EXAMINING GENDER DIFFERENCES IN THE DIAGNOSIS OF OBSTRUCTIVE AIRWAY DISEASES

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ABSTRACT

Gender disparities in the diagnosis of cardiovascular diseases have been well established. Not much is known about gender differences in obstructive airway diseases (OADs). The aim of this thesis is to 1) conduct a systematic review and meta-analysis to synthesize the existing evidence on gender bias in the diagnosis of chronic obstructive pulmonary disease (COPD), 2) conduct a secondary data analysis to examine gender diagnostic bias in patients who meet spirometry criteria for COPD and 3) conduct a secondary data analysis to examine gender diagnostic bias in patients who meet spirometry criteria for asthma.

The Cochrane handbook for systematic reviews of interventions was used as a guide for standard methods used in systematic reviews. Literature search was conducted using MEDLINE (PubMed), EMBASE and CINAHL. Relevant articles were selected for descriptive and quantitative synthesis, and the Inverse Variance (IV) random effect model was used for analysis. For the secondary data analysis, multivariate logistic regression was used to assess the effect of sex on diagnostic outcomes (physician-diagnosed COPD or physician-diagnosed asthma, misdiagnosis, referral to a specialist, referral for spirometry and referral for chest x-ray), while controlling for additional patient factors.

Results from the meta-analysis suggests that gender disparities do exist in primary care for COPD, as men were about two times more likely to receive a correct diagnosis for COPD, and women with respiratory symptoms were less likely to be referred for spirometry. For the secondary analysis of data, no significant differences between genders were observed for all diagnostic outcomes in patients who meet spirometry criteria for COPD. However, for patients with spirometrically-defined asthma, women were less likely than men to receive a

correct diagnosis for asthma, less likely to be referred for spirometry, but more likely than men to be referred for chest-x-ray.

STATEMENT OF CO-AUTHORSHIP

I hereby declare that in all cases, the key ideas, primary contributions, experimental designs, data analysis, interpretation, and writing of manuscripts were performed by L.A., under the supervision of W.K. M. The contribution of co-authors was generally through the provision of new ideas, suggestions and corrections. M.A.B contributed to the literature search, study selection, quality assessment and data extraction for the paper presented in chapter two. Data for the paper presented in chapter three had already been collected by W.K.M and his research team members. W.K.M also contributed to the statistical analysis of the paper presented in chapter three. P.D and J.F provided feedback on refinement of ideas and editing of papers presented in chapters two and three.

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DEDICATION

To my dear parents,

Mr. and Mrs. Acheampong

for their unflinching love and support and putting me through the best education possible.

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LIST OF ABBREVIATIONS

PubMed	Search engine for Published Medical Literature
CINAHL	Cumulative Index of Nursing and Allied Health Literature
EMBASE	Excerpta Medica database
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
USPSTF	US Preventive Services Task Force
CI	Confidence Interval
OR	Odds ratio
SPSS	Statistical Package for the Social Science
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
OADs	Obstructive Airway Diseases
COPD	Chronic Obstructive Pulmonary Disease
CAD	Coronary Artery Disease
ACQ	Asthma Control Questionnaire
CAT	COPD Assessment Test
SABA	Short-Acting Beta-Agonists
LABA	Long-Acting Beta-Agonists
PFT	Pulmonary Function Test
mMrc	Modified Medical Research Council
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity

LIST OF PUBLICATIONS

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LIST OF PRESENTATIONS

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CHAPTER ONE

Introduction

1.1 Background

1.1.1 Obstructive Airway Diseases remain a Global Burden

Obstructive airway diseases (OADs) are also called obstructive lung diseases. They are a category of respiratory diseases characterized by airway obstruction. Many OADs result from narrowing or loss of elastic recoil of the lower airway tubes and may be characterized by inflamed and easily collapsible airways, shortness of breath, chest tightness, problems exhaling and frequent medical clinic visits and hospitalizations (1, 2). Amongst the conditions that fall under the category of OADS (asthma, bronchiectasis, COPD [chronic bronchitis and emphysema]) asthma and COPD represent the most significant diseases based on high prevalence and health care system burden (1-3). Asthma and COPD also represent the most common cases of respiratory diseases worldwide (4).

Prevalence of asthma is increasing globally (4, 5). The disease prevalence in Canada has been increasing over the last 20 years, and it is estimated that currently, over three million Canadians have asthma (5, 6). The prevalence of COPD is also rising, and reports predict that by the year 2030, COPD will be the third most common cause of mortality worldwide (6). The burden asthma and COPD pose to Canada's economy is large (3, 5, 6). The two conditions negatively impact the lives of Canadians in terms of their mental health, limitations to activities of daily living, work, and social and recreational activities. Chronic lung diseases account for more than 6% of health care costs annually in Canada (5,6). The cost associated with asthma is

estimated at CAD648 million per year (5), while direct and indirect costs of COPD are estimated at CAD1997.81 per patient annually (3, 5, 6). Existing data on obstructive airway disease prevalence suggests a high burden on primary care, which is the first healthcare contact for most patients with respiratory diseases (7).

COPD and asthma share similar symptoms, such as chronic cough, wheezing, chest tightness, sputum production, and difficulty in breathing (8, 9). Nonetheless, they are distinct conditions with different etiology, frequency of symptoms and reversibility of airway obstruction (8, 9). COPD is said to be an adult-onset disease and results in a progressive permanent damage to the lower airways, usually as a result of excessive smoking (2). Asthma, on the other hand, is typically diagnosed in children and has been linked to an immune response to allergen exposure (1). Though they share similar symptoms, the symptoms may be experienced differently. For instance, patients with COPD are more likely to experience an early morning cough with increased sputum production and persistent symptoms. On the other hand, symptoms experienced by asthma patients are more likely to be episodic or may occur at night. Unlike COPD, airflow obstruction in asthma can usually be reversed by medications (1, 2).

The differential diagnosis of asthma and COPD was much easier historically, as COPD used to be a disease of older men who smoked (10). In recent times, however, many women and youth are also smoking, and this has made it difficult to differentiate between the two conditions (11). There are currently several guidelines that provide directions for diagnosis and treatment of asthma and COPD (1, 2). Nonetheless, both diseases remain underdiagnosed, misdiagnosed and undertreated (12). Early diagnosis is vital due to profound differences between asthma and COPD in treatment and disease progression (12). There is evidence that about 80% of COPD cases are undiagnosed until the latter stages of the disease when severe organ damage has

occurred (13-16). Interestingly, there are many patients in primary care who have been diagnosed with asthma when in fact they have COPD and vice versa (17-19).

1.1.2 The Issue of Diagnostic Bias

Gender inequalities in healthcare service utilization have been discussed for many years. Despite the best intentions of health workers to provide standard treatment to all, gender disparities in health care persist, and this may lead to an unwarranted increase in morbidity and mortality for some patients (20). Many factors may be responsible for these disparities, including implicit bias (an unintentional, unconscious attribution of particular qualities to a particular social group) usually influenced by experience, intuition or prejudice (20, 21). "Implicit bias may contribute to health care disparities by shaping physician behavior and producing differences in medical treatment along the lines of race, ethnicity, gender or other characteristics"- Elizabeth N. Chapman, MD (20). A bias in diagnosis arises when medical and psychological diagnosis is influenced by the sex of the patient consciously or unconsciously, resulting in unequal medical practices for men and women (20, 21). Gender differences in referral for diagnostic tests have been identified in other chronic diseases like heart diseases, depression and autoimmune disorders (22, 23).

Evidence for gender bias in the diagnosis of cardiovascular diseases is extensive (22-25). Heart diseases have been considered for many years as a disease of men (26). The notion that women could suffer more from breast cancer than from cardiovascular diseases has been deeply ingrained, and this may put women at risk of underdiagnosis (26). Young women with cardiovascular diseases are often treated late, or the diagnosis may be missed entirely (26, 27). Evidence suggests that if a woman and man presented to the emergency clinic with symptoms

characteristic of a heart attack, the woman is less likely to undergo diagnostic catheterization (aRR=0.75, 95%CI: 0.68-0.83) and also less likely to be given a thrombolytic therapy (aRR=0.93, 95%CI: 0.90-0.96) within 60 minutes of admission, as compared to her male counterpart (25). In the inpatient setting, studies of women with stroke have reported longer wait times on arrival at the emergency department, coupled with less aggressive treatment and less therapeutic workup during admission (28-30). Studies conducted in North America and Europe have found women with cardiovascular diseases to be less likely than men to receive appropriate diagnostic imaging or carotid revascularization (31-34).

Subsequently, the risk of heart diseases in women has been underestimated, under-recognized and underdiagnosed, leading to less aggressive treatment strategies, an increase in mortality and lower numbers of women being represented in clinical trials (35). Ironically, women are as likely as men to have heart failure (36). Moreover, women with heart failure have higher mortality rates than men with the same condition (36).

Gender disparities have also been seen for depression (37). In developed countries, women are twice as likely as men to be diagnosed with depression, even though higher rates of successful suicides have been recorded in men with depression (37). Men with depression are often diagnosed later than women, and sometimes, diagnosis of depression in men is missed entirely (37, 38). Diagnostic bias has been noted in autoimmune diseases such as systemic lupus erythematosus, which is considered a genetic disease of women (39). A greater delay in diagnosis and treatment of the disease is often seen in men who present with similar symptoms as women. Consequently, men with the disease end up with worsened outcomes and more physiological damage than women (40).

In recent years, pulmonary researchers have begun to explore the impact gender may have on the diagnosis of airway diseases. Whether women with COPD or asthma receive the same medical care for their conditions as men, and whether they are at risk of different outcomes as a result, is unknown.

The burden of COPD in women is increasing quickly (41). COPD is now responsible for more deaths in women than many cancers (41). Epidemiological studies conducted in USA and Denmark have shown an increase in COPD deaths in women compared to men (42, 43). Studies conducted across Italy, Sweden, UK, and the USA have reported similar COPD prevalence in men and women (44), while another conducted in Canada reported a higher prevalence of COPD in women smokers than in men smokers (8.2% vs 3.5%) (45). A Dutch study reported an increase in prevalence of 20.5% for women and a decline of 48.8% for men over the same time period (46). A number of factors may contribute to the increasing prevalence of COPD in women. There may be increases in smoking rate amongst women, increased use of biomass as fuel for cooking in underdeveloped countries, or exposure to occupational risk factors (47).

Despite these observations, there is often a disregard for COPD as a woman's healthcare issue. One reason for this may be a gender bias that exists in the perception that COPD is a disease of older, male, smokers, still influencing clinical decision making. Women may not report symptoms like sputum production and cough due to the societal stigma associated with them, and that may also lead to delayed diagnosis or misdiagnosis (48).

In an Epidemiological Study (EPI-SCAN) conducted in Spain, the odds of receiving a correct family physician's diagnosis for COPD was two times more for men compared to women, after adjusting for age, smoking, education level, mMRC dyspnea score and COPD

severity (49). After controlling for confounders, Martinez et al. found women with COPD were more likely than men to report diagnostic delay (OR=1.66, 95%CI: 1.13-2.25, p=0.01) and difficulty in reaching their physicians (OR=2.54, 95%CI: 1.33-4.86, p=0.004) (50). In validated vignette questionnaires, primary-care physicians have stated COPD as the most probable diagnosis more often for the man as compared to the woman (58% vs 42%, $p<0.05$) (51), while a greater percentage of women than men have been misdiagnosed with asthma (48% vs 32%) (51).

Although gender bias in diagnosis of OADs is reduced by the use of spirometry, this tool remains underused among primary-care physicians. Studies have shown that a large proportion of patients diagnosed with COPD have no history of spirometry testing and less than one-third of COPD patients undergo spirometry before their first prescription (14). It has been reported that referrals for spirometry may be less in women with respiratory symptoms. After adjusting for age, pack-years, country and dyspnea scores, the *Confronting COPD survey* found that women were less likely to have had spirometry (aOR=0.84, 95% CI: 0.72-0.98) as compared to men with COPD (52).

Asthma is the second highest differential diagnosis to COPD. Chapman et al. revealed that "there is considerable diagnostic confusion between COPD and asthma, the most common alternative diagnosis offered by physicians" (51). Dales et al. found that despite no significant differences in bronchodilator responsiveness between genders, physician-diagnosed asthma was two times higher in women than in men (53). Together, these data suggest that women or men with COPD or asthma may be less likely to be diagnosed and subsequently less likely to be treated for their condition (41, 50, 53). Gender inequalities in diagnostic processes may impact the therapeutic strategies, symptoms and health-related quality of life of patients.

1.1.3 Symptoms and Health-related Quality of Life may differ

Diagnosis of asthma or COPD first starts with the patients reporting their symptoms to their physician. Symptoms associated with respiratory diseases can be debilitating, alarming and sometimes life-threatening. Depending on the severity of the disease, a patient with asthma or COPD may experience some or all of the following symptoms - cough, sputum production, dyspnea, fatigue, chest tightness, weight loss and wheezing (1, 2). Comparing responses from two groups of patients, authors found that problems such as difficulty breathing, tiredness, depression, loneliness, anxiety, financial instability, limited ability to engage in activities, difficulty sleeping, stress, boredom and lower health-related quality of life are reported more often by people with COPD as compared to patients without the condition (54). Dyspnoea (shortness of breath) is the most significant symptom in COPD and the main determinant of health-related quality of life, prognosis and disability in people with the disease (55). Dyspnea was found to be the most reported symptom in a study of 68 patients with respiratory disease, with fatigue being the second most prevalent (56).

Symptoms of COPD may differ by sex. Women with COPD are more likely than are men to report dyspnea and less likely to report sputum production (52, 57). Women report higher degree of dyspnea, despite fewer pack-years and similar degree of pulmonary impairment (52). In a Spanish study, women reported less sputum than men but cough, wheezing and dyspnea were reported with the same frequency (41). In the PLATINO study on sex-related differences in COPD, dyspnea was more common among women with or without COPD (58). Women may have worse COPD symptoms than men (52, 57, 58). COPD exacerbations have been reported more often in women than men, while comorbidities such as anxiety and depression are also more common in women (59, 60). Evidence suggests that women with COPD experience a more

impaired health-related quality of life at an earlier age in their lifetime than men with COPD (58, 60).

Like COPD, there may be gender differences in the clinical expression of asthma. Women with asthma report more symptoms than men. Out of 400 patients interviewed by Zillmer et al., the proportion of women who reported troublesome symptoms like cough with sputum, chest tightness and shortness of breath, were greater than men (61). Also, the proportion of women who reported that their asthma had caused them to feel lack of control over their lives and affected the way they felt about themselves, were also greater than men (61). In a separate study by mcCallister et al., women were more likely than men to report symptoms such as nocturnal awakenings, activity limitation, and shortness of breath, and to feel bothered by their cough or triggers, despite having similar overall asthma control as men (62). Women with asthma have also reported poorer health-related quality of life than men (63-66).

The reasons behind gender differences in the clinical expression of OADs could be multifactorial. Societal concept of athleticism may cause men to report less dyspnea than women (67). Also, social and cultural factors may result in women being less likely to report the production of phlegm or sputum (68). Furthermore, differences in the physiological and biological make-up of men and women may influence the expression of the disease (69). Moreover, bias in the care given by health care workers could also lead to worse symptoms or poorer health-related quality of life for men or women with respiratory diseases (52, 68).

1.1.4 Management differences

Management of respiratory conditions involves the use of pharmacological and non-pharmacological means. The main component of non-pharmacological therapy is pulmonary

rehabilitation. Aspects of a rehabilitation program are education (smoking cessation, information on COPD or asthma, allergen avoidance, etc.), specific respiratory muscle training, nutritional intervention, exercise training and motivational coaching. The aim of non- pharmacological management is to improve patients' quality of life, reduce symptoms and number of hospitalizations, improve exercise tolerance, reduce anxiety and depression, and increase survival (1, 2, 70).

Pharmacological management of respiratory conditions involves the use of medications to treat the conditions. There are currently no medications to cure COPD or fully reverse the extent of the damage. Pharmacotherapy is aimed at preventing and controlling symptoms, reducing frequency and severity of exacerbations, slowing disease progression, improving health status and reducing mortality (1, 2, 70). Like COPD, asthma has no cure. However, airway narrowing in asthma can be fully reversed by medications, but only temporarily. Asthma pharmacotherapy is aimed at achieving and maintaining clinical control (1).

Authors of clinical guidelines recommend that pharmacological and non-pharmacological therapies be used together to manage patients with COPD or asthma (1, 2). For both asthma and COPD, pharmacological therapy employs the following medications: short-acting beta-agonists (SABA), long-acting beta-agonists (LABA), anticholinergics, corticosteroids and combination therapy (1, 2). While the same medications are used for both conditions, answers to the questions of 'when, how and why' these medications are used may differ. For instance, inhaled corticosteroids are advantageous in both conditions, but are used at different stages of the diseases. In asthma, inhaled steroids are used in the early stages of the disease. However in COPD, inhaled steroids are added after the patient has developed severe acute COPD with multiple exacerbations. Also, while LABAs are conveniently used for the

initial COPD treatment, LABAs are not used in asthma until the patient has gotten to the moderate persistent stage of the disease (1, 2).

