve the AUC beyond that of the fractal value alone. We also found that height, weight, BMI and age influenced the ROC curves of all three emphysema estimates. This

was most evident for the objective measurements of emphysema. For men of increased weight or age, %LAA was not able to differentiate individuals with COPD from those with normal lung function.

Contribution to the field. Based on these results, radiologist scores of emphysema can best differentiate COPD in a sample of current and ex-smokers, followed by the fractal value and the %LAA. It is possible that the radiologist score is detecting attributes of emphysema that are not captured by current, objective methods. One of these attributes may be the size of the emphysematous spaces, which is also captured by the fractal value and may be why the fractal value was the next best predictor of COPD. This is an important finding worthy of further study. Currently the %LAA is commonly used to objectively estimate emphysema but may not be able to accurately distinguish individuals with clinically important disease from those with reduced lung density but normal lung function. This was especially evident in older and heavier men. As COPD tends to occur in older individuals, the measurement of emphysema must be accurate in the older age groups. Based on the results of this study, further development of the fractal value could yield a better method of objectively and reliably measuring emphysema in COPD patients.

In Chapter Two (Epidemiology of COPD) and Chapter Three (Phenotypes in COPD) we describe how the measurement tool may influence the conclusions regarding gender or sex differences in COPD. Therefore in this current ROC study assessing three emphysema measurement tools, it was important to consider if our results were consistent for both men and women. We found that in this instance, sex did not significantly impact the ranking of the three emphysema measurements.

The radiologist estimate of emphysema had the greatest AUC of all the measurements, in any of the subgroups we analyzed. However, the objective measurements did yield higher AUC values for women, and as mentioned, men of increased weight or age had the lowest AUC values for %LAA of any of the subgroups. Further analysis in larger samples of men and women would allow for more rigorous tests of interactions between age, body size and/or sex and the objective measurement of emphysema.

6.1.4 Structural and Functional Differences Between Tobacco Smoke- and Biomass Smoke-Induced Chronic Obstructive Pulmonary Disease in Mexican Women

Summary of Findings. Indoor air pollution from biomass burning has been implicated as a risk factor for the development of chronic bronchitis and chronic obstructive pulmonary disease (COPD), especially in developing countries (14-19). Little is known about the COPD phenotype related to biomass smoke exposure because the pathological processes which lead to COPD following biomass smoke exposure are poorly understood. In Chapter Five, we compared MDCT scans of women with COPD due to biomass smoke exposure with women whose COPD was related to tobacco smoke exposure. We hypothesized that biomass smoke exposure is associated with an airway-predominant phenotype of COPD, with increased airway wall thickness and air-trapping, while tobacco-related COPD would be a mix of emphysema and airway phenotypes. We found that on MDCT, women with biomass smoke exposure had evidence of more airway remodeling, with thicker

airway walls and more air trapping, while women with tobacco smoke exposure were more likely to have emphysema with larger emphysematous spaces as judged by radiologists. To our knowledge, this study represents the first direct comparison of COPD phenotypes in individuals exposed to biomass versus tobacco smoke, using both quantitative MDCT and radiologists' assessments of emphysema and airway remodeling.

Contribution to the field. Much of our understanding of COPD comes from learning how *cigarette* smoke impacts the lungs. Although biomass smoke and cigarette smoke share many of the same constituents, the mode of exposure is very different. There may be valuable information to be gained from examining the pathogenesis of COPD related to risk factors other than cigarette smoke. We show that the women with COPD and long-term exposure to biomass smoke have evidence of increased airway remodeling compared to women exposed to cigarette smoke. This is a novel finding. Women who have COPD related to exposure to biomass smoke represent a significant, but largely ignored, percentage of the global burden of this disease. Studies aimed at defining the extent of this problem and the potential unique mechanisms involved in its pathogenesis helps to focus attention on this devastating problem. This study also encourages researchers and clinicians to consider COPD as more than just a smoker's disease. It occurs in never-smokers, individuals exposed to occupational substances, and as demonstrated in Chapter Five, in women exposed to biomass smoke. Each different exposure may result in a different pathophysiologic pathway. Numerous novel treatment modalities are being developed by pharmaceutical companies to treat COPD. It is likely that the

therapeutics will be aimed at curtailing the excessive proteolysis responsible for emphysema or the excessive fibrosis responsible for the bronchiolitis, but not both. We believe that the individual determination of the predominant pathophysiologic pathway will one day be important in selecting therapy.