Authors of the Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend the same therapy for both sexes (1, 2). Nonetheless, it is unclear whether the implementation of these guidelines differs between men and women in real practice.

Differential treatment of chronic diseases, on the basis of gender, has been discussed in many studies. For instance, in the cardiovascular literature, out of those patients who were ideal candidates for an aspirin therapy, women were less likely than men to be given this therapy within 24 hours of hospitalization (aRR=0.94, 95%CI: 0.92-0.95) (25). Similarly, in two different studies, women were less likely to receive antiplatelet, β-blocker, or lipid-lowering therapies for peripheral artery diseases (71, 72). An unequivocal bias in management was established in a study by Abuful et al. where a 2-part study was designed to compare physicians' attitudes with their actual clinical practice in preventive therapy for coronary artery disease (CAD) (73). In the *Attitude study*, hypothetical case scenarios of a man and woman with the same age, identical clinical and laboratory data, and mild coronary atherosclerosis on angiography were presented to participating physicians. In the *actual clinical study*, authors examined lipoprotein levels and prescriptions for lipid-lowering medications from medical records of men and women with angiographic evidence of CAD. The *Attitude study* revealed that despite the similar clinical patient data, physicians considered the male patient to be at higher risk and therefore prescribed aspirin (91% vs 77%, $p<0.01$) and lipid-lowering medications (67% vs 54%, $p<0.07$) more often for the man. In the *Actual clinical practice study*, chart reviews showed that 77% of males were prescribed a lipid-lowering medication compared to 47% of

females ($p<0.001$). The authors concluded that they found clear evidence of gender bias in both the attitude and the actual clinical practice of prevention therapies for patients with CAD (73).

Similarly in the pulmonary literature, women have been less likely than men to get a prescription for nicotine patches but have been more likely to receive advice to quit smoking (52, 74). Dales et al. found that women were less likely than men to be prescribed medications if COPD was mild or moderate, but were as likely as men to be on respiratory medications if COPD was severe (53). Despite having similar symptoms and disease severity, women have been reported to be less likely than men to be on anticholinergic agents (57). Two studies found no difference in prescription for corticosteroids between genders (52, 75). Also, after controlling for potential confounders, men have been reported to be more likely than women to be on dry powder inhalers and to have "appropriate inhaler combinations" (75, 76).

1.2 Rationale and justification

Unlike the extensive work done in cardiovascular diseases, evidence of gender disparities in the diagnosis of OADs is still in the elementary stages. A bias in diagnosis may result in delayed or misdiagnosis, potentially leading to suboptimal treatment and worsened outcomes for men or women. Despite the growing evidence supporting a potential bias in COPD diagnosis, there have been limited research studies and evidence is inconclusive. While a number of narrative reviews (14, 48, 68) exist on this topic, no systematic review has been conducted as a more objective, less-biased method to synthesize existing evidence and draw appropriate conclusions.

Research in other jurisdictions has shown that a bias may exist in the diagnosis of COPD (41, 49, 77). However, very few studies on gender disparities in care have been conducted in

North America. In a Canadian study on physicians' attitudes towards men and women, primary-care physicians were found to be more likely to diagnose COPD in men as compared to women, even though men and women may present with the same history, physical findings and disease severity (51). That study could, however, be limited, as the validated vignette questionnaires may not represent actual clinical practice. Moreover, the study was conducted over a decade ago and has not been updated to see if the trend exists in more recent years. Again, while some work has been done in COPD, gender diagnostic bias has been rarely investigated in asthma. The population considered in a study by Leynaert et al. was patients with asthma-like symptoms and bronchial hyper- responsiveness (78). Thus, this may be the first project to dissect gender diagnostic bias in patients with objectively known asthma.

1.3 Purpose

The purpose of this project is to compare family physician's diagnostic processes between men and women who meet objective criteria for COPD or asthma. We also hypothesized that gender inequalities in diagnostic processes may impact the therapeutic strategies, symptoms and health-related quality of life of patients. Therefore, as a secondary objective, we explored differences in cardinal symptoms, health-related quality of life and medication prescription patterns of men and women with COPD or asthma. To achieve this purpose, we first conducted a systematic review and meta-analysis for COPD. However, a systematic review and meta-analysis was not conducted for asthma as a literature search indicated lack of relevant studies. We also performed a secondary data analysis for COPD and asthma.

1.4 Significance

Women, have been reported to have poorer outcomes in OADs than men in terms of mortality rates, hospitalization frequency, emergency visits, dyspnea symptoms and health-related quality of life. The rapid rise in prevalence and worsened outcomes in women as compared to men with asthma/COPD could be because of gender differences in diagnosis of the disease. Exploring and assessing the gender disparities in diagnosis of obstructive airway diseases may provide valuable information to develop hypotheses as to why these differences might exist, to reduce these disparities, and to identify areas for future research. The end goal is to achieve improved interventions and outcomes for both men and women.

1.5 Program of research for thesis

This thesis is comprised of two studies aimed at addressing the gaps, limitations and current knowledge surrounding gender diagnostic bias. Firstly, a systematic review and meta-analysis was conducted to summarize and synthesize existing literature on gender bias in COPD diagnosis, and to obtain a single, more precise estimate of the extent of bias, using meta-analysis. (Research study #1)

A secondary analysis of data obtained from the Epidemiology of Shortness of Breath (EpiSOB) study, conducted in Edmonton and Saskatchewan, was then conducted to explore gender disparities in a Canadian setting, and to address diagnostic, symptoms and treatment gaps identified by the review. (Research study #2)

1.6 Research questions

In patients with COPD, does being a man as compared to being a woman influence the diagnosis of the condition?

In patients with asthma, does being a man as compared to being a woman influence the diagnosis of the condition?

1.7 Specific Research Objectives

1.7.1 Primary objectives (diagnostic outcomes):

i. To compare rate of physician-diagnosed COPD between men and women who meet spirometry criteria for COPD (Research study #1 and Research study #2)

ii. To compare rate of misdiagnosis between men and women who meet spirometry criteria for COPD (Research study #2)

iii. To compare referral rate to a specialist between men and women (Research study #2)

iv. To compare referral rate for spirometry between men and women (Research study #1 and Research study #2)

v. To compare referral rate for chest x-ray between men and women (Research study #2)

vi. To compare referral rate for methacholine test between men and women (Research study #2)

vii. Repeat the above for patients with asthma (Research study #2)

1.7.2 Secondary objectives

viii. To compare medication prescription patterns for men and women (Research study #1 and Research study #2)

ix. To compare symptoms of men to those of women (Research study #1 and Research study #2)

x. To compare health-related quality of life of men to those of women (Research study #1 and Research study #2)

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CHAPTER TWO

Research Study #1: Is there Gender Bias in the Diagnosis of COPD? A Systematic Review and Meta-analysis.

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SUMMARY AT A GLANCE:

We conducted a systematic review and meta-analysis to explore gender differences in family physicians' diagnosis of COPD

A version of this chapter has been submitted to the *Journal of COPD*

2.1 Abstract

Background and objective:

Recent studies have reported gender bias in the diagnosis of chronic diseases including those of cardio-pulmonary origin. A comprehensive systematic review has not been conducted to synthesize the existing evidence for chronic obstructive airway diseases. In this review, we studied the differences in the diagnosis of chronic obstructive pulmonary diseases (COPD) among men and women. As a secondary objective, we explored differences in medication prescription patterns, symptoms and health-related quality of life of men and women with COPD.

Methods:

We followed standard methods for conducting a systematic review and meta-analysis, as outlined in the Cochrane handbook for systematic reviews of interventions. An exhaustive literature search was conducted using 3 electronic databases including MEDLINE (PubMed), EMBASE and CINAHL. Appropriate studies related to the research question were identified, screened and selected. Two reviewers independently assessed the selected articles for relevance and methodological quality. Relevant articles were selected for descriptive synthesis and quantitative synthesis. The Inverse Variance (IV) random effect model was used for analysis. Heterogeneity between studies was explored and publication bias was checked visually and quantitatively.

Results:

Of the 967 studies retrieved, 28 were included in the descriptive synthesis and 18 studies in the quantitative synthesis (meta-analysis). Gender bias in COPD diagnosis may exist, as men were more likely to be correctly diagnosed with COPD by primary care physicians (OR=2.09, 95% CI: 1.44-3.05), and women with respiratory symptoms were less likely to be referred for spirometry (OR=0.86, 95% CI: 0.77-0.96). Also, men with COPD had a better health-related quality of life than women based on the SGRQ scores (Standardized mean difference= -0.19, 95% CI: -0.29 to -0.09).

Conclusion:

There exist gender differences in diagnosis of COPD and referral for spirometry. Women with COPD are more likely to report lower health-related quality of life than men. There was insufficient evidence to support or refute gender bias in physicians' prescription patterns for COPD medications.

Keywords:

COPD, gender differences, gender bias, primary-care physicians, family physicians, meta-analysis, systematic review.

Word Count: 325

2.2 Introduction

Gender inequalities in healthcare services remain a topic for discussion. Gender biases may result in unequal medical practices or outcomes between men and women. Gender differences in referral for diagnostic tests have been identified in chronic heart disease, which has been considered a "male disease", putting women at risk of underdiagnoses (1, 2).

In recent years, pulmonary researchers have begun to explore the impact gender may have on the diagnosis of airway diseases. COPD has historically been considered to be an illness of men, due to the perceived higher smoking rates in men as compared to women (3). Increasing evidence, however, suggests that many women are now smoking, and more and more women are employed in industries where air pollution is pronounced (4).

Epidemiological studies conducted in USA and Denmark have shown an increase in COPD deaths in women compared to men (5, 6). In Canada, COPD prevalence was found to be 8.2% in women who smoke compared to 3.5% in men who smoke (7). Despite these observations, evidence suggests that the diagnosis of COPD is made much more often, and more correctly in men (8, 9). Conversely, women are more likely to be diagnosed with asthma when the correct diagnosis is COPD, due to the perception that COPD is not a woman's disease (8-10).

An objective measure of lung function, spirometry, has proven to be a good measure to confirm COPD or asthma diagnosis and to differentiate between the two diseases (11, 12). Authors of clinical guidelines highly recommend using spirometry before diagnosing COPD (11, 12). Unfortunately, it has been reported that very few physicians make use of this tool in their investigation of chronic respiratory symptoms, with women being less likely to be referred for spirometry (8, 9, 13). Gender bias in diagnosis may impact treatment and health outcomes. A

number of epidemiological studies are available that suggest that diagnostic efforts are lower in women with COPD (8, 9, 13-15). However, a comprehensive systematic review has not been conducted to synthesize the existing evidence and draw appropriate conclusions.

The aim of this study is to systematically review, summarize and synthesize existing literature on gender bias in COPD diagnosis, and to simultaneously combine estimates from eligible studies (based on comparable outcomes and population), using meta-analysis, to obtain a single, more precise estimate of the extent of bias.

This review addresses the following question: In patients with COPD, does being a man as compared to being a woman influence the diagnosis of the condition? As a secondary objective, we explored cardinal symptoms, health-related quality of life and medication prescription patterns of men and women with COPD.

2.3 Methods

We followed standard methods for conducting a systematic review and meta-analysis, as outlined in the Cochrane handbook for systematic reviews of interventions (16). The review was also conducted and reported on the basis of the Preferred Reporting Item for Systematic Review and Meta-analysis (PRISMA) checklist (17) and the checklist of Meta-analysis of Observational Studies in Epidemiology (MOOSE) (18).

2.3.1 Outcome measures

Our primary outcomes were the rate of physician-diagnosed COPD and referral for spirometry in men and women who meet objective criteria for COPD. We defined physician-diagnosed COPD as patient self-reported diagnosis of COPD from a primary-care physician, or a

primary-care physician's diagnosis based on validated case scenarios. Also, referral for spirometry was defined as the proportion of patients that had undergone spirometry before diagnosis, or up to one year after diagnosis of COPD. Our secondary outcomes were differences in medication prescription patterns, cardinal COPD symptoms (dyspnea, cough and sputum production) and health-related quality of life.

2.3.2 Literature search

We conducted the literature search using MEDLINE (PubMed), EMBASE and CINAHL, including articles published from inception of the databases to December 2017. We maximized retrieval of searches by using MeSH terms and keywords, and a combination of the two. The MeSH terms used were "Pulmonary Disease", "Chronic Obstructive", and "Sexism". Keywords used were "COPD", "chronic obstructive pulmonary disease", "gender difference", "gender factor", "gender bias" and "sex bias".

Reference lists of eligible articles as well as reference lists of narrative reviews on gender differences in COPD were hand searched to identify additional studies. We also contacted some study authors to obtain additional information on studies that were relevant. Our literature search strategy focused on studies conducted in humans, with no restriction on language. The intensive search started on the 10th of September 2017 and the last search was completed on December 15, 2017. The final search string used for searching studies in PubMed, Embase and CINAHL is shown in appendix A.

2.3.3 Study selection

Two authors (LA, MAB) independently screened titles and abstracts of articles yielded by the initial database search. Full text articles of relevant studies were retrieved and reviewed by two authors (LA, MAB) to determine eligibility.

The inclusion criteria captured retrospective cohort studies, cross-sectional studies, case-control and matched case-series studies that compared the differences between men and women in terms of diagnosis, medication prescribing, symptoms or health-related quality of life. Studies were included if: (1) diagnostic outcomes were stated as physician-diagnosed COPD, correct diagnosis of COPD, prior physician diagnosis of COPD and referral for spirometry or anything similar, (2) health-related quality of life was assessed using a validated tool, (3) at least one cardinal COPD symptom was assessed and (4) medication prescription pattern was defined as the likelihood of the man or woman being prescribed with COPD medications (e.g. short-acting beta agonists, long acting beta agonists, anticholinergics, etc.).

We excluded studies that only measured COPD prevalence by gender, rather than correct physician diagnosis by gender. Interventional studies such as clinical trials were excluded since we were only interested in medication prescription patterns of physicians, rather than the implementation of any intervention on drug prescription for COPD patients. We also excluded commentaries, narrative reviews, case reports and editorials. Studies were included in the quantitative synthesis (meta-analysis) if (1) they investigated the association between gender and physician-diagnosed COPD, referral for spirometry, symptoms, health-related quality of life and treatment, (2) if they also used odds ratio (OR) or relative risks (RR) with corresponding 95% confidence intervals (CI) as measures of associations. Also studies were included if summary measures of continuous or scale outcomes were reported as mean difference and interquartile

range (IQR). Any disagreement in study selection was resolved by discussion, while adhering strictly to the inclusion/exclusion criteria.

2.3.4 Data extraction

We developed a standardized form to guide in the data extraction process. The following data were extracted: author's first name and year of publication, country of study, characteristics of the population sampled, number of men and women compared, and outcomes such as physician-diagnosed COPD, referral for spirometry, cardinal COPD symptoms (cough, dyspnea and sputum production), health-related quality of life scores and adjusted confounders. Study results are summarized in Tables 2.1 to 2.4.

2.3.5 Quality Assessment

A quality assessment of articles that passed the inclusion/exclusion criteria was undertaken using the US Preventive Services Task Force (USPSTF) Quality Rating Criteria assessment of research bias for cohort and case-control studies (19). Two authors (LA, MAB) independently assessed the methodological quality and risk of bias of each study and graded each study as good, fair or poor using USPSTF criteria. Names of authors, study titles and journal of publication were blacked out by an independent reviewer to ensure a fair assessment free from assessor bias. Any disagreements between authors during assessment were resolved by discussion until a consensus was reached.

2.3.6 Statistical Analysis

Meta-analysis was done using the Review Manager (RevMan) vs. 5.3 software provided by the Cochrane Collaboration, and Comprehensive Meta-analysis (CMA) software. The

weighted mean difference (WMD) or standardized mean difference (SMD) with their corresponding 95% confidence interval (CI) was calculated for continuous outcomes such as health-related quality of life scores. Estimates that were reported in median (and IQR) were converted to mean (and SD) before analysis. To facilitate comparability, the directions of associations were reversed if lower scores indicated more impairment. For example, health-related quality of life scales that were in opposite direction to St. George's respiratory questionnaire (SGRQ) scale were reversed to the same direction by multiplying the mean values from that set of studies by −1 (20). Also, the oxygen cost diagram (OCD) dyspnea scale was reversed to the same direction as the modified medical research council (MMRC) dyspnea scale.

For dichotomous outcomes (e.g. Physician-diagnosed COPD or referral for spirometry), estimates of association measures such as odds ratio (OR) were calculated. Heterogeneity and homogeneity were assessed using Cochran (Q-statistics) and I^2, and a random effects model was employed due to suspected heterogeneity. Publication bias was visually examined using a funnel plot. Egger's and Begg's tests were conducted to test for funnel plot asymmetry, as a quantitative assessment of publication bias. Sensitivity analysis was conducted to assess the influence of outliers on results. In cases where meta-analysis could not be performed, the data were summarized descriptively.