Although in Chapter Four we were not able to detect between-sex differences in airway parameters in individuals exposed to cigarette smoke, in Chapter Five we were able to detect within-sex differences in airway wall dimensions in women exposed to different inhaled substances, using HRCT. HRCT may be able to detect differences when the size of the difference is large, or when specific attributes of the study groups are controlled, such as sex. However, similar to Chapters Three and Four, we did find that again body size had an impact on the relationships between exposure group and HRCT measurements of emphysema and airway wall thickness. Further research is required to determine the applicability of HRCT to measurement of emphysema and airway wall dimensions in groups of men and women with different body sizes and exposure histories.

6.2 SYNTHESIS OF THE RESEARCH FINDINGS

The research that comprises this dissertation addresses sex and/or gender differences in COPD from different disciplinary perspectives. There are a number of reasons why COPD prevalence, pathophysiology, clinical phenotypes and functional impact could be different in men and women. These include differences in exposure, deposition of particles, response to the exposure and/or perception of

dysfunction. Alternatively differences could be measurement artefact; i.e., related to the variable accuracy or precision of the measurement tools in women as compared to men. We found important differences that may be related to the influence of gender-related factors on measurements. There are three important factors which are consistent across all four studies.

First, it is apparent that the choice of measurement tool can have a profound effect on the apparent sex and/or gender differences in COPD. In Chapter Two, measuring COPD prevalence using data from physician and hospital billing records yielded a lower prevalence for women compared to men, which was in contrast to the self-report data reported by Health Canada. In addition, using different billing codes yielded different prevalence estimates for women versus men. In Chapter Three, we did not detect thicker airway walls in women compared to men using HRCT, although thicker airway walls had been detected in women with COPD in other studies using histological samples. In Chapter Three we also discussed how the choice of the dyspnea measurement tool may yield different results, based on the wording of the questions. In Chapter Four we found that subjective measures of emphysema could detect COPD patients better than objective measures, and although the interaction terms of sex X measurement tool were not statistically significant, the shape of the ROC curves were different in men and women, especially when separated into sub-categories of height, weight or age. The measurement tools that were used in these studies have been validated to some degree, but the validity of these tools has not been compared between men and women. The necessity of developing gender-neutral or gender-sensitive

measurement tools in a variety of disciplines is a key finding of this research.

A second consistent finding is that when measuring between sex- or within-sex differences in COPD, body size is important. This was evident in Chapter Three where we found that weight was significantly associated with %LAA in men, but not in women, and that height influenced the relationship between sex and dyspnea. In Chapter Four, we also found that body size was an important factor when measuring the ability of three different emphysema measurement tools to differentiate smokers with airflow obstruction from those with normal lung function. For men who had a high body weight or BMI, the %LAA had a very low area under the curve (AUC). Within-sex body size was also important; in Chapter Five, weight was related to SQRTWA and WA% in the biomass exposed group, yet this relationship was not significant in the tobacco exposed group. It isn't clear whether these differences are due to true differences in COPD phenotypes in individuals of different body size; or if the validity of the measurement tools themselves is different in individuals of different height or weight. Clearly one of the fundamental differences between men and women is body size. Since women are systematically smaller than men this is an important distinction but one that is difficult to resolve in the absence of sex-specific validation of the measurement tools. We need to better understand the influence of body size on the validity of our measurements and on the pathophysiology of the disease process. We also need to determine how body size interacts with other key factors, such as sex, age, pulmonary anatomy and physiology, and external risk factors to influence the pathophysiology of COPD.

Finally, Chapter Five highlights the importance of understanding COPD outside the paradigm of a cigarette-smokers disease. The vast majority of research in COPD is conducted in human populations or animal models exposed to cigarette smoke. While cigarette smoking is the fundamental risk factor for men and women in developed countries, biomass smoke exposure puts women and children in many developing countries at risk for pulmonary disease. Exposure to inhaled risk factors is often different by gender, whether the exposure is biomass smoke, or occupational dusts and fumes. Our understanding of the characteristics of COPD due to risk factors other than cigarette smoke will both facilitate our understanding of the pathophysiology of this disease, as well as improve our ability to accurately measure the true burden of COPD.

6.3 STRENGTHS OF THE THESIS RESEARCH

In this dissertation we describe a detailed examination of sex and gender influences in COPD; specifically in the areas of epidemiology, pathophysiology, measurement and unique risk factors. The four research studies which comprise this dissertation were strengthened by gender- and sex based analysis strategies which facilitated the examination of the research topics from both biological (sex) and psychosocial (gender) perspectives.

Another important strength of these studies was the availability of data from multiple sources. In Chapter Two we assessed gender differences in COPD epidemiology using retrospective data from the British Columbia Ministry of Health.

In Chapters Three and Four we analyzed spirometry, anthropometric, imaging and detailed questionnaire data. In Chapter Five we enrolled a small sample of women with COPD but epidemiologic, lung function, health status, functional activity and imaging data was collected from each woman. As a result of the diversity of data sources, this dissertation was able to address questions on sex and gender in COPD from a variety of disciplines and perspectives.

The studies in Chapters Two, Three and Four were also strengthened by the large sample sizes. In Chapter Two we described differences in the epidemiology of COPD using a sample of over 77,000 identified cases. The studies described in Chapters Three and Four recruited over 3000 individuals from 10 international sites, 1000 of whom also underwent CT scanning.

All of the studies were also enhanced by the contributions of local, provincial and international collaborators. To conduct the epidemiological study of COPD, we worked with members of the British Columbia Ministry of Health Chronic Disease Management team who extracted the data and provided the summary data. This study had the benefit of both respiratory disease and data analysis experts working together on the project. The phenotype and ROC studies were enhanced by our collaboration with members of the International Genetics Network, a research network funded by GlaxoSmithKline. The network is a group of world-renowned respirologists, radiologists, and scientists who provided valuable feedback on the design, analysis and interpretation of the results of this study. To conduct the biomass study, we collaborated with respirologists and radiologists from the Institute of Respiratory Diseases in Mexico City.

6.4 LIMITATIONS OF THE THESIS RESEARCH

The measurement tools used in these studies have been evaluated to some extent but rarely have they been validated in men and women separately. Using measurement tools that have been previously validated in both men and women would have been the optimal approach and may have led to different results and conclusions.

A second limitation is the fact that technology changes rapidly, especially in imaging methods. At study conception measuring %LAA and fractal value on HRCT were considered state of the art techniques. The speed at which new equipment and analysis programs are introduced make it difficult to adequately propose, fund, conduct and publish validation studies. By the time these techniques are thoroughly explored and validated, they often have become obsolete.

A third limitation of this body of research is that we do not have complete data on other risk factors which could have influenced our results. Although we have evidence that gender or sex play a role in COPD, we do not have detailed histories of other risk factors such as exposure to other inhaled substances, past respiratory history, or socioeconomic status. Without these we cannot determine with certainty to what degree biology (and what components of biology) influences the outcome measured versus 'gendered' factors. Similarly, with the exception of the ROC curve analysis, we grouped men and women into just two groups. Other subgroups of men and women may have yielded different results for between-sex comparisons,

as well as for within-sex comparisons; for example, pre-menopausal versus post-menopausal women.

6.5 FUTURE RESEARCH DIRECTIONS

In Chapter One we identified three major themes or research questions for this program of research; 1) is a predisposition to parenchymal destruction versus airway wall remodeling influenced by sex? 2) how have the measurement tools used influenced the conclusions of the studies? and 3) how do unique exposures, specifically biomass smoke exposure, impact the lung health of women? New ideas for future research relate to these three themes. The issue of gender-sensitive or gender-neutral measurement tools is of primary importance and will be discussed first.