2.4 Results

2.4.1 Systematic search

Our initial broad database search identified 967 publications (PubMed=157, Embase=365, Cinahl=445). Scanning through the reference lists of narrative reviews yielded an additional 10 articles. 33 of these publications were identified as duplicates and excluded, with a

total of 944 articles remaining. The titles and abstracts of 944 articles were screened for relevance by two reviewers (LA, MAB), of which 873 articles were excluded for improper study outcomes. The full-texts of the remaining 71 articles, published in English and Spanish (one article) were retrieved for further assessment. After assessing all 71 full text articles, 43 articles were excluded because they did not meet the inclusion/exclusion criteria, leaving a remaining number of 28 articles for the review (See Figure 2.1).

2.4.2 Description of included studies

The 28 selected papers were made up of 5 retrospective cohort studies, 20 cross-sectional studies, 1 case-control and 2 matched case-series studies. The publication years of the studies ranged from 1999 to 2017. The studies were conducted in the USA, Denmark, Spain, Canada, France, UK, Japan, Uruguay, Italy, Brazil and Norway. Important confounders such as age, smoking status, education level, level of dyspnea, COPD severity, and comorbidities were adjusted for by most studies. Most studies reported effect size as odds ratios (ORs) or relative risk (RR) for dichotomous outcomes and mean difference (SD), or median (IQR) for continuous outcomes. Some others reported study results using frequency tables. Thus, out of 28 studies, 18 qualified for meta-analysis based on appropriately reported effect estimate, comparable population and comparable outcomes.

COPD was defined by most studies as $FEV_1/FVC < 0.7$ after the use of a bronchodilator, while few others also used the criterion FEV1/FVC < lower limit of normal (LLN). The outcome "physician-diagnosed COPD" was defined by four studies as a self-reported diagnosis of COPD, based on participants' response to the questionnaire "Has your family physician ever told you that you have COPD?" The reported diagnosis of COPD was considered correct if it matched

the spirometric COPD criteria (post bronchodilator $FEV_1/FVC < 0.7$ or FEV1/FVC < LLN) used by the authors and experts at the time of the study visit. The proportion of correct diagnosis was compared between men and women.

Three other studies assessed "physician-diagnosed COPD" using validated vignette questionnaires (8, 9, 21). In those studies, hypothetical case scenarios of a man and woman with similar symptoms, disease severity and similar information on patient history and physical findings were presented to participating physicians. Characteristics presented were typical of a person with COPD. Physicians were then asked to state the most probable diagnosis based on the information provided them, and then choose the diagnostic study(s) they would recommend for the man versus the woman, like they would in real practice.

Referral for spirometry was assessed by studies as the proportion of patients who had undergone at least one spirometry in the period of 6 months before their first prescription or diagnosis to 12 months after their first prescription or diagnosis of COPD. This data was extracted from patient registers by two studies while two other studies used recall.

Studies that compared "symptoms" and "health-related quality of life" between men and women randomly sampled COPD patients from clinics. The 3 main symptoms of COPD (dyspnoea, cough and sputum production) were assessed using the following clinically validated questionnaires: modified medical research council (mMRC) dyspnea scale and chronic respiratory questionnaire (CRQ) dyspnea domain. For health-related quality of life, questionnaires used were St. George's respiratory questionnaire (SGRQ), chronic respiratory questionnaire (CRQ), euroqol-5D (EQ-5D) scale, short form 12 (SF-12) questionnaire and short form 36 (SF-36) scales. For "medication prescription patterns by gender", medical records of

patients were screened for data in three studies, while patient self-report data were used in two studies.

2.4.3 Quality assessment

The quality score for each paper is summarized in Tables 2.5 and 2.6. Overall, the articles chosen were of "fair" quality (i.e. 13 good, 14 fair and 1 poor). Across all studies, sampling was done randomly. The possibility of selection bias was reduced by incorporating matching into the study design of two studies, while 24 studies controlled for this bias at the data analysis stage by adjusting for potential confounders (e.g. age, smoking status, educational level, level of dyspnea, COPD severity, and comorbidities). Recall bias may however be high for studies in which participants self-reported "physician-diagnosed COPD". A satisfactory response rate was seen across studies. Only one out of the 28 papers was given an overall "poor" assessment due to poor methodology, with lack of appropriate attention to confounders. This study was therefore excluded from the meta-analysis (9). However, "fair" quality articles were included in the meta-analysis because they satisfied key bias domains (response rate, adjustment for potential confounders, and all important outcomes considered) relevant to our outcomes (22). In all, 18 studies were included in the meta-analysis.

Insert (Tables 2.5 and 2.6 here)

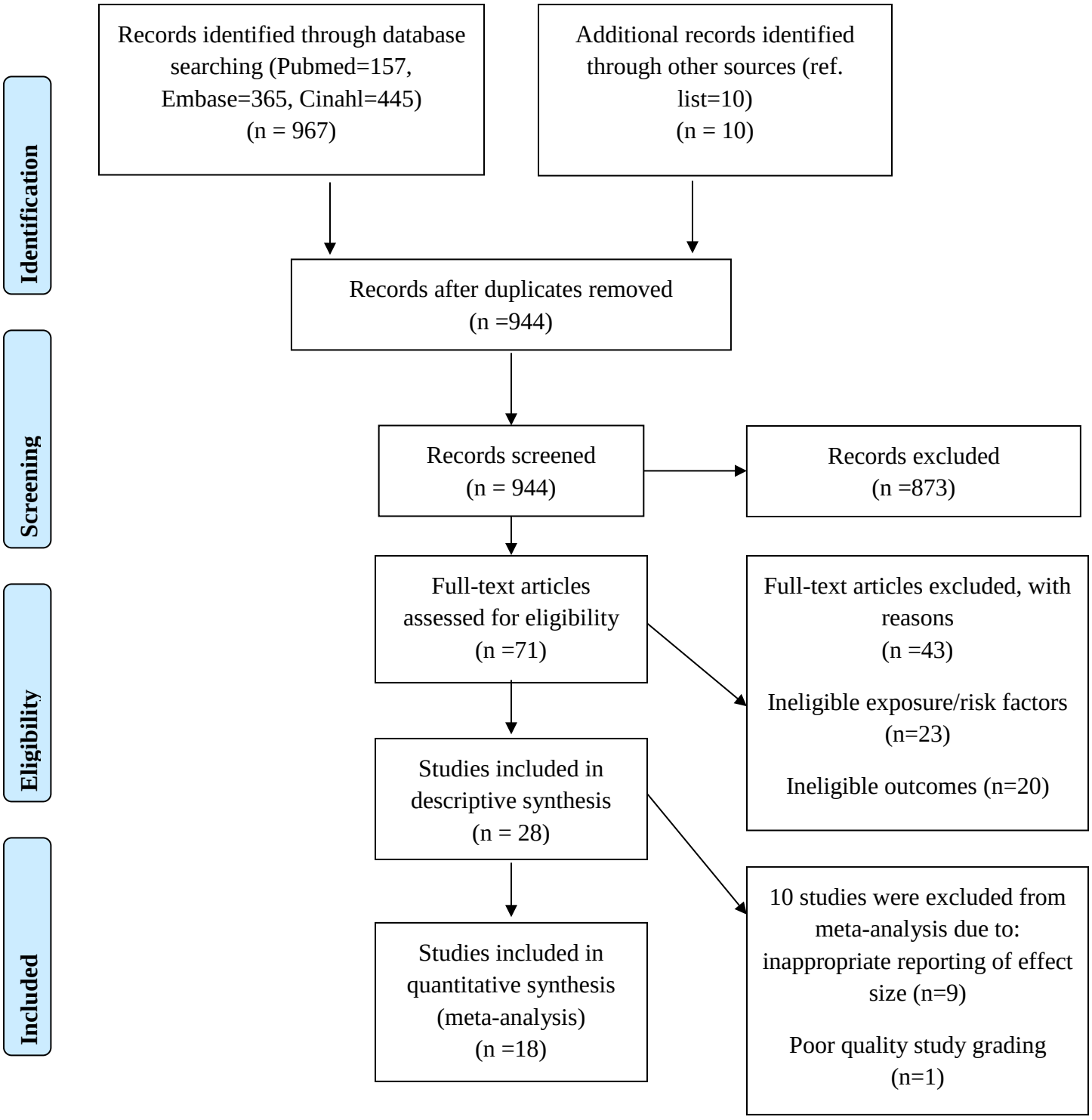

Figure 2.1 PRISMA flow diagram

2.4.4 Descriptive analysis of outcomes

2.4.4.1 Physician-diagnosed COPD

Seven studies compared the likelihood of a physician-diagnosed COPD in men as compared to women (8, 9, 21, 23-26). Four studies, using odd ratios and relative risks as measures of association, found that men were more likely to have had a correct diagnosis of COPD as compared to women after controlling for potential confounders such as age, smoking history, education level, mMRC dyspnea, COPD severity and comorbidities. Three studies compared physician diagnosis behaviour among men and women using frequency measures (9, 25, 26). Chapman et al. found that men (58%) were more likely to be diagnosed with COPD than women (42%) with $p<0.05$ (9). Martinez et al. found that women were more likely to report COPD diagnostic delay (OR=1.66, 95%CI: 1.13-2.45, p=0.01) (25), while Roberts et al. reported that more men than women had a correct COPD diagnosis (87.5% vs 73.9%, p=0.021) (26). Meta-analysis was possible for four out of these seven studies (8, 21, 23, 24).

2.4.4.2 Referral for spirometry

Four studies reported on spirometry use and found that women were less likely to be referred for spirometry, after adjusting for potential confounders namely age, pack-years of smoking, country, dyspnea severity, sex, race, comorbidity and number of pulmonary medications received. Specifically, Watson et al found women were 0.84 times less likely than men to be referred for spirometry (OR=0.84, 95%CI: 0.72-0.98) (13). Shawn et al found women were 0.96 times less likely than men to be referred for spirometry (OR=0.96, 95%CI: 0.82-1.12) (14). Delgado et al found women were 0.43 times less likely than men to be referred for spirometry (OR=0.43, 95%CI: 0.23-0.81) (21) and Koefoed et al found women were 0.86 times

less likely than men to be referred for spirometry (OR=0.86, 95%CI:0.82-0.90) (27). Meta-analysis was possible for all four studies (13, 14, 21, 27).

2.4.4.3 Medication prescription patterns

Physician behavior on prescribing medications for men and women was explored by five studies. Rinne et al. reported that women were less likely than men to be prescribed short-acting beta agonists (SABA) (OR=0.83, 95%CI: 0.72-0.95), short acting muscarinic antagonists (SAMA) (OR=0.76, 95%CI: 0.67-0.86), long-acting beta agonists (LABA) (OR=0.87, 95%CI: 0.77-0.99) and long acting muscarinic antagonists (LAMA) (OR=0.74, 95%CI: 0.63-0.87) (28). However, there was no difference in inhaled corticosteroids (ICS) (OR=0.96, 95%CI: 0.85-1.09) and oral steroids (OR=1.01, 95%CI: 0.88-1.16) use between genders. Also, women received fewer "appropriate inhaler combinations" (OR=0.83, 95%CI: 0.74-0.93) and had more "inappropriate drug combinations" (OR=1.33, 95%CI: 1.17-1.51) compared to men (28). Watson et al. found no difference between genders in ICS use (OR=1.01, 95%CI: 0.84-1.21) (13). Sherman et al. reported that women were less likely to receive a prescription for nicotine patches or gum (OR=0.5, 95%CI: 0.3–0.9) (29). In a study by Carrasco-Garrido et al., men received a larger number of drugs for COPD than women, with a greater frequency of LABA (9.8% vs 7.9%, $p<0.05$), anticholinergic drugs (85.6% vs 82.4%, $p<0.05$) and theophyllines (13.2% vs 7.6%, $p<0.05$). However, no gender differences were recorded in the frequency of prescription of inhaled corticosteroids (22.1% vs 22.2%, $p>0.05$) and oral corticosteroids (4.4% vs 5.3%, $p>0.05$) (30).

Data from studies suggest that women may be less likely to receive some medical treatments. However, not enough studies have been done on each drug class, as different studies

reported prescription behaviour on different drug classes. We were able to quantitatively synthesize data on only one drug class (ICS) obtained from only 2 studies (13, 28).

2.4.4.4 Symptoms

Cough, dyspnoea, and sputum production are the major symptoms that patients with COPD complain of (31). As a secondary objective, we explored differences between men and women in their expression of COPD disease. Dyspnoea is the most significant symptom in COPD and the main determinant of quality of life, prognosis and disability in people with the disease (32). Almost all studies reported that women experience worse dyspnea than men. Two studies (13, 33) reported effect estimates as odds ratio, and were combined in a separate meta-analysis from those that reported dyspnoea scores (34-36). Data for cough and sputum production was mostly reported as frequencies, thus, it was not possible to summarize them quantitatively. One study, using odds ratio, reported that women were less likely to report sputum production (OR=0.84, 95%CI: 0.72-0.98) but were as likely as men to report cough (OR=1.08, 95%CI: 0.92-1.27) (13). Naberan et al. reported that sputum production was more frequent among men (73.3% vs 64.7%, $p<0.001$) but frequency of cough did not differ between genders (80% vs 77.6%, p=0.75) (37). Raherison et al. however found no significant differences between genders in frequency of cough (men, 75.6% vs women, 78.5% p=ns) or production of sputum (men, 62% vs women, 64.2% p=ns) (38). Available data on sputum production appeared inconsistent across studies. For instance, while two studies reported a higher frequency of sputum production in men than in women (13, 37), one study found no significant difference between genders (38). Available data however suggested that women may report cough with the same frequency as men (13, 37, 38).

2.4.4.5 Health-related Quality of life

Almost all studies found women to have lower health-related quality of life than men. Two studies (34, 39) however found no significant differences between men and women in health-related quality of life scores. Specifically, Roche et al found no significant difference between men and women in SGRQ health-related quality of life scores (median, IQR: m 43, 30-59 vs w 46, 32-60, p=0.35] (34) and Skumlien et al also found no significant difference in SGRQ health-related quality of life scores (mean±SD: 56.5±16 vs 58.7±14.1) (39). Nine out of 13 papers on health-related quality of life were quantitatively summarized (15, 34, 37, 39-42)

Insert (Table 2.1 to 2.4 here)

2.4.5 Results of Meta-analysis

Four studies were synthesized with the outcome "*physician-diagnosed COPD*". The forest plot below shows an inverse variance (IV) random effect model with pooled odds ratio of 2.09 and 95% confidence interval of 2.10 to 7.21 and p-value of 0.0001. This means that men are 2.09 times more likely to have a COPD diagnosis by their primary physicians as compared to women, even though both may have COPD based on spirometry criteria. This effect estimate is however compromised since substantial heterogeneity exists with I^2=61% and Chi^2=7.66, with df=3, p=0.05. We did not subgroup the four studies because of the small number of studies included.

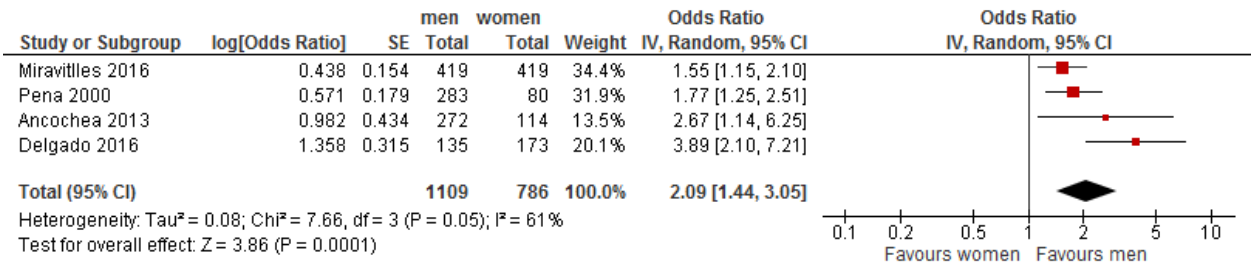

Figure 2.2 Forest Plot assessing whether men are more likely than women to be diagnosed with COPD

Four studies were synthesized with the outcome of "percent referral for spirometry." Results from the meta-analysis as shown in the forest plot in Figure 2.3 shows an overall summary effect odds ratio with 95% confidence interval as 0.86 (0.77,0.96). Hence women are significantly less likely to be referred for spirometry compared to men. The pooled effect estimate is acceptable since heterogeneity was moderate, I^2=54%.

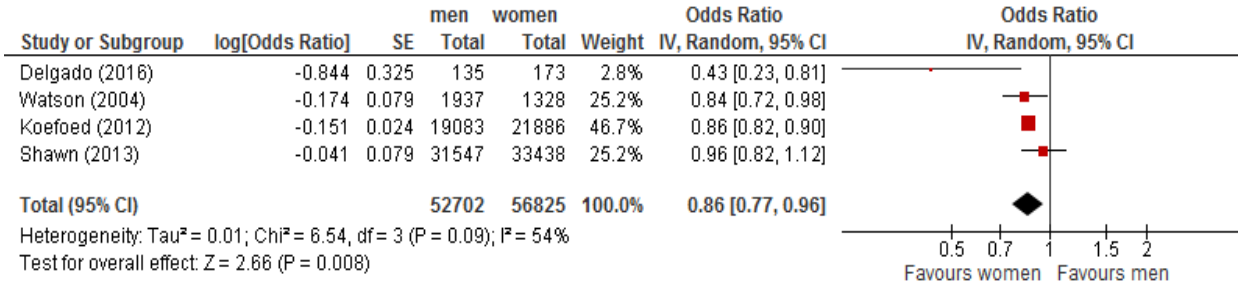

Figure 2.3 Forest Plot assessing whether women are less likely than men to be referred for spirometry

Two studies were synthesized with the outcome of prescription of ICS. The combined effect of 0.97(95%CI: 0.88-1.08) shows that although women were slightly less likely to be prescribed with ICS than men, the association was not statistically significant (Figure 2.4).

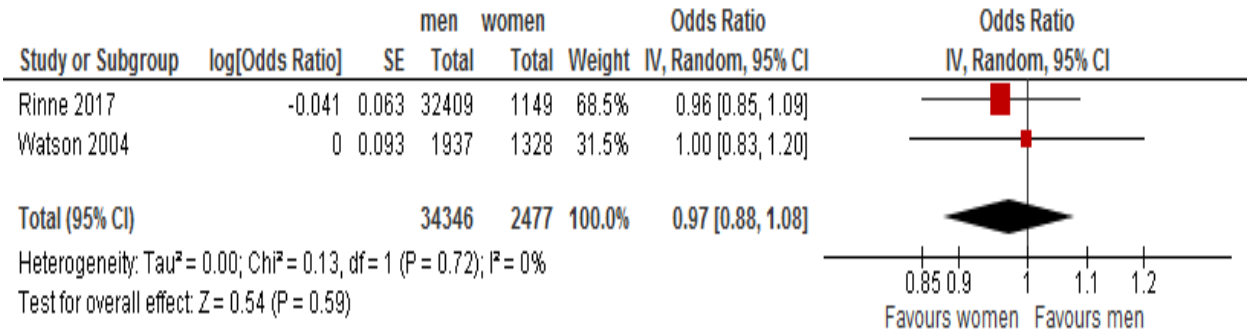

Figure 2.4 Forest Plot assessing whether women are less likely to be prescribed inhaled corticosteroids. (ICS)

Figures 2.5 and 2.6 indicate that women are significantly more likely to have worse dyspnoea than men. However, the small number of studies makes this inconclusive. The analyses presented in Figure 2.5 are those studies that reported only odds ratios (ORs) and that presented in Figure 2.6 are studies that reported mean difference (SMD).

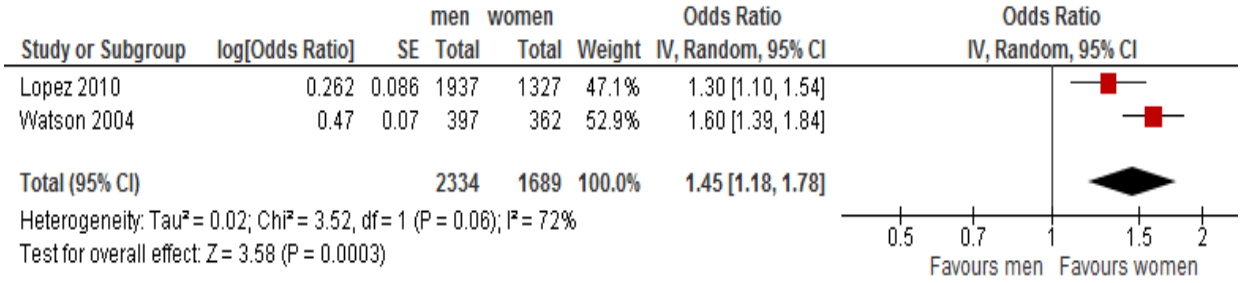

Figure 2.5 Forest Plot assessing whether women are more likely than men to have dyspnoea (dichotomous)

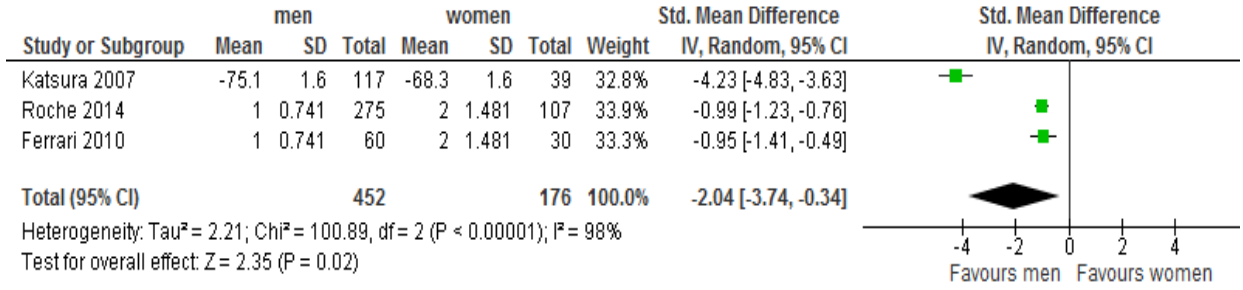

Figure 2.6 Forest Plot assessing whether women have worse dyspnoea than men (in terms of scores)

Nine of the studies measured health related quality of life (HRQOL) using SGRQ, ED-5Q, AQ2O and SF-12 scores. The pooled standard mean difference of -0.25 (95%CI: -0.34 to -0.17) indicates a lower score on health related quality of life, and the lower the score, the better the health-related quality of life. Thus, the pooled effect standardized mean difference of -0.25(p <0.00001) as shown in the forest plot in Figure 2.7 indicates that men had better health-related quality of life than women with COPD. However there exist substantial heterogeneity which suggest that the results are not similar from study to study (I^2=83%, p<0.00001).

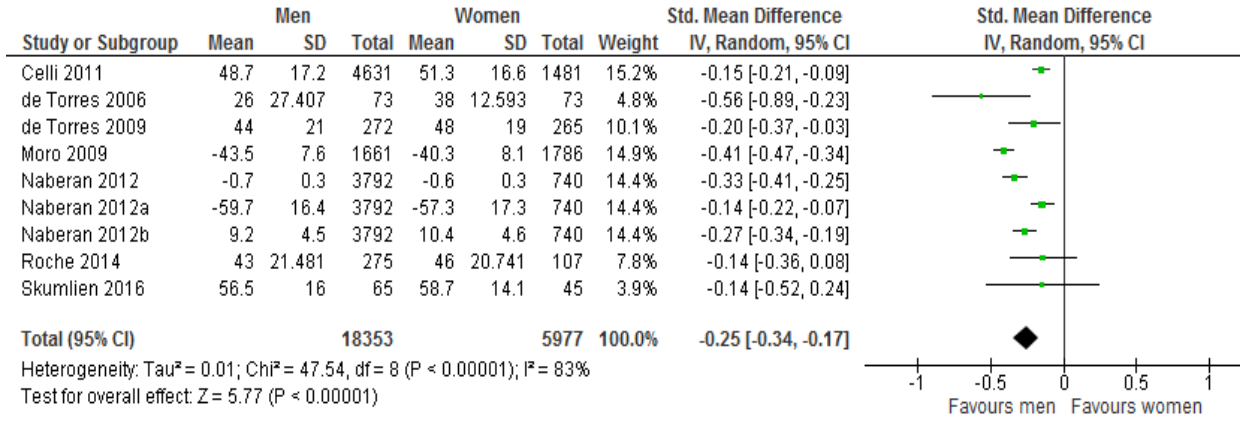

Figure 2.7 Forest Plot assessing whether women have worse health-related quality of life than men (in terms of scores)

2.4.5.1 Subgroup analysis of Health-related quality of life (HRQoL)

Heterogeneity can be explored based on clinical or methodological differences across studies, for example, differences in outcome assessments (20). Thus, to identify the source of heterogeneity among the included studies, studies which measured health-related quality of life with SGRQ were classified as one group, while the remaining studies with other health-related quality of life measures, namely ED-5Q, AQ2O and SF-12 were classified into another subgroup. The first subgroup recorded an I^2 of 32% with p-value of 0.21, meaning the observed combined effect is not significantly influenced by heterogeneity. The second subgroup recorded an I^2 of 88%, meaning the observed combined effect is significantly influenced by heterogeneity. The heterogeneity is likely due to the differences in the measured instruments/measures used with different domains.

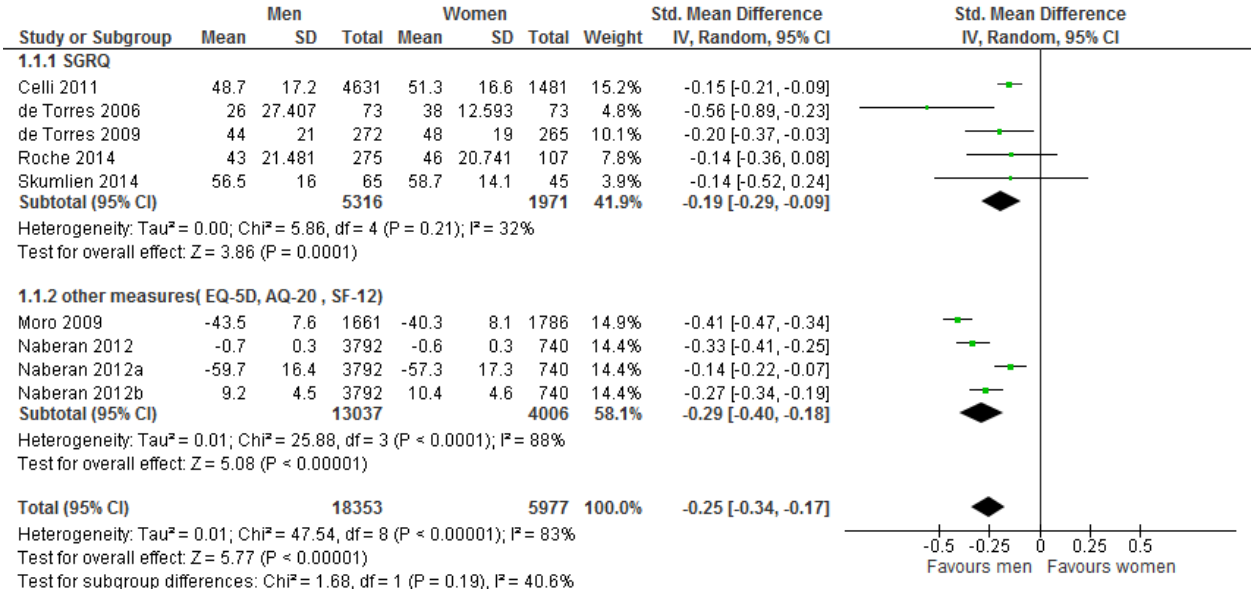

Figure 2.8 Forest Plot assessing whether women have worse health-related quality of life than men (subgroup analysis by different scales)

2.4.5.2 Publication bias

The visual assessment and detection of publication bias was performed using funnel plot. Publication bias check for forest plots in Figures 2.4, 2.5 and 2.6 were not performed due to the smaller number of the studies (3 or 2 studies) included at the synthesis stage.

By inspecting Figure 2.9, there seems to be some funnel plot asymmetry indicating a possible publication bias in the studies that assessed men as having a higher likelihood of COPD diagnosis than women. This means that it is possible that only studies with significant findings have been published for this outcome, while similar studies with non-significant results remain unpublished (43). Thus, a meta-analysis of those published studies may lead to an overestimation of the combined effect (43).

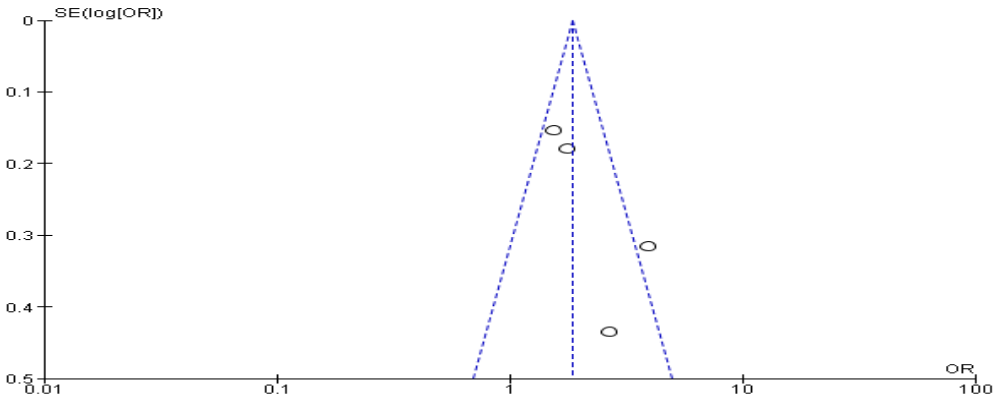

Figure 2.9 Publication bias check for studies assessing whether men are more likely than women to be diagnosed with COPD

Similarly, visual inspection of Figure 2.10 clearly demonstrates a possible publication bias among the 4 studies that measured referral rate for spirometry, implying a possible overestimation of the overall effect estimate for this outcome.

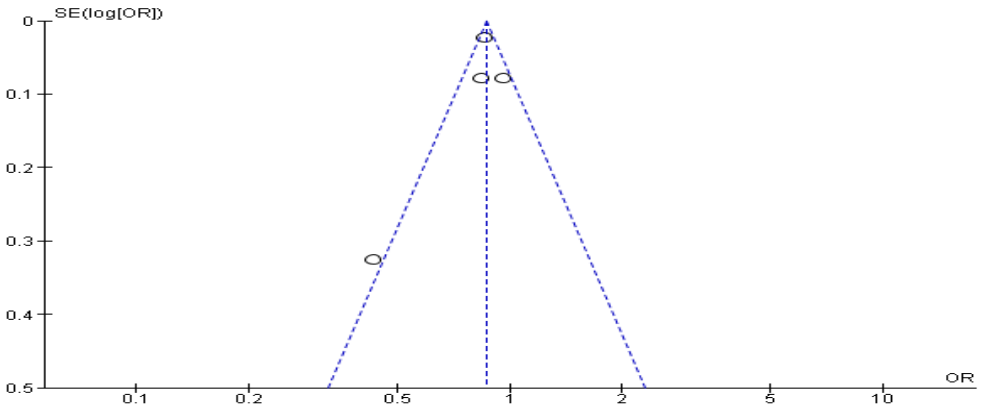

Figure 2.10 Publication bias check for studies assessing whether women are less likely than men to be referred for spirometry.

The funnel plot of studies that assessed patients' health-related quality of life seems to be symmetric indicating a low likelihood of publication bias in the studies selected for the synthesis **(**Figure 2.11). However, results from the Beggs (one tailed p-value for the Beggs and Mazumdar rank correlation test = 0.14857) and Eggers (one-tailed p-value = 0.40016) test confirm that there is no significant publication bias of this outcome (Table 2.7).

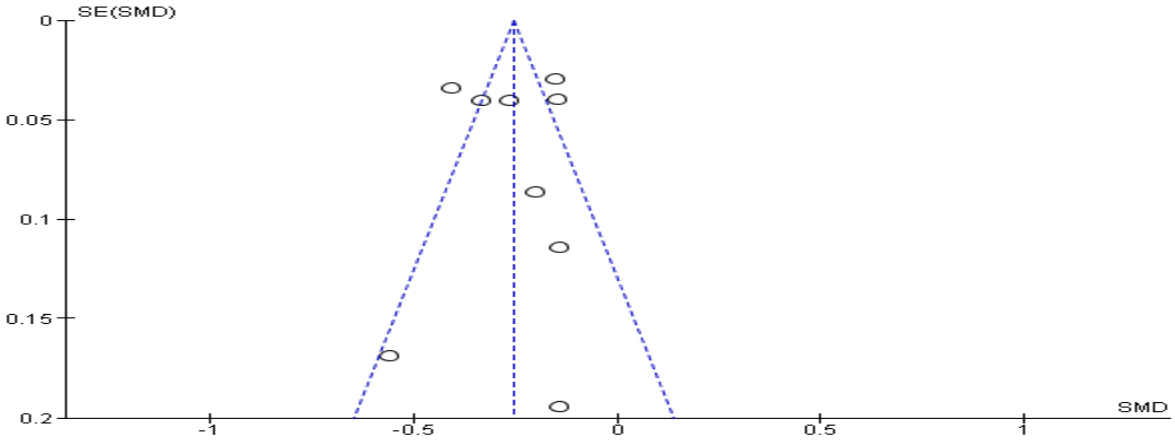

Figure 2.11 Publication bias check for studies assessing whether women have lower health-related quality of life than men (in terms of scores)

Insert (Table 2.7 here)

2.4.5.3 Sensitivity analysis

A sensitivity analysis was performed on the forest plot that assessed whether women were less likely to be referred for spirometry than men, to test the effect of the outlier on the results. By removing the study conducted by Delgado (2016) with a wider confidence interval, studies in the reduced forest plot were homogeneous with I^2=0%, p=0.38 with no significant heterogeneity (see appendix). Therefore, we may conclude that women are significantly less likely to be referred for spirometry than men (OR= 0.87, 95% CI: 0.83-0.90).