6.5.1 Future Research in Measurement Tools

Future research in gender and the epidemiology of COPD using administrative health services data should focus on the impact of the case definition on the study findings. Creating an accurate case definition for COPD is crucial to describing epidemiologic trends using administrative health services data yet little work has been done to confirm the validity of case definitions in men and women separately. In Chapter Two we show that gender differences in disease prevalence may change depending on which measurement method is used. Future research should focus on why women have a greater prevalence of COPD based on self-

report, which is not apparent when administrative health data are analyzed. Are women who self-report having COPD coded with ICD-9 490, the other COPD codes, or are they coded as having asthma? In addition, further investigation into the population coded with ICD-9 490 is warranted. Research questions should focus on the health care utilization of this group over time. Do individuals coded with ICD-9 490 eventually get coded with the COPD codes ICD-9 491, 492, or 496 or with other respiratory codes such as ICD-9 493 (asthma)? What is their medication profile – do they eventually receive inhaled medications for COPD or are antibiotics consistently prescribed? How does gender affect their disease trajectory? Are there geographical tendencies to use ICD-9 490? These initial questions can be answered with further research linking administrative and survey data, but it is likely that medical chart validation studies would also need to be conducted to provide robust answers.

We did not find a difference in HRCT measurements of airway wall thickness between men and women, after adjusting for covariates. Yet Martinez et al (7) found that based on measurement of airways in resected lung tissue, women with severe emphysema were more likely to have thickened airway walls compared to men. We discuss the possibility that the measurement of airway dimensions using HCRT is not gender-neutral. If possible, data on previous validation studies on HRCT should be pooled and/or re-analysed to confirm if the results are consistent in men and women. Alternatively, as new CT imaging techniques become widely available, such as volumetric CT scanning or optical coherence tomography, they should be validated against pathologic studies (not HRCT) to ensure they adequately measure

airway dimensions in both men and women. These new imaging tools may be better able to measure subtle differences in airway wall thickness between men and women. As previously mentioned, the impact of body size and age on the accuracy of the measurement tool must also be determined.

We found that subjective scores of emphysema best differentiated COPD patients from smokers with normal lung function. Of the two objective measures (the fractal dimension and %LAA) the fractal dimension was the best predictor of COPD. Further research to validate the fractal dimension is warranted. Does this measurement change with age or as the disease progresses? The development of an emphysema index, which incorporates information on both emphysema severity and the organization of the emphysematous spaces may be an better alternative to existing objective measures.

We also show that dyspnea is reported more frequently in women but again the issue of measurement may have impacted our results. The ATS questionnaire has not been validated separately in men and women and little work on how the questions are interpreted, or if they measure similar constructs, has been done. Other questionnaires use different methods to measure dyspnea. For instance, the Chronic Respiratory Questionnaire (20) requires each respondent to create a list of five activities that cause dyspnea. The respondent then rates the severity of dyspnea when performing each activity. Critics of this individualized approach to dyspnea measurement have stated that the CRQ creates a dyspnea measurement that cannot be compared between subjects (21). However, the alternate approach of creating standard activities may also not provide an accurate measure of dyspnea

if the activities are deemed more difficult by different population groups. Further research into this area could involve analyzing the activities listed in the Chronic Respiratory Questionnaire by gender – do women report different activities then men? How do dyspnea ratings using an individualized approach compare with dyspnea scores using standardized activities? Qualitative research methods would also be useful to better understand how activity causes dyspnea in men and women and how questions on dyspnea are interpreted.

6.5.2 Future Research in Sex/Gender Differences in COPD Phenotypes

In the absence of validated imaging tools, questions about sex differences in COPD phenotypes may best be answered using histology studies. Unfortunately, it is difficult to obtain resected airways from enough individuals with mild-to-severe COPD. There may be an opportunity to pool the results of previous studies from different investigators, using the network of tissue and data registries that have been developed. With gender-neutral or gender-sensitive research tools, future research on sex/gender differences in COPD phenotypes should focus on the differences in the natural history of the disease. By collecting longitudinal data, from randomly-sampled, population-based populations, we can confirm if men versus women are predisposed to an emphysema versus airway remodeling phenotype. The Burden of Lung Disease (BOLD) Study (22) may be the best opportunity to conduct this type of research if continued over many years. If male and female populations of current, ex-, and never-smokers are followed over time, with epidemiological, exposure, medical history, imaging and lung function data collected periodically, we can

answer questions on the pathogenesis of COPD in men versus women. If these individuals then consent to the release of their administrative health services data, we can also follow their health utilization patterns, including diagnosis, coding by physicians, and treatment outcomes.

6.5.3 Future Research in Gender and the Epidemiology of COPD

With a case definition for COPD validated in both men and women, future investigations into gender differences in the epidemiology of COPD should focus on health outcomes. Are there gender differences in hospitalization and re-hospitalization rates? What predicts poor health outcomes in men and women? How do other factors, such as geographic location, medication use, socioeconomic status, co-morbidities and access to other health services affect health outcomes in men and women with COPD? Are these outcomes affected by other factors, such as age, or ethnicity? What is the epidemiology of COPD in men and women from vulnerable populations, such as aboriginal groups, individuals with low-income, or immigrant populations?

6.5.4 Future Research in Biomass Smoke and COPD

We have shown that women with COPD and biomass smoke exposure were more likely to have evidence of airway wall remodeling, while women with COPD due to tobacco smoke exposure were more likely to have emphysema. This finding is important since the future of drug development in COPD will likely focus on phenotype-specific treatments. The more immediate need is research aimed at

evaluating prevention efforts. Does changing ventilation or other physical factors lead to an improvement in lung function or slow the development of the disease? In addition, we studied two groups of women with exposure to either biomass smoke, *or* tobacco smoke. The combined effect of cigarette smoking and biomass smoke needs to be further investigated. Cigarette smoking is highly prevalent in males in many developing nations, and the prevalence is increasing among women and girls. Very young children are frequently exposed to biomass smoke while being carried on their mothers' backs during cooking. Are boys with early exposure to biomass smoke more likely to develop emphysema or airway wall remodeling? What is the impact of cigarette smoking on female lungs chronically exposed to biomass smoke?

6.6 POTENTIAL APPLICATIONS OF RESEARCH FINDINGS

The Public Health Agency of Canada is developing a national surveillance system for chronic lung disease, which includes COPD. Based on the results of this research, they are considering eliminating ICD-9 490 from their case definition of COPD. Although including ICD-9 490 in the case definition increased the prevalence of COPD, it is not clear whether these individuals truly have the disease. Further scrutiny of this group is planned. Our findings regarding the ability of HRCT to detect differences in airway dimensions should caution researchers regarding the validity of this tool. Researchers should also consider including measurement of the fractal value in their objective assessment of emphysema. Finally, our research on the impact of biomass smoke will continue to bring

awareness both to this important public health problem, as well as stimulate research on the pathogenesis of COPD associated with non-tobacco risk factors.

6.7 CONCLUSION

In this dissertation we describe a detailed examination of sex and gender in COPD in the specific areas of epidemiology, pathophysiology, measurement and unique risk factors. The findings of this dissertation suggest that although it is likely many differences exist between men and women in the epidemiology and phenotypes of COPD, the study of these differences is hampered by the lack of gender-sensitive or gender-neutral measurement tools. We found that how COPD is defined can impact the results of gender differences in COPD prevalence, and that HRCT may not be a valid measurement tool for comparing airway dimensions in men and women. Our ROC analysis of three emphysema measurement tools show that although these tools provide comparable results in men and women, the commonly-used objective method of estimating emphysema, %LAA, did not differentiate COPD from non-COPD as well as the subjective radiologist estimate or the objective, fractal value. This research also detailed the phenotypic characteristics of COPD related to biomass smoke exposure, which is a risk factor for COPD that predominantly affects women and girls. Recommendations for research that arise from this dissertation include the development and validation of gender-neutral or gender-sensitive measurement tools, and further study into the

sex differences and gender influences on the pathogenesis of COPD related to cigarette smoke exposure, as well as to other risk factors such as biomass smoke.

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APPENDIX 1.