(See Appendix A).

2.5 Discussion

The findings from this review show a statistically significant association between male gender and a previous diagnosis of COPD and referral for spirometry. Female gender was associated with more dyspnea and lower health-related quality of life. There was no significant difference between men and women in the use of inhaled corticosteroids (ICS).

COPD has been perceived as a typical disease of an elderly man, plagued by cough and breathlessness after many years of cigarette smoking (3). Some epidemiological studies have reported growing prevalence of COPD in women (5, 6, 23). Our findings suggest that COPD underdiagnoses may be high in women, with men being about two times more likely to be diagnosed with the condition after adjusting for potential confounders. However, due to considerable heterogeneity among studies (I^2>60%), this finding remains inconclusive. The exact reasons for a possible biased diagnosis remain unclear. One of the underlying reasons may be the inaccurate, outdated perception of COPD being a male-dominated disease, still affecting clinical decision making. Also, there could be lack of awareness of symptoms amongst women (10).

Additionally, women often feel embarrassed by symptoms such as cough and sputum production, due to the stigma associated with them (popularly called the smoker's cough), and may not report it, resulting in delayed diagnosis or mis-diagnosis (10).

Even though spirometry forms an integral part of COPD diagnosis, this tool remains underutilized among primary care physicians. Studies have shown that a large proportion of patients diagnosed with COPD have no history of spirometry testing and only one-third of COPD patients undergo spirometry before their first prescription (44). Our findings further suggest that women are less likely to be referred for spirometry. Interestingly, a flawed diagnostic process may affect the health outcomes of COPD patients. Previous narrative reviews have reported that women experience worse COPD symptoms than men (45, 46). Results of this study show that women with COPD have a lower health-related quality of life, after adjusting for age, degree of airflow obstruction, pack-years of smoking, FEV_1 and dyspnoea severity. Most studies in the review found women to be more dyspnoeic than men. Nonetheless, we could not obtain a credible pooled estimate due to low number of studies represented at the meta-analysis level. Also, individual studies highlighted possible gender disparities in medication prescription patterns. However, not enough studies have been done on each drug class and the two studies done on ICS use obtained a pooled effect that was not significant between genders.

Our study findings are in agreement with five narrative reviews that have reported that:

1. There is COPD diagnosis bias in favor of men (10, 45-47).

2. Spirometry is mandatory to confirm a COPD diagnosis, but it is underused in women (10, 45).

3. Women may experience a higher level of shortness of breath than men (10, 45-48).

4. Women with COPD experience a more impaired health-related quality of life than men (10, 46-48).

2.5.1 Study strengths

We adhered to a strict priori inclusion and exclusion criteria for studies. Outcomes were chosen a priori, and studies that did not report the outcomes of interest were excluded. We abided strictly by standard procedures of conducting systematic reviews and meta-analysis, using the Cochrane approach, PRISMA and MOOSE checklists, and as such any differences will be attributed to chance or random error. Included studies were rigorously evaluated using the USPSTF quality rating criteria assessment of bias tool. Most studies chosen were cross-sectional in nature, which is an appropriate design to answer questions of this nature, to prove or disprove assumptions and create new theories for further studies.

2.5.2 Study limitations

All 4 studies that assessed "physician-diagnosed COPD" at the meta-analysis level were conducted in Spain and may only represent primary physician behaviour in Spain, but not in other countries or jurisdictions. Self-report of "physician-diagnosed COPD" may have introduced recall bias. Validated vignette questionnaires may not represent physician behaviour in real practice. Most of the studies used in the review were cross-sectional in design, and as with any cross-sectional association, it is not possible to determine a cause and effect relationship. Most studies presented effect measures as frequencies and percentages and this made meta-analysis and hence credible conclusions on some outcomes, impossible. Studies of fair quality may have introduced bias that may compromise findings of this study. Lastly, publication bias

due to possible existence of unpublished studies with non-significant results may also overestimate findings of this review.

2.6 Conclusion

Our evidence suggests that primary care physicians may be less likely to suspect COPD when confronted by women with respiratory symptoms, than when confronted by men, and therefore less likely to refer them for spirometry. However, more studies need to be completed before concrete conclusions can be drawn. Women with diagnosis of COPD were found to have a lower health-related quality of life than men.

2.6.1 Implications for further research and practice

Studies on gender bias in the diagnosis of COPD should be updated and conducted across countries in a standardized fashion to see if the trend exists worldwide.

2.6.2 Acknowledgements

We thank Michelle Swab, a librarian at the Health Science Library of Memorial University of Newfoundland, who assisted in the comprehensive literature search.

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Summary of findings tables

Table 2.1 Summary of findings for diagnostic outcomes (physician-diagnosed COPD/referral for spirometry)

Article	Study type/design	Country/ patient population	No. of men	No. of women	Outcomes assessed	Results	Adjusted variables
Ancochea et al (2013)	Cross-sectional	Spain: A total of 4274 subjects were randomly chosen by telephone in 11 centres with mean age of 56.6.	272 men were found to have COPD based on spirometry criteria	114 Women with COPD based on spirometry criteria	Prevalence of COPD Physician-diagnosed COPD, underdiagnoses, symptoms such as cough, sputum, dyspnea and wheezing.	Men were more likely to be previously diagnosed with COPD (RR=2.67, 1.14-6.26)	Age, smoking, education level, mMRC dyspnea, COPD severity.
Delgado et al (2016)	Cross-sectional	Spain: 457 family physicians were interviewed on primary care for COPD using validated vignette questionnaires.	A case scenario of 135 men with COPD; Number of male physicians was 264	A case scenario of 173 women COPD; Number of female physicians was 193	COPD as the most likely diagnosis, ordering of spirometry, referral to specialist, considering tobacco as major risk factor.	Men were more likely to be diagnosed with COPD. (3.89, 2.097-7.214) Men were more likely to be referred for spirometry (OR: 2.323, 1.229-4.392).	Adjusted for age of physician, gender of physician, postgraduate training.
Miravitlles et al (2006)	Cross-sectional	Spain: 838 family physicians were surveyed on diagnostic attitudes towards COPD using validated vignette questionnaires	A case scenario of 419 male patients with COPD; Number of male family physicians were 419	A case scenario of 419 female patients with COPD; Number of female family physicians were 419	COPD as the most likely diagnosis	Men were more likely to be diagnosed with COPD(OR=1.55, 1.15-2.1)	Adjusted for age of physician, gender of physician, disease severity

Pena et al (2000)	Cross-sectional	Spain: A total of 5827 participants were randomly contact via telephone.	283men were found to have COPD based on spirometry criteria	80 women with COPD based on spirometry criteria	Prevalence of COPD prior physician diagnosis of COPD	Men were more likely to be previously diagnosed with COPD (OR=1.77, 1.24-2.5)	Age, educational level, smoking history, comorbidities.
Watson et al (2004).	Cross-sectional study	United Kingdom: 3265 subjects with Physician diagnosis of COPD, emphysema or chronic bronchitis were interviewed. All patients were aged 45 years and older.	Out of the total subjects, 1937 men were interviewed	Total number of women with COPD were 1328.	Management of COPD including ever had spirometry test, ever had smoking advice, hospitalization, ED visit, ICS use, ever had inhaler training.	Women were less likely to have had spirometry (OR: 0.84, 95% CI: 0.72-0.98).	Adjusted for age, pack-years of smoking, country and dyspnea severity.
Shawn et al (2013)	Retrospective cohort study	U.S.A: 64985 medicare beneficiary population who were newly diagnosed with COPD between 1999 to 2008	31547 men with copd diagnosis	33438 women with copd diagnosis	Spirometry performed within 365 days of the first claim with a COPD diagnosis.	Women were less likely than men to have used spirometry (OR:0.96,95% CI 0.95-1.03)	Age, sex, race, comorbidity
Koefoed et al (2012)	Retrospective cohort study	Denmark: 40,969 patients were identified through national registers from 2007 to 2010.	19,083 men with obstructive lung disease	21,886 women with obstructive lung disease.	Spirometry use	Women were less likely to have had spirometry(OR: 0.86; 95% CI 0.82-0.9)	Age, number of pulmonary medications received
Roberts et al (2015).	Cross-sectional study	United Kingdom: A total number of 445 participants with a provisional diagnosis of suspected COPD or definite COPD by a GP were referred to a community Respiratory unit.	Overall, 81 men had a correct diagnosis of COPD participated	Overall, 57 females had a correct diagnosis of COPD participated.	Differences and role of spirometry in COPD patients.	More men (87.5%) were significantly more likely to have their GP COPD diagnosis confirmed as compared to 73.9% of females (p=0.021).	Age, sex

Chapman et al (2001)	Cross-sectional study	Canada: A random sample of 192 primary-care physicians (96 Americans and 96 Canadians) were surveyed.	Out of the 192 primary care physicians surveyed, 154 were men	54 out of the total 192 primary care physicians were women.	Diagnosis of COPD	57% of the physicians offered COPD as the most likely diagnosis. More men (58%) were more likely to be diagnosed with COPD than women (42%) with $p<0.05$.	
Martinez et al (2012)	Cross-sectional study	USA: The study analysed data on 295 females and 273 male participants with COPD.	273 men with COPD	295 females with COPD	Symptoms, care delivery of COPD	Women were more likely to report COPD diagnostic delay with adj OR 1.66 with 95% CI: 1.13-2.45, p=0.01. Other significant predictors were anxiety and history of exacerbations. Females were more likely to have difficulty in reaching their physicians. (OR 2.54, 1.33-4.86).	Adjusted for depression, use of oxygen,

Table 2.2 Summary of findings for cardinal COPD symptoms (Dyspnea, cough, and sputum production)

Article	Study type/design	Country/ patient population	No. of men	No. of women	Outcomes assessed	Results	Adjusted variables
Katsura et al (2007)	Cross-sectional	Japan: 156 patients with copd at a teaching hospital	117 men with COPD matched to women by age and FEV1 in a ratio of 3:1	39 women with COPD	dyspnea , health related quality of life, anxiety and depression	Women had greater dyspnoea (=lower OCD dyspnea scores) than men(m75.1±1.6 vs w68.3±1.6)p<0.05	Age, degree of airflow obstruction
Watson et al (2004).	Cross-sectional study	USA: 3265 subjects with Physician diagnosis of COPD, emphysema or chronic bronchitis were interviewed. All patients were aged 45 years and older.	Out of the total subjects, 1937 men were interviewed	Total number of women with COPD was 1328.	Dyspnea, sputum, cough, hospitalization, emergency room visits , ever had spirometry test, ever had smoking advice, ICS use	Women were significantly more likely to report dyspnea than men (OR: 1.30, 1.10-1.54). Women were less likely to report sputum production(OR:0.84,0.72-0.98) Women were as likely as men to report cough(OR: 1.08, 0.92-1.27)	Adjusted for age, pack-years of smoking, country and dyspnea severity.
De Torres et al (2005)	Matched Case-series study	Spain: 140 COPD patients attending a pulmonary clinic	53 men with COPD were matched for FEV1.	53 women with COPD matched with men with same FEV1 ±2%	Dyspnea, quality of life, exacerbations in the last year	Women reported higher degree of mMRC dyspnoea (28% vs 6%, p=0.05)	FEV1

Lopez et al (2010)	Cross-sectional study	Uruguay: Total subjects eligible for the study were 6711. Out of this 5314 completed questionnaire and spirometry test and 759 were identified as COPD patients.	Out of the 759 COPD patients 397 were males.	And 362 were females.	Health status perception, dyspnoea, physical activity.	Female sex was found to be explaining dyspnoea (OR: 1.60, 1.40-1.84) and SF-12 physical score (OR -1.13, 95% CI -1.56- -0.71).	Age
Marco et al (2006)	Case-control	Italy: A total number of 202 patients attending pulmonary clinic were compared to non-patients on prevalence of symptoms were enrolled in the study.	Male patients were 155.	Female patients were 47.	Anxiety and depression in COPD patients compared to controls. Secondary outcomes include symptoms, Quality of life (QoL) in men and women with COPD	Female patients had higher levels of dyspnea than men.	Age
Naberan et al (2012)	Cross-sectional	Spain: 4574 patients attending primary care and pulmonary clinics. Aged 40 years and older	3792 males with COPD diagnosis	740 females with COPD diagnosis	Quality of life, anxiety, depression, dyspnoea, sputum production, cough, exacerbations, emergency room visits	Dyspnea was more frequent among females than males (60.1% vs 55.1%, p=0.01) while sputum production was more frequent among men. (73.3% vs 64.7%, p<0.001). Frequency of cough did not differ btw gender. (80. % vs 77.6%, p=0.75).	Age, FEV1
Ferrari et al 2010	Cross-sectional	Brazil: 115 consecutive COPD patients treated at the outpatient clinic of a single institution.	60 men were matched to the women in 2:1 ratio	30 women were matched to the women	Dyspnoea, quality of life, BODE index, determinants of qol	Women had greater dyspnea (=higher mmrc dyspnea scores) than men. Median,IQR 1(1-2) vs 2(1-3), p=0.05	FEV1

Roche et al 2014	Cross-sectional	France: 688 COPD patients used for the analysis were recruited in an ongoing BPCO cohort study, from 17 pulmonary units of university hospitals located throughout France.	275 men with COPD were matched to 107 women by age and FEV1.(1:3)	107 women with COPD were matched to 275 men with COPD by age and FEV1.	Dyspnea, quality of life, BOD index	Women had greater dyspnea (=higher mmrc dyspnea scores) than men. Median, IQR 1(1-2) vs 2(1-3), p=0.05	Age, FEV1
Raherison et al 2014	Cross- sectional	France: 146 physicians were made to recruit 446 patients as they visited the clinics.	183 men with COPD	247 women with COPD	Quality of life, prevalence of cough, sputum production	Frequency of cough (men, 75.6% vs women, 78.5% p=NS) and sputum production (men 62% vs 64.2% p=NS), did not differ significantly between genders.	Age, FEV1

Table 2.3 Summary of findings for health-related quality of life

Article	Study type/design	Country/ patient population	No. of men	No. of women	Outcomes assessed	Results	Adjusted variables
Katsura et al (2007)	Cross-sectional	Japan: 156 patients with copd at a teaching hospital	117 men with COPD matched to women by age and FEV1 in a ratio of 3:1	39 women with COPD	dyspnea , health related quality of life, anxiety and depression	More women had poorer quality of life than men (= higher SGRQ quality of life scores) (40% vs 30%) p<0.001 More women than men had lower scores (=poorer qol) for all domains of SF-36 quality of life questionnaire.	Age, degree of airflow obstruction
De Torres et al (2005)	Matched Case-series study	Spain: 140 COPD patients attending a pulmonary clinic	53 men with COPD were matched for FEV1.	53 women with COPD matched with men with same FEV1 ±2%	Dyspnea, quality of life, exacerbations in the last year	Women had worse SGRG quality of life than men(44% vs 34%; p=0.08)	FEV1
Lopez et al (2010)	Cross-sectional study	Uruguay: Total subjects eligible for the study were 6711. Out of this 5314 completed questionnaire and spirometry test and 759 were identified as COPD patients.	Out of the 759 COPD patients 397 were males.	And 362 were females.	Health status perception, dyspnoea, physical activity.	Female sex was found to be explaining SF-12 physical quality of life score (OR: 1.13, 95% CI -1.56- -0.71). More females reported their health status as fair-to-poor.	Age, FEV1
Skumlien (2014)	Cross-sectional study	Norway: 110 COPD patients admitted for	Total of 65 men with COPD	45 women with COPD	Health related quality of life of COPD patients.	No significant difference in SGRQ qol scores.	Age, degree of airflow obstruction

		pulmonary rehabilitation.				(mean, SD: 56.5±16 vs 58.7±14.1)	
Marco et al (2006)	Case-control	Italy: A total number of 202 patients attending pulmonary clinic were compared to non-patients on prevalence of symptoms were enrolled in the study.	Male patients were 155.	Female patients were 47.	Anxiety and depression in COPD patients compared to controls. Secondary outcome include symptoms, Quality of life (QoL) in men and women with COPD	Higher levels of anxiety and depression was attributed to female patients and females recorded worse symptom-related QoL compared with men.	FEV1
Naberan et al (2012)	Cross-sectional	Spain: 4574 patients attending primary care and pulmonary clinics. Aged 40 years and older	3792 males with COPD diagnosis	740 females with COPD diagnosis	Quality of life, anxiety, depression, dyspnoea, sputum production, cough, exacerbations, emergency room visits	Qol was assessed using 3scales; Women showed poorer quality of life than men (=had lower EQ-5D index scores) mean,sd: (w0.6±0.3 vs m0.7±0.3; p<0.001). Women also had lower scores for EQ-5D VAS scale mean, sd: (57.3,17.3 vs 59.7,16.4) p<0.001 Women also had poorer qol using the AQ20 quality of life questionnaire (higher scores= poorer qol. Mean, sd (w10.4 ±4.6 vs m9.2±4.5, p<0.001)	FEV1
De Torres et al (2009)	Retrospective cohort	Spain: 1384 patients with COPD recruited from several clinics.	272 men with COPD matched to 265 women by region and COPD severity.	265 women with COPD matched to 272 men by region and COPD severity.	Mortality, quality of life.	Women had worse quality of life than men(= higher SGRQ qol scores)	age

						mean ± SD: w48±19 vs m44±21)	
Low et al (2006)	Cross-sectional	Canada: 67 married community-dwelling older adults with COPD.	43 men with COPD	24 women with COPD	Quality of life	Women had worse SIP Psychosocial HRQOL scores (13.3±13 vs 10.5±12.2) p=0.02	
De Torres et al (2006)	Matched case-series	Spain: 146 patients with COPD from a pulmonary clinic	73 men with COPD matched with 73 women with similar degree of airflow obstruction	73 women with COPD matched with 73 men with similar degree of airflow obstruction	Quality of life Determinants of quality of life.	Women had lower quality of life than men (=higher SGRQ scores) (median, IQR- w38 (30–47) vs m26 (15–52), p = 0.01	FEV1
Moro et al (2009)	Cross-sectional	Spain: Total of 9405 patients recruited by general practitioners and pneumologists.	1661 men matched with women by age and COPD severity	1786 women with COPD matched with men by age and COPD severity	Quality of life	Women had lower qol than men(=lower SF-12 quality of life scores: Mean ±SD: w40.3±8.1 vs m43.5±7.6); p<0.0001	`Age
Celli et al (2011)	Cross-sectional	USA: total of 1,481 women and 4,631 men with COPD were enrolled in TORCH study	4631 men with COPD	1481 women with COPD	All-cause mortality Quality of life dyspnea	Women had lower quality of life than men(= higher SGRQ qol scores) mean±SD: m48.7 ±17.2 vs w 51.3 ±16.6)	FEV1
Roche et al 2014	Cross-sectional	France: 688 COPD patients used for the analysis were recruited in an ongoing BPCO cohort study, from 17 pulmonary units of university hospitals located throughout France.	275 men with COPD were matched to 107 women by age and FEV1.(1:3)	107 women with COPD were matched to 275 men with COPD by age and FEV1.	Dyspnea, quality of life, BOD index	No significant difference between men and women in sgrq qol scores. Median, IQR: (m 43,30-59 vs w 46 ,32-60) p=0.35	Age, FEV1