Global Initiative for Obstructive Lung Disease – Classification of COPD Severity by Spirometry

Stage	**Criteria**
Stage 0: Normal	Normal Lung Function
Stage 1 : Mild	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted
Stage 2: Moderate	$FEV_1/FVC < 0.70$ $50\% \leq FEV_1 < 80\%$ predicted
Stage 3: Severe	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 < 50\%$ predicted
Stage 4: Very Severe	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted *plus* chronic respiratory failure

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ETHICS CERTIFICATE OF EXPEDITED APPROVAL

PRINCIPAL INVESTIGATOR:	DEPARTMENT:	UBC-PHC REB NUMBER:
Robert D. Levy	UBC/Medicine, Faculty of/iCAPTURE	H07-00053

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
Providence Health Care	St. Paul's Hospital

Other locations where the research will be conducted:
British Columbia Ministry of Health

COINVESTIGATOR(S):
Jeremy D. Road
Don Sin
Patricia Camp

SPONSORING AGENCIES:
N/A

PROJECT TITLE:
An Administrative Health Data Analysis of Gender Differences in COPD

THE CURRENT UBC-PHC REB APPROVAL FOR THIS STUDY EXPIRES: March 18, 2009

The UBC-PHC Research Ethics Board Chair or Associate Chair, has reviewed the above described research project, including associated documentation noted below, and finds the research project aceeptable on ethical grounds for research involving human subjects and hereby grants approval.

DOCUMENTS INCLUDED IN THIS APPROVAL:		APPROVAL DATE: March 18, 2008
Document Name	**Version**	**Date**
Protocol:		
BC Ministry of Health Summary of Analysis	1	February 1, 2004
Chronic Disease Registers and Performance Measures	2	September 20, 2004

CERTIFICATION:

1. The membership of the UBC-PHC REB complies with the membership requirements for research ethics boards defined in Part C Division 5 of the Food and Drug Regulations of Canada.
2. The UBC-PHC REB carries out its functions in a manner fully consistent with Good Clinical Practices.
3. The UBC-PHC REB has reviewed and approved the research project named on this Certificate of Approval including any associated consent form and taken the action noted above. This research project is to be conducted by the principal investigator named above at the specified research site(s). This review of the UBC-PHC REB have been documented in writing.

Approval of the UBC-PHC Research Ethics Board or Associate Chair, verified by the signature of one of the following:

Dr. I. Fedoroff, Chair

Dr. J. Kernahan, Associate Chair

UBC/PROVIDENCE HEALTH CARE
OFFICE OF RESEARCH SERVICES
Research Ethics Board

Certificate of Research Ethics Board Approval - Amendment *Revised*

Principal Investigator:	Department:	Reference Number:
Dr. P. Paré	Medicine	P99-0270

Institution(s) Where Research Will be Carried Out:

St. Paul's Hospital

Co-investigators:

Dr. Levy

Sponsoring Agencies:

GlaxoSmithKline

Project Title:

A Two-Year, Multi-Site Family Study to Identify the Genetic Determinants Associated with Susceptibility to Chronic Obstructive Pulmonary Disease

Amended Title: GSK COPD Network Patient Recontact Study

Date of Initial Approval	Term of Initial Approval	Amendment Approved:
March 30, 2000	1 Year	April 21, 2005

Documents Included in this Approval:

Amended Study Title; Protocol – Version 1 (February 1, 2005); Patient Letter for Participants Living Within the Lower Mainland – Version 3 (April 4, 2005); Patient Letter for Participants Living Outside the Lower Mainland – Version 3a (April 4, 2005); Interest Level Survey for Lower Mainland Residents – Version 3 (April 4, 2005); Interest Level Survey for Outside Lower Mainland Residents – Version 3a (April 4, 2005)

The Chair/Associate Chair of the UBC/PHC REB has reviewed the amendment(s) for the above-named project and the accompanying documentation was found to be acceptable on ethical grounds for research involving human subjects.

The REB approval period for this amendment expires on the one-year anniversary date of the REB approval for the entire study.

CERTIFICATION
In respect of clinical trials:

1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards as defined in part C Division 5 of the *Food and Drug Regulations.*
2. This Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices and
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial, which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

Approval on behalf of the Clinical Research Ethics Board by one of:

Dr. I. Fedoroff, Chair
Dr. A. McLeod, Associate Chair

Date: AUG 16 2005

UBC/PROVIDENCE HEALTH CARE
OFFICE OF RESEARCH SERVICES

Certificate of Final Approval

Principal Investigator:	Department:	Reference Number:
Dr. P. Pare	Medicine	P99-0270
Co-investigators: **Dr. Levy**		
Sponsoring Agencies: Glaxo Wellcome		Term (Years): 3
Project Title: A two-year, multi-site family study to identify the genetic determinants associated with susceptibility to chronic obstructive pulmonary disease		
Date Submitted: December 13, 1999	Date Ethical Approval: March 30, 2000	Date Final Approval: April 14, 2000

The above-mentioned study has recently been approved by the UBC/PHC Research Ethics Board. All other necessary departmental approvals (*Nursing & Contract with Glaxo-Wellcome*) are now in place and I am pleased to inform you that you have the permission of the hospital to begin your study.

Vice President, Research
Providence Health Care

Date: April 14, 2000

INER

INSTITUTO NACIONAL DE ENFERMEDADES RESPIRATORIAS

"ISMAEL COSÍO VILLEGAS"

2006. Año del Bicentenario del natalicio del Benemérito de las Américas, Don Benito Juárez

Dra. Alejandra Ramírez Venegas
Investigadora Principal

DI/CCB/110/06

Asunto: DICTAMEN DEL COMITÉ DE CIENCIA Y BIOÉTICA EN INVESTIGACIÓN. APROBACIÓN.

Título del proyecto: ***Exposición a biomasa y EPOC en mujeres mexicanas ¿ Enfisema o Enfermedad de la vía aérea?. Un estudio piloto de tac de tórax de alta resolución.***

Código asignado por el Comité: ***C20-06.***

Le informamos que su proyecto de referencia ha sido evaluado por el Comité y las opiniones acerca de los documentos presentados se encuentran a continuación:

	Nº y/o Fecha Versión	*Decisión*
Protocolo	*12-julio-2006*	*APROBADO*
Carta de autorización y consentimiento informado.	*12-julio-2006*	*APROBADO*

Le recordamos que este proyecto deberá ser nuevamente aprobado por el Comité antes de febrero de 2007 y en caso de término, informar al mismo.

Para ello, le rogamos tenga en cuenta que deberá enviar al Comité un reporte de progreso al menos 40 días antes de la fecha de caducidad anterior. El Comité dispone en su página electrónica de un formato estándar de reporte de progreso que deberá usarse al efecto.

Atentamente.

8 de agosto de 2006

Dr. Guillermo Cabrajal Sandoval
Presidente del Comité de Ciencia y Bioética
En Investigación del INER

PROVIDENCE HEALTH CARE
Research Institute

Providence Health Care Research Institute
Office of Research Services
11th Floor Hornby Site
c/o 1081 Burrard St, Vancouver, BC V6Z 1Y6
Phone: (604) 806-8567 Fax: (604) 806-8568

Providence Health Care
Institutional Certificate of Final Approval

Principal Investigator:	Department:	Reference Number:
Peter D. Pare	UBC/Medicine, Faculty of/Medicine, Department of Respiratory	PHC REB H07-00095

Sponsoring Agencies:

Canadian Institutes of Health Research (CIHR)

GlaxoSmithKline (Canada) Inc.

Project Title:

Biomass smoke and COPD in Mexican Women: Emphysema or Airway Disease. A pilot study.

Date Ethical Approval:

June 3, 2008

The UBC-PHC Research Ethics Board granted ethical approval for the above-referenced research project on the date stated above. I am now pleased to inform you that all necessary hospital department/facilities approvals and institutional agreements/contracts are now in place and that you have permission to begin your research.

Dr. Yvonne Lefebvre
Vice President Research and Academic Affairs, Providence Health Care
President, Providence Health Care Research Institute

Date: June 26, 2008

St. Paul's Hospital
Holy Family Hospital
Mount St. Joseph's Hospital
St. Vincent's Hospital-Brock Fahrni Pavilion
St. Vincent's Hospital-Langara
Youville Residence