Raherison et al 2014	Cross- sectional	France: 146 physicians were made to recruit 446 patients as they visited the clinics.	183 men with COPD	247 women with COPD	Quality of life, factors associated with health-related quality of life.	Quality of life was more impaired in women than in men (=higher SGRQ scores for women) mean±SD: 50.6 vs 45.4 , p=0.019	FEV1

Table 2.4 Summary of findings for medication prescription patterns

Article	Study type/design	Country/ patient population	No. of men	No. of women	Outcomes assessed	Results	Adjusted variables
Rinne et al (2017)	Cross-sectional study (retrospective observational study)	USA: 33,558 unique veterans with COPD admitted to 130 VA facilities were identified.+	32,409 men with COPD were identified.	1149 women with COPD were identified.	Primary outcome was prescriptions for baseline COPD medications. Secondary outcomes include severity of disease including LOS.	Women were less likely than men to be prescribed with short-acting beta agonists (SABA) [OR, 95%CI 0.83(0.72-0.95)] , SAMA(0.76(0.67-0.86), LABA(0.87(0.77-0.99), and LAMA(0.74(0.63-0.87).No difference in ICS(0.96(0.85-1.09) and oral steroids(1.01(0.88-1.16) Women received fewer appropriate inhaler combinations with OR 0.83 and 95% CI: (0.74-0.93) and also women had more inappropriate drug combinations compared to men.	Baseline characteristics such as age, race, health insurance, number of home ZIP codes in the year prior to hospitalization, and discharge against medical device were controlled for.

						Similar rates of inhaled steroids were prescribed for both men and women. Hospital outcomes were similar.	
Watson et al (2004).	Cross-sectional study	USA: 3265 subjects with Physician diagnosis of COPD, emphysema or chronic bronchitis were interviewed. All patients were aged 45 years and older.	Out of the total subjects, 1937 men were interviewed	Total number of women with COPD was 1328.	ICS use, Dyspnea, sputum, cough, hospitalization, emergency room visits , ever had spirometry test, ever had smoking advice	No difference between gender in ICS use OR,95% CI : 1.01 (0.84,1.21)	Adjusted for age, pack-years of smoking, country and dyspnea severity.
Cydulka et al (2005)	Prospective cohort study	USA & Canada: 579 patients with exacerbation of asthma and or COPD were enrolled. Total of 397 patients with physician-diagnosed COPD were used. One cohort comprises 224 patients with COPD. 173 patients were having mixed COPD and asthma. Had average age of 68 years.	191 men with diagnosis of COPD	206 Women with diagnosis of COPD	ED visits with exacerbation of COPD	Women used inhaled corticosteroids with same frequency as men (ICS) (%) 47% vs 51% p=0.44 More men were on anticholinergics (69% vs 59%) p=0.04	age, pack-years
Sherman et al (2005)	Cross-sectional	USA: 1941 smokers with COPD with at least 3 with at least 3 primary care visits to the hospital	1812 males smokers with COPD	129 female smokers with COPD	Prescription for nicotine patches Advice for smoking cessation	Females were less likely to receive a prescription for nicotine patches or gums (OR 0.5, 95% CI 0.3–0.9).	Age
Carrasco-Garrido et al (2009)	observational and descriptive	Spain: COPD patients were recruited from health	8097 men with COPD	2613 women with COPD	COPD treatment, quality of life.	Men received a larger number of drugs for COPD than women.	packyears

	epidemiological study	centres and medical records and through physicians.		significantly greater among males was the percentage use of long-acting b2-adrenergic agonists (9.8% vs7.9% in females, $p < 0.05$), anticholinergic drugs (85.6%vs 82.4%, $p < 0.05$), theophyllines (13.2% vs 7.6%, $p < 0.05$) and mucolytic agents (9.3% vs 7.7%, $p < 0.05$). no gender differences were recorded in the frequency of prescription of inhaled corticosteroids – (22.1% in males vs 22.2% in females) and oral corticosteroids (4.4% vs 5.3%).

Assessment of bias Tables

Table 2.5 Assessment of bias of articles using USPSTF Quality criteria for Cohort studies

Article	Assembly of comparable groups	Maintenance of comparable groups	No important differential loss to follow-up or overall high loss to follow-up	Measurements: equal reliable, valid (includes masking of outcome assessment)	Clear definition of intervention	All-important outcomes considered	Analysis: Adjustment for potential confounders	Overall assessed quality
Shawn et al(2013)-retrospective cohort	good	good	fair	good	good	good	good	**Good**
Koefoed et al (2012)-retrospective cohort	good	good	fair	good	good	good	good	**Good**
De Torres (2009)-retrospective cohort	good	good	fair	poor	good	good	good	**Fair**
Cydulka et al (2005)	good	unclear	poor	fair	fair	good	good	**Fair**
Roche et al (2014) retrospective cohort	good	good	good	fair	good	fair	good	**Good**

Table 2.6 Assessment of bias of articles using USPSTF Quality criteria for Case-control and Cross-sectional studies

Article	Accurate ascertainment of cases	Non-biased selection of cases/controls with exclusion and inclusion applied to both	Response Rate	Diagnostic testing procedures applied equally to each group	Measurement of exposure accurate and applied equally to each group	Appropriate attention to potential confounding variable	Overall assessed quality
Ancochea et al	good	good	good	good	fair	good	**Good**

(2013) – cross-sectional							
Delgado et al(2016)- cross-sectional	good	fair	good	good	fair	good	**Good**
Miravitlles et al(2006) - cross-sectional	fair	fair	good	good	fair	good	**Fair**
Pena et al(2000)- cross-sectional	good	good	good	unclear	fair	good	**Good**
Watson et al (2004)- cross-sectional	fair	unclear	good	fair	fair	good	**Fair**
Roberts et al (2015)- cross-sectional	good	unclear	fair	good	fair	good	**Fair**
Chapman et al (2001)- cross-sectional	unclear	unclear	fair	good	fair	poor	**Poor**
Martinez et al (2012)- cross-sectional	fair	unclear	good	fair	good	good	**Fair**
Katsura et al (2007) - cross-sectional	good	fair	good	fair	fair	good	**Fair**
De Torres et al (2005)- case series	good	good	good	good	fair	fair	**Good**
Lopez et al (2010) - cross-sectional	fair	unclear	good	fair	good	good	**Good**
Skumlien (2014) - cross-sectional	good	fair	fair	fair	fair	good	**Fair**
Marco et al (2006) – case-control	fair	fair	fair	unclear	fair	good	**Fair**
Naberan et al (2012) - cross-sectional	good	good	good	unclear	fair	good	**Good**
Low & Gutman (2006)- cross-sectional	good	good	good	good	fair	good	**Good**

De Torres et al (2006)- case-series	good	good	good	unclear	fair	good	**Fair**
Moro et al (2009)- cross-sectional	good	good	good	good	fair	unclear	**Good**
Celli et al (2011)- cross-sectional	good	fair	good	unclear	fair	unclear	**Fair**
Rinne et al (2017)-Cross-sectional study	good	good	fair	good	good	good	**Good**
Sherman et al (2005) – cross-sectional	good	good	good	unclear	fair	unclear	**Fair**
Rahison et al 2014 - cross-sectional	good	good	good	fair	fair	fair	**Fair**
Ferrari et al 2010 - cross-sectional	good	good	fair	good	fair	good	**Good**
Carrasco-Garrido et al (2009)- cross-sectional	good	good	good	fair	fair	unclear	**Fair**

Table 2.7 Test for funnel plot asymmetry

Egger's regression	
Intercept	-1.08486
Standard error	4.12907
95% lower limit (2-tailed)	-10.84857
95% upper limit (2-tailed)	8.67884
t-value	0.26274
df	7.00000
P-value (1-tailed)	0.40016
P-value (2-tailed)	0.80032

Begg and Mazumdar rank correlation	
Kendall's S statistics (P-Q)	-10.00000
Kendall's tau without continuity correction	

Tau	-0.27778
z-value for tau	1.04257
P-value (1 tailed)	0.14857
P-value (2-tailed)	0.29715
Kendall's tau with continuity correction	
Tau	-0.25000
z-value for tau	0.93831
P-value (1 tailed)	0.17404
P-value (2-tailed)	0.34808

CHAPTER THREE

Research Study #2: Examining Gender Differences in the Diagnosis of Obstructive Airway Diseases in Patients with Shortness of Breath with Prescription for Inhaler Medications

A version of this chapter will be submitted to the *Journal of COPD*

3.1 Abstract

Background: There is evidence from across Europe that gender differences exist in the diagnosis of COPD. Available data suggests that women with COPD may be less likely to receive a doctor's diagnosis of the disease. We sought to investigate any potential gender disparities in the diagnosis of COPD and asthma from family practice physicians, using data collected in the Epidemiology of Shortness of Breath (EpiSOB) study conducted in Alberta and Saskatchewan, Canada. As a secondary objective, we explored differences in medication prescription patterns, symptoms and health-related quality of life of men and women with COPD or asthma.

Methods: The population was 328 patients with shortness of breath. Standard diagnosis of COPD, asthma and other respiratory conditions was made by expert pulmonologists at the time of the study using guidelines-approved methods (ATS/ERS criteria) of diagnosis. Data on physician-diagnosed COPD or asthma, referral for spirometry and other diagnostic outcomes were obtained from participants through structured questionnaires. Medical records were assessed for medication prescription patterns of physicians.

Analysis: Diagnostic outcomes, symptoms and medication prescription patterns of men and women were compared using descriptive statistics. Multivariate logistic regression was used to assess the effect of sex on physician-diagnosed COPD or asthma, misdiagnosis, referral to see a specialist, referral for spirometry, referral for chest x-ray and referral for methacholine tests while controlling for additional patient factors.

Results: Out of the 328 patients with shortness of breath, 97 patients were identified with COPD and 149 with asthma by expert pulmonologists at the time of the study, mainly using

spirometry. After accounting for confounders, no significant difference was observed between genders for all diagnostic outcomes in patients with spirometrically-defined COPD. However, in patients with spirometrically-defined asthma, women were significantly less likely than men to have a physician-diagnosed asthma (OR=0.535, 95%CI: 0.295-0.969, p=0.039) and less likely to be referred for spirometry (OR=0.446, 95%CI: 0.200-0.994, p=0.048), but more likely than men to be referred for chest x-rays (OR=2.062, 95%CI: 1.030-4.128, p=0.041).

Conclusion: This study did not provide support for the existence of gender disparities in the diagnosis of COPD. However, we found some evidence of gender inequalities in primary care for asthma in this study. More studies with larger sample size are required to draw concrete conclusions.

Keywords: gender differences, family physicians, primary care, gender disparities, gender bias, COPD, asthma.

3.2 Introduction

The medical profession strives for equal treatment for all patients. Nonetheless, disparities in health care are prevalent (1). “Cultural stereotypes may not be consciously endorsed, but their mere existence influences how information about an individual is processed and leads to unintended biases in decision-making, so called ‘implicit bias’”- *Elizabeth N. Chapman* (1). Physician behavior and practices may be unconsciously shaped by experience, prejudice or intuition, leading to differences in medical treatments and to healthcare disparities (1). Disparities in health services utilization may impact health outcomes of patients.

There is increasing evidence to support gender bias in the diagnosis of COPD. Being stereotyped as a disease of men for many years, the notion that a woman with respiratory symptoms is less likely to have COPD has lingered over time. Particularly, women have more often reported a delay in COPD diagnosis and have been less likely to receive a correct diagnosis for COPD as compared to men (2-7). A systematic review conducted by our research group found that the odds of having a previous doctor diagnosis in people who meet spirometry criteria for COPD was 2.09 (95%CI: 1.44–3.05) for men versus women, after controlling for potential confounders (8). This finding may however only represent Spanish physician behavior, as all the four studies included in the meta-analysis were from Spain. Physician diagnosis and treatment patterns for men and women in Canada are yet to be ascertained.

Women have been reported to be less likely to be prescribed some classes of COPD medications and have also been reported to have lower health-related quality of life and more dyspnea than men (7, 9-12). Though little is known about a bias in asthma diagnosis, this condition has often been the next most likely differential diagnosis for COPD (13-15). It is

possible that some women diagnosed by family physicians as having asthma may meet the spirometry criteria for COPD or other obstructive airway diseases instead (5, 16) . The analysis presented in this study examined physician diagnostic behavior for patients with shortness of breath who meet spirometry criteria for COPD or asthma. As a secondary objective, we explored medication prescription patterns, symptoms and health-related quality of life of men and women who meet guideline criteria for COPD or asthma.

3.3 Methods

3.3.1 Study design and participants

This study is a cross-sectional secondary analysis of primary data from the Epidemiology of Shortness of Breath (EpiSOB) study conducted between 2009 and 2013.The methods and materials for the EpiSOB research program have been described in full details elsewhere (17). In brief, the baseline sample of the EpiSOB program was a cross-sectional survey of community patients who had been prescribed an inhaler medication for relief of shortness of breath symptoms, by their family physicians. The primary aim of the study was to determine the disease status of community patients with shortness of breath, using guidelines-approved methods of diagnosis, and then compare the research finding to the diagnosis given to them by their primary-care physicians.

Community pharmacists recruited all patients with inhaler prescriptions. Eligible respondents were enrolled after obtaining informed consent. Subjects were eligible if they were 18 years and older. Another inclusion criteria was if subjects had an active or recent prescription (within the past six months) for any one of the following class of medications: short-acting beta-2-agonist (SABA), short-acting anticholinergic (SAAC), long-acting beta-2-agonist (LABA),

long-acting anticholinergic (LAAC), as well as combination products and inhaled corticosteroids, prescribed by their family physicians for relief of their shortness of breath symptoms. Patients were excluded from the study if they were unable to communicate in English, unable or refused to take a physical exam and pulmonary function tests (PFTs), pregnant, or did not provide a signed informed consent form.

Three hundred and eighty-four (384) patients from Edmonton and 91 from Saskatoon gave consent but a total of 328 patients were available for spirometry testing and analysis. The EpiSOB study was funded by ASTHMA-C project council, The Alternate Reimbursement Plan Innovation fund, Capital Health of the Alberta Health Services and Alberta Health and Wellness, and was authorized by the ethics committees at the University of Alberta (# 7530) and the University of Saskatchewan (Bio-REB # 09-132).

3.3.2 Study Measures

Pre-post-bronchodilator spirometry and methacholine challenge testing was performed by trained and certified technicians at the time of the study according to procedures recommended by the standard manual of the American Thoracic Society (ATS) (18). COPD was defined as post-bronchodilator FEV_1 <80% predicted, together with an FEV_1/FVC <0.70. Asthma was defined as an increase in FEV_1 by 12% or 200 mL after bronchodilation or a positive response to a methacholine test. In cases where PFT data did not provide the clear indication of asthma or COPD diagnosis, a two-third consensus was sought from three expert pulmonologists.

3.3.3 Questionnaire data

Patients were asked to complete a questionnaire on socio-demographic factors, smoking history, comorbidities, respiratory symptoms, previous emergency room visits and

hospitalizations, family physician's diagnosis and previous test procedures performed for diagnostic evaluation for shortness of breath. Additionally, patients were asked to complete an asthma control questionnaire (ACQ) and a COPD assessment test (CAT) survey for measurement of their health-related quality of life. Pharmacists also presented a list of medications each patient was using within the past six month.

3.3.4 Definition of outcome variables

Physician-diagnosed COPD was defined as patient self-reported diagnosis of COPD from a family physician. Physician-diagnosed asthma was defined as patient self-reported diagnosis of asthma from a family physician. Misdiagnosis of COPD was considered when participants had post bronchodilator FEV1 /FVC <0.7, but were given a diagnosis for asthma by a family physician. Misdiagnosis of asthma was considered when participants showed airway reversibility (increase in FEV_1 by 12% or 200 mL with respect to baseline) but was given a diagnosis for COPD by a family physician. A prior test was defined as performed when the question, "*have you ever had any of the following tests for your SOB symptoms- spirometry, chest x-ray, and methacholine?*" was answered affirmatively. This information was also confirmed from the patient records.

Physician-diagnosed COPD or asthma was based on questionnaire response "*Has your family physician ever given you a diagnosis for your shortness of breath symptoms? If yes, what diagnosis*?". The reported diagnosis of COPD or asthma was considered correct if it matched spirometry results at the time of the study visit. Referral to see a specialist was based on questionnaire response *"Have you ever seen a specialist for your shortness of breath symptoms? If yes, were you referred by your family doctor?"*

3.3.5 Sample Size Considerations

This is a *secondary analysis of primary data* of a cross-sectional survey, the EpiSOB study. Approximately, 384 participants were obtained from Edmonton and 91 from Saskatoon, however, 328 samples were used for analysis. Power calculations using a type I error rate of 5%, incidence rates derived from the literature and assumed 2-sided test conducted using Stata and command prompt *stpower cox* are summarized in **Table 3.1** for primary outcomes.

From the power calculations conducted, this study has at least a power of 0.1701 to detect an effect size of 1.5 and a power of 1.000 to detect an effect size of 5.0. A similar study conducted, the EPI-SCAN study, had 386 participants with COPD (2). Also, in another study by Leynaert et al., 769 participants with asthma-like symptoms and bronchial hyper-responsiveness were used (19). Lastly, in a study by Pena et al., 363 patients with COPD were used (20).

3.3.6 Data analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 22. Continuous variables were described using specific measures of central tendencies such as mean and standard deviation. Categorical variables were summarized using frequency tables and proportions. Significance tests between men and women were conducted using t-tests for continuous variables and chi-square tests for categorical variables. Univariate analysis was carried out for all potential confounders. Any variable having a significant univariate test at 0.2 levels was selected as a candidate for the multivariate analysis. Logistic regression, using the backward variable selection procedure, was used to assess the influence of sex (with male as the reference) on physician-diagnosed COPD or asthma, misdiagnosis, referral to a specialist, referral for spirometry, referral for chest x-ray and referral for methacholine tests,

while controlling for potential confounders. Statistical significance level was set at $p < 0.05$ and individual estimators were overlapped with 95% confidence intervals.

3.3.7 Ethics consideration

The gender study presented in this chapter has received ethical approval from the Provincial Human Research Ethics Board (HREB) at the Memorial University of Newfoundland (#2018.138)

3.4 Results

3.4.1 Characteristics of participants

The sociodemographic and baseline characteristics of the 328 participants with shortness of breath in the EPI-SOB study corresponded to 140 (42.7%) men and 188 (57.3%) women **(Table 3.2).** The cohort had an average age of 49 years. The race of the cohort was distributed as follows: 86% were Caucasians and 14% Black, Aboriginal, Hispanic, or Oriental. A greater percentage of women than men were Caucasians (90.4% vs. 80.7%, p=0.011). There were fewer smokers among the women (p=0.05), and women had fewer pack years, better oxygen saturation (p=0.002) and better spirometry values for % predicted FEV_1 (p=0.001), FVC (p= 0.022), FEV_1/FVC (p=0.002) and PEF (p=0.02) at baseline. The comorbidities allergies, osteoporosis, depression, anxiety and anemia were reported more often in women than in men, while more men than women reported coronary artery disease (CAD). All other sociodemographic and clinical variables did not differ significantly between men and women.

Among the 97 participants with spirometrically-defined COPD, 51 (52.6%) were men and 46 (47.4%) were women **(Table 3.3)**. The average age of all COPD participants was 62

years. The comorbidities osteoporosis and depression were reported more often in women than in men. Heart rate and respiratory rate were significantly higher for women than men. All other sociodemographic and clinical variables did not differ significantly between men and women.

Among the 149 participants with spirometrically-defined asthma, 62 (41.6%) were men and 87 (58.4%) were women **(Table 3.4)**. The average age of all asthma participants was 43 years. A greater percentage of women than men were Caucasians (77.4% vs. 94.3%, p=0.002). Women had fewer pack years of smoking and better spirometry values for percent-predicted FEV_1 (p=0.00), FVC (p= 0.042), FEV_1/FVC (p=0.001) and PEF (p=0.00). Hypertension was reported more often in men than in women while depression and anemia were most often reported by women as their comorbidity. All other comorbidities were reported with the same frequency amongst men and women.

3.4.2 Symptoms

For patients with COPD, women reported more severe dyspnea than men (MRC 3-4: 37% vs 23.5%). However, the difference failed to reach statistical significance (p= 0.149) (**Table 3.5 and Figure 3.3)**. Again, with respect to other respiratory symptoms, there were no significant differences by sex in frequency of nocturnal cough, sputum production, chest tightness or wheeze. Levels of fatigue and hospitalization for respiratory conditions were higher in women than in men, but again failed to reach statistical significance.

For participants with asthma, the less severe end of the dyspnea spectrum recorded more men than women, while the more severe end recorded more women than men. Again, the difference was not statistically significant. With respect to other respiratory symptoms, there were no significant differences by sex in nocturnal cough, sputum production, chest tightness or

wheeze. However, fatigue was significantly more common in women than in men (p=0.039) and more women than men reported having had a recent hospitalization or emergency room visit (p=0.026) (**Table 3.5 and Figure 3.4)**.

3.4.3 Health-related quality of life

Women with COPD had higher scores for all domains of the COPD Assessment Test (CAT), indicating a greater impact of disease on health-related quality of life for women than for men **(Table 3.6)**. However, statistically significant levels were reached for only two of the domains. Specifically, women reported more breathlessness when walking up a hill (p=0.04) and fewer women were comfortable leaving home (p=0.05). The overall CAT score failed to reach statistical significance (p=0.09).

There was no trend in Asthma Controlled Questionnaire (ACQ) scores for men and women with asthma. Impairment was generally low for both genders in all the domains. However, men had significantly higher scores for the domain "How many times did you wheeze?" indicating more impairment for that domain. Total ACQ score was not different between men and women **(Table 3.7)**.

3.4.4 Pharmacological Treatment

Table 3.8 compares men and women in terms of medication prescription patterns. For patients with COPD, there were no significant differences between men and women in the use of beta agonists, corticosteroids, anticholinergics, methylxantines or leukotriene receptor antagonists (LTRA).

For patients with asthma, significantly more men than women were on SABA (p=0.038). Frequency of use of all other drug classes did not differ significantly between men and women with asthma.

3.5.5 Comparing family physician's diagnosis of patients with spirometrically-defined COPD

Table 3.9 and Figure 3.1 summarize primary-care physicians' diagnostic patterns for men and women who met spirometry criteria for COPD. Out of 97 patients with COPD by spirometry criteria, only 24 (24.7%) had had a diagnosis of COPD from their family-care physician. This number was unevenly distributed by gender, being 21.6% for men and 28.3% for women. Forty-five (46.4%) patients with spirometrically-defined COPD were misdiagnosed with asthma by family physicians, and this represented 47.8% women and 45.2% men. Also, 23% women and 22% men were referred by their family physician to see a specialist. Only 49 (50.5%) of all COPD patients reported a previous spirometry performed, representing 54.9% men and 45.7% women. Again, 73.9 % women and 64.7% men had had chest x-ray, and only 2 out of 97 spirometrically-defined COPD patients reported a methacholine test, 2.2% women and 2.0% men.

On univariate analysis, sex (male as reference) was not significantly associated with physician-diagnosed COPD (correct diagnosis), physician-diagnosed asthma (misdiagnosis), referral to a specialist, referral for spirometry or referral for chest x-ray. Other variables that were associated with diagnostic outcomes at a level of p-value < 0.2 were age, weight, marital status, educational status, smoking history, FEV_1/FVC, cough, total CAT score, fatigue, allergy and comorbidities as shown in **Table 3.10**.

After adjusting for potential confounding factors, and forcing sex into the model in multivariate analysis, the non-significant results persisted. Sex was not significantly associated with any of the primary outcome measures **(**see **Table 3.11)**. Multivariate analysis was not possible for "referral for methacholine" due to the small number of people (<3) who had that test performed.

3.5.6 Comparing family physician's diagnosis of patients with spirometrically-defined asthma

Table 3.9 and Figure 3.2 summarize primary-care physicians' diagnostic patterns for men and women who met spirometry criteria for asthma. Out of 146 patients with asthma by spirometry criteria, 102 (68.5%) reported a family physician's diagnosis of asthma, and this comprised 74.2% men and 64.4% women. Also, out of 146 patients with spirometrically-defined asthma, 9 (6%) were misdiagnosed with COPD by their family physician, and this group comprised 9.7% men and 3.4% women. Out of those referred to see a specialist, 27.6% were women and 25.8% were men. Also, 43.5% men and 28.7% women were referred for spirometry. Referrals for chest x-ray were more in women (47.1%) than in men (27.4%). Also, 1.6% men and 0% women reported a methacholine test.

On univariate analysis, sex (male as reference) was significantly associated with referral for chest x-ray (OR=2.359, 95%CI: 1.173-4.746, p=0.016). However sex was not significantly associated with physician-diagnosed asthma (correct diagnosis), physician-diagnosed COPD (misdiagnosis), referral to a specialist, or referral for spirometry at 0.05 levels. Other variables that were associated with diagnostic outcomes at a level of p-value < 0.2 were age, educational

status, pack years, FEV_1% predicted, total ACQ score, respiratory rate, dyspnea, cough, allergy and comorbidities **(Table 3.12)**.

After adjusted models for patients with spirometrically-defined asthma, sex was found to be significantly associated with physician-diagnosed asthma, referral for spirometry and referral for chest x-ray. Women were found to be less likely than men to have had a physician diagnosis of asthma (OR=0.535, 95%CI: 0.295-0.969, p=0.039), less likely to be referred for spirometry (OR=0.446, 95%CI: 0.200-0.994, p=0.048), but more likely than men to be referred for chest x-rays (OR=2.062, 95%CI: 1.030-4.128, p=0.041). All other diagnostic outcomes failed to reach statistical significance as depicted in **Table 3.13.** Again, multivariate analysis was not possible for "referral for methacholine" due to the small number of people (<3) who had that test performed.

3.5 Discussion

In our study, there were no significant differences between men and women in terms of physician-diagnosed COPD, referral to a specialist or referral for spirometry and other diagnostic tests in patients with spirometrically-defined COPD. In addition, there were no significant differences between gender in overall dyspnea and health-related quality of life scores. No difference was seen for cough, sputum production or medication prescription patterns. Comparing these results to those of previous studies however, reveals contradictory findings. For instance, in the EPI-SCAN study, male sex was found to be significantly associated with a previous diagnosis of COPD (2). Also in the *Confronting COPD study*, women with respiratory symptoms were found as less likely to have had a referral for spirometry, with three other studies corroborating that finding (3, 7, 21, 22). On the other hand, although a number of previous

studies have associated female sex with more dyspnea and poorer health-related quality of life, a study by Skumlien et al. found no significant difference between genders (23).

Results of this study however corroborate previous findings that underdiagnoses of COPD is generally high in both men and women, and in line with reports by other studies, less than 30% of people who meet spirometry criteria for COPD actually had a previous physician's diagnosis for their condition (2). Also, the number of people with COPD who were misdiagnosed with asthma was as high as 46.4% for both men and women alike. Guidelines for COPD recommend spirometry as the 'gold standard' in the evaluation of patients with respiratory symptoms suggestive of COPD (24). Spirometry can be used to confirm obstruction in airways and to differentiate COPD from asthma (24, 25). In our cohort, referrals for spirometry were as low as 50.5% for both men and women, and this corroborates results from previous studies (26, 27).

Men and women with spirometrically-defined asthma in our cohort had similar age and BMI, but men had smoked more than women. Women with asthma reported higher levels of fatigue and more emergency room visits than men. After controlling for confounders, women were less likely than men to be given a correct diagnosis for asthma, less likely to be referred for spirometry, but more likely to be referred for chest x-ray.

Evidence on diagnostic bias in asthma is limited. It has been suggested that COPD is more likely to be misdiagnosed as asthma in women than in men (5), but we do not know if women are also more likely to have a physician's diagnosis of asthma, amongst men and women who both meet guidelines criteria for asthma. Interestingly, we found that women in our cohort

of asthma patients were less likely to receive a physician's diagnosis of the disease after controlling for confounders.

Although we were expecting women to be more likely to be diagnosed with asthma since asthma has been subtly tagged as a "woman's disease" especially after the age of 35 years (5, 19), it is however possible that apart from known physician stereotypes, there is a general underestimation or misunderstanding of women's risk for health problems or complications (28). Another factor may be due to differences in the way men and women report their symptoms to the physician, as this could influence diagnostic decisions. Women tend to describe what they experience using a more personal, narrative approach as compared to men, who typically describe symptoms in a more straightforward, factual manner with fewer comments (7, 28). Women's narrative presentation style may contribute to physicians making more diagnostic errors in their evaluations of conditions, and especially when the use of objective measures of diagnosis are minimal (28).

Authors of GINA guidelines recommend that the diagnosis of asthma be based on the history of characteristic symptom patterns and evidence of variable airflow limitation, confirmed by spirometry (25). As reported by previous studies however, spirometry use in primary care diagnosis remains low, as less than 40% of patients had had a previous spirometry in our cohort. Why women should receive even less referrals for spirometry is difficult to explain.

On the other hand, more women than men were referred for chest x-ray. Given that chest x-ray is not a lung function test, and could be indicated for varied reasons (for example, as a tool in the examination of patients with an exacerbation of asthma or as an initial imaging evaluation

in individuals with symptoms of asthma (29)), it is unclear why more women than men were referred for chest x-rays.

It has been reported that women suffer from asthma symptoms and exacerbations more frequently and more severely than men (30, 31). We however found no significant differences between genders for dyspnea, cough or health-related quality of life. Women in our cohort however reported higher levels of fatigue and more frequent hospitalization than men. They also reported higher frequencies of comorbidities like anxiety, depression and osteoporosis, than men but lower frequency of hypertension. It is unclear to what extent these data are influenced by physician bias or differences in the care received. Lastly medication prescription patterns were similar for both genders, except for short acting beta agonists that were prescribed significantly more often in women than men.

There are several limitations to this study. Firstly, our patients were recruited from people with shortness of breath attending community pharmacies for medications and may therefore not represent the entire COPD or asthma population at large. Our cohort of patients appears to have mild disease (i.e. average FEV_1% predicted of >70%), and this may have impacted the findings of the study. Again, there were marked differences in baseline characteristics. Although variables that were strongly associated with the primary outcomes were adjusted for in the multivariate analysis, there is the possibility of residual confounding influencing findings of the study. Also, a very small number of respondents for some sub analysis may have impacted the results, while the many statistical tests increase the probability of a type I error. Even though physician-diagnosed asthma, referral for spirometry and referral for chest x-ray showed significant differences between men and women, the wide confidence intervals associated with the odds ratio may be due to the

small number of patients with spirometrically-defined asthma in the study sample. Moreover, patients recruited in this study were all 40 and older, and it is not clear whether this finding can be applied to all age groups. Another limitation of this study is that it relies heavily on self-response. Even though some outcomes were validated by a crosscheck with patients' records, we cannot rule out the possibility of recall bias.

3.6 Conclusion

There is some evidence of gender inequalities in primary care for asthma in this study. More studies with larger sample size are still required to draw concrete conclusions.

3.7 References

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Table 3.1 Power calculations for physician diagnoses of COPD and asthma, the primary outcome of the study

Outcome	**Exposure**	**Incidence in the population** (reference)	**Effect Size of 1.5**	**Effect Size of 2.0**	**Effect Size of 2.5**	**Effect Size of 3.5**	**Effect Size of 5.0**
Physician diagnosed COPD	Women	7.51 (2)	0.1701	0.4052	0.6232	0.8747	0.9790
Physician diagnosed COPD	Men	19.70 (2)	0.3706	0.7956	0.9575	0.9989	1.0000
Physician diagnosed asthma	Women	17.03 (19)	0.3282	0.7357	0.9284	0.9968	1.0000
Physician diagnosed asthma	Men	13.70 (19)	0.2739	0.6418	0.8668	0.9874	1.0000

All the above calculations were based on assumed two-sided alpha of 0.05 and expected event rates from previous studies; and a data consisting of 328 patients with shortness of breath, of which 97 were COPD patients and 149 were asthma patients.

Table 3.2 Sociodemographic and clinical characteristics of 328 participants of the EPI-SOB study, by sex.

	Men #(%)	**Women #(%)**	**p-value**
No. of Participants	140(42.7)	188(57.3)	
Age in years (mean ± SD):	50.8±18.3	48.2±17.9	0.209
AGE1			0.406
Ages< 50	65(46.4)	96(51.1)	
Ages >50	75(53.6)	92(48.9)	
Marital status:			0.282
Single/Never Married	38(27.1)	48(25.5)	
Separated/Divorced/Widowed	17 (12.1)	35(18.6)	
Married/Common-Law	85(60.7)	105 (55.9)	
Educational status:			0.202
Post-Secondary Education	63(45)	98(52.1)	
Other	77(55)	90(47.9)	
Race:			0.011
Caucasian	113 (80.7)	170(90.4)	
Other	27(19.3)	18(9.6)	
Smoking history:			0.05
Current	26(18.6)	39(20.7)	
Past	60(42.9)	57(30.3)	
Never smoked	54(38.6)	92(48.9)	
Second hand exposure to cigarette smoke:			0.527
Yes	126(90)	165(87.8)	
No	14(10)	23(12.2)	
Pack years(mean ± SD)	5.4±6.8	3.4±4.8	0.002
Co-morbidities:			
Allergies	99(70.7)	156(83)	0.008
Coronary Artery diseases	17(12.1)	11(5.9)	0.044
Chronic bronchitis	29 (20.7)	53(28.2)	0.122
Sinusitis or nasal polyps	38(27.1)	65(34.6)	0.151
Diabetes	13(9.3)	16(8.5)	0.807
Hypertension	41(29.3)	44(23.4)	0.229
High Cholesterol	25(17.9)	33(17.6)	0.943
Heart Failure	4(2.9)	2(1.1)	0.231
Arrhythmias	16(11.4)	28(14.9)	0.362
Malignancy	6(4.3)	16 (8.5)	0.130
Osteoporosis	7(5)	31(16.5)	0.001
Depression	31(22.1)	73(38.8)	0.001
Anxiety	29(20.7)	59(31.4)	0.031
GERD/Heartburn	56(40)	86(45.7)	0.299

Anaemia	8(5.7)	34(18.1)	0.001
Physical exam:			
weight(mean ±SD)	88.6±16.8	79.4±22.4	0.001
height(mean ±SD)	172.9±8.8	161.7±7.0	0.001
BMI (mean ±SD)	29.9±7.9	30.4±8.4	0.599
Heart rate (mean ±SD)	73.8±11.2	76.1±11.7	0.067
Respiratory rate (mean ±SD)	18.9±2.9	19.4±2.7	0.244
Blood pressure (Systole)	126.3±17.1	123.6±19	0.185
Blood pressure (Diastole)	78.9±11.6	76.7±10.4	0.067
Oxygen saturation	95.4±1.9	96.0±2.1	0.007
FEV_1% predicted, m±SD	79.5±17.6	88.5±20.5	0.001
FVC % predicted, m±SD	97.3±17.6	101.7±16.8	0.022
FEV_1/FVC	81.8±13.3	86.7±14.5	0.002
PEF	93.0±24.7	105.6±25.6	0.02

Table 3.3 Characteristics of 97 spirometrically-defined COPD individuals in the EPI-SOB Study, by sex.

	Men #(%)	**Women #(%)**	**p-value**
Patients	51(52.6)	46(47.4)	
Age in years (mean ± SD):	62.4±14.8	61.9±14.1	0.900
AGE1			0.810
Ages< 50	11(21.6)	9(19.6)	
Ages >50	40(78.4)	37(80.4)	
Marital status:			0.060
Single/Never Married	8(15.7)	7(15.2)	
Separated/Divorced/Widowed	11(21.6)	20(43.5)	
Married/Common-Law	32(62.7)	19(41.3)	
Educational status:			0.315
Post-Secondary Education	24(47.1)	17(37.0)	
Other	27(52.9)	29(63.0)	
Race:			0.487
Caucasian	43(84.3)	41(89.1)	
Other	8(15.7)	5(10.9)	
Smoking history:			0.464
Current	12(23.5)	15(32.6)	
Past	26(51.0)	18(39.1)	
Never smoked	13(25.5)	13(28.3)	
Second hand exposure to cigarette smoke:			0.253
Yes	47(92.2)	39(84.8)	
No	4(7.8)	7(15.2)	

Pack years(mean ± SD)	7.5±7.1	6.4±6.7	0.5
Co-morbidities:			
Allergies	33(64.7)	37(80.4)	0.084
Coronary Artery diseases	11(21.6)	7(15.2)	0.422
Chronic bronchitis	12(23.5)	15(32.6)	0.319
Sinusitis or nasal polyps	16(31.4)	18(39.1)	0.424
Diabetes	7(13.7)	6(13.0)	0.922
Hypertension	18(35.3)	21(45.7)	0.299
High Cholesterol	13(25.5)	11(23.9)	0.857
Heart Failure	2(3.9)	1(2.2)	0.620
Arrhythmias	8(15.7)	10(21.7)	0.444
Malignancy	4(7.8)	9(19.6)	0.091
Osteoporosis	4(7.8)	19(41.3)	0.00
Depression	12(23.5)	20(43.5)	0.037
Anxiety	9(17.6)	15(32.6)	0.088
GERD/Heartburn	19(37.3)	25(54.3)	0.091
Anaemia	3(5.9)	5(10.9)	0.373
Physical exam:			
BMI **(mean ±SD)**	29.2±5.1	30.6±10.1	0.360
weight(mean ±SD)	86.9±14.1	77.7±27.8	0.039
height(mean ±SD)	172.8±6.6	158.8±7.4	0.00
Heart rate	73.1±11.9	78.2±13.0	0.047
Respiratory rate	19.1±3.6	21.0±2.9	0.021
Blood pressure(Systole)	129.9±18.5	130.6±19.5	0.868
Blood pressure(Diastole)	79.2±10.9	78.9±10.1	0.953
Oxygen saturation	94.6±2.1	94.3±2.5	0.458
FEV_1% predicted, m±SD	66.2±16.9	66.3±20.3	0.99
FVC % predicted, m±SD	90.4±15.5	93±20.3	0.48
FEV_1/FVC	72.8±12.8	71.2±13.8	0.56
PEF	79.3±23.8	80.8±24.3	0.75

Table 3.4 Characteristics of 149 spirometrically-defined asthma individuals in the EPI-SOB Study, by sex.

	Men #(%)	**Women #(%)**	**p-value**
Patients	62(41.6)	87(58.4)	
Age in years (mean ± SD):	44.9±16.6	41.7±17.3	0.3
AGE1			0.382
Ages< 50	37(59.7)	58(66.7)	
Ages >50	25(40.3)	29(33.3)	
Marital status:			0.935
Single/Never Married	20(32.3)	26(29.9)	
Separated/Divorced/Widowed	3(4.8)	5(5.7)	
Married/CommonLaw	39(62.9)	56(64.4)	
Educational status:			0.515
Post-Secondary Education	28(45.2)	44(50.6)	
Other	34(54.8)	43(49.4)	
Race:			0.002
Caucasian	48(77.4)	82(94.3)	
Other	14(22.6)	5(5.7)	
Smoking history:			0.720
Current	13(21.0)	15(17.2)	
Past	23(37.1)	30(34.5)	
Never smoked	26(41.9)	42(48.3)	
Second hand exposure to cigarette smoke:			0.997
Yes	57(91.9)	80(92.0)	
No	5(8.1)	7(8.0)	
Pack years(mean ± SD)	5.7±7.7	3.0±4.3	0.007
Co-morbidities:			
Allergies	53(85.5)	77(88.5)	0.586
Coronary Artery diseases	2(3.2)	1(1.1)	0.374
Chronic bronchitis	13(21)	22(25.3)	0.540
Sinusitis or nasal polyps	16(25.8)	24(27.6)	0.809
Diabetes	4(6.5)	6(6.9)	0.915
Hypertension	16(25.8)	10(11.5)	0.023
High Cholesterol	8(12.9)	8(9.2)	0.471
Arrhythmias	6(9.7)	7(8.0)	0.728
Malignancy	0(0)	4(4.6)	0.087
Osteoporosis	1(1.6)	7(8.0)	0.086
Depression	10(16.1)	28(32.2)	0.027
Anxiety	10(16.1)	25(28.7)	0.074
GERD/Heartburn	22(35.5)	34(39.1)	0.655
Anaemia	3(4.8)	17(19.5)	0.009

Physical exam:			
BMI **(mean ±SD)**	30.5±10.1	29.6±8.1	0.557
weight(mean ±SD)	89.5±17.5	78.6±21.1	0.001
height(mean ±SD)	172.9±10.4	163.0±6.3	0.00
Heart rate	74.6±10.9	75.5±11.9	0.642
Respiratory rate	19.1±2.6	18.9±2.3	0.684
Blood pressure(Systole)	124.9±15.1	118.8±15.3	0.019
Blood pressure(Diastole)	79.7±11.1	75.4±10.2	0.017
Oxygen saturation	95.4±1.9	96.6±1.7	0.000
FEV1 % predicted, m±SD	79.9±15.6	92.4±15.4	0.00
FVC % predicted, m±SD	99.1±18.6	104.5±13.3	0.042
FEV1/FVC	81.2±12.8	88.1±12.6	0.001
PEF	91.3±25.8	110.9±21.3	0.000

Table 3.5 Symptoms of men and women with spirometrically-defined COPD or asthma

	COPD (n=97)				**Asthma (n=146)**		
	Men #(%)	**Women #(%)**	**p-value**		**Men #(%)**	**Women #(%)**	**p-value**
MRC Dyspnea scale							0.298
1-Not troubled by breathlessness	16(31.4)	10(21.7)	0.439		25(40.3)	25(28.7)	
2- Short of breath when hurrying on a level or when walking up a slight hill	23(45.1)	19(41.3)			29(46.8)	48(55.2)	
3- Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace	8(15.7)	13(28.3)			5(8.1)	12(13.8)	
4- Stops for breath after walking 100 yards, or after a few minutes on level ground	4(7.8)	4(8.7)			3(4.8)	2(2.3)	
MRC points%			0.149				0.589
MRC 1-2 (mild dyspnea)	39(76.5)	29(63)			54(87.1)	73(83.9)	
MRC 3-4 (severe dyspnea)	12(23.5)	17(37)			8(12.9)	14(16.1)	
Cough symptoms							
Nocturnal cough	5(9.8)	8(17.4)	0.437		9(14.5)	10(11.5)	0.367
Sputum production	9(17.6)	8(17.4)	0.222		11(17.7)	16(18.4)	0.943
Chest tightness	8(15.7)	7(15.2)	0.885		16(25.8)	19(21.8)	0.617
Wheeze	7(13.7)	14(30.4)	0.158		12(19.4)	19(21.8)	0.953
Other symptoms							
Fatigue	6(11.8)	9(19.6)	0.552		9(14.5)	22(25.3)	0.039
Recent hospitalization or ER visit	8(15.7)	13(28.3)	0.320		4(6.5)	17(19.5)	0.026

Table 3.6 COPD Assessment Test (CAT) scores for patients with spirometrically-defined COPD

	COPD (n=97)		
CAT items.	**Male, mean ±SD**	**Female, mean ±SD**	**p-value**
Cough all the time (0-5)	2.1±1.2	2.3±1.5	0.365
Chest full of mucus (0-5)	2.1±1.6	2.4±1.5	0.508
Chest feels very tight (0-5)	1.5±1.5	1.6±1.4	0.626
Very breathless walking up hill (0-5)	2.4±1.6	3.1±1.6	0.04
Limited doing activity (0-5)	1.4±1.5	2±1.8	0.125
Not comfortable leaving home (0-5)	0.5±1.1	1.1±1.5	0.050
Don't sleep soundly (0-5)	1.5±1.5	1.6±1.7	0.862
Have no energy (0-5)	2.3±1.3	2.9±1.6	0.061
Total CAT SCORE	**13.7±8.1**	**17±8.9**	**0.090**

0= no impact 5=maximum impact

Table 3.7 Asthma Control Questionnaire (ACQ) scores for patients with spirometrically-defined asthma

	ASTHMA(n= 146)		
ACQ items	**Men, mean ±SD**	**Women, mean ±SD**	**p-value**
How often were you woken by asthma at night during the past week? (0-6)	0.5±1.0	0.7±1.0	0.382
How bad were your asthma symptoms when you woke up in the morning (0-6)	1.4±1.4	1.3±1.2	0.885
How limited were you in your activities because of your asthma? (0-6)	1.0±1.2	1.0±1.2	0.951
How much shortness of breath did you experience because of asthma? (0-6)	1.8±1.5	1.9±1.2	0.619
How many times did you wheeze? (0-6)	2.1±1.6	1.5±1.4	0.030
The number of puffs of short acting bronchodilator used each day? (0-6)	1.3±1.3	0.9±0.9	0.074
TOTAL ACQ SCORE	**7.5±5.4**	**7.4±5.1**	**0.920**

0=no impairment, 6= maximum impairment

Table 3.8 Inhaler medications used within the past 6 months for patients with spirometrically-defined COPD or asthma.

	COPD (n=97)				**Asthma (146)**		
	Male	**Female**	**p-value**		**Male**	**Female**	**p-value**
Anticholinergic, long-acting	10(19.6)	10(21.7)	0.796		3(4.8)	1(1.1)	0.170
Anticholinergic, short-acting	5(9.8)	4(8.7)	0.851		2(3.2)	2(2.3)	0.730
short-acting B_2 agonist	34(66.7)	34(73.9)	0.436		45(72.6)	75(86.2)	0.038
long-acting B_2 agonist	4(7.8)	1(2.2)	0.207		2(3.2)	5(5.7)	0.473
Inhaled corticosteroid	16(31.4)	8(17.4)	0.111		14(22.6)	28(32.2)	0.199
Steroid oral	2(3.9)	1(2.2)	0.620		3(4.8)	5(5.7)	0.808
Combination/symbicort	17(33.3)	20(43.5)	0.304		23(37.1)	31(35.6)	0.855
Combination/Advair	18(35.3)	15(32.6)	0.780		18(29)	18(20.7)	0.241
Theophylline(methylxanthine)	2(3.9)	2(4.3)	0.916		1(1.6)	0(0.0)	0.235
Leukotriene receptor antagonists(LTRA)	3(5.9)	4(8.7)	0.593		4(6.5)	8(9.2)	0.544

Table 3.9 Descriptives of family physician's diagnosis of patients with spirometrically-defined COPD or asthma

	Spirometrically-defined COPD					Spirometrically-defined Asthma			
Diagnostic outcomes	**All COPD patients(n=97)**	**Men(n=51)**	**Women(n=46)**	**p-value**		**All asthma patients(n=146)**	**Men (n=62)**	**Women (n=87)**	**p-value**
Ever given diagnosis for COPD by your GP?	24(24.7)	11(21.6)	13(28.3)	0.446		9(6)	6(9.7)	3(3.4)	0.130
Ever given diagnosis for asthma by your GP?	45(46.4)	23(45.1)	22(47.8)	0.788		102(68.5)	46(74.2)	56(64.4)	0.203
Ever referred to see a specialist by your GP?	45(46.4)	22(43.1)	23(50)	0.499		40(26.8)	16(25.8)	24(27.6)	0.809
Ever had a spirometry performed?	49(50.5)	28(54.9)	21(45.7)	0.363		52(34.9)	27(43.5)	25(28.7)	0.062
Ever had a chest x-ray performed?	67(69.1)	33(64.7)	34(73.9)	0.327		58(38.9)	17(27.4)	41(47.1)	0.015
Ever had methacholine test performed?	2(2.1)	1(2.0)	1(2.2)	0.941		1(0.7)	1(1.6)	0(0)	0.235

Table 3.10 Univariate analysis for patients with spirometrically-defined COPD (Only p-values are presented in the table, see appendix c for output summary)

Independent variable	**Outcome variables (p-values)**				
	Physician-diagnosed COPD	Physician-diagnosed asthma	Referral to a specialist	Referral for spirometry	Referral for chest x-ray
Sex	0.447	0.788	0.499	0.364	0.329
Age	**0.121**	**0.009**	**0.018**	**0.002**	0.906
Weight	**0.200**	0.301	**0.200**	0.713	0.864
BMI	0.733	0.626	0.863	0.862	**0.082**
Race	0.883	0.543	0.567	0.739	0.513
Marital status	**0.064**	0.960	0.293	0.517	0.358
Educational status	0.687	**0.001**	0.690	0.907	0.562
Smoking history	**0.071**	**0.078**	0.883	0.890	0.493
Pack years	0.252	0.748	0.673	0.669	0.934
Second hand smoke	0.597	**0.076**	0.227	**0.131**	0.783
FEV_1% predicted	0.663	0.729	0.445	**0.025**	**0.062**
FEV_1/FVC	**0.200**	0.581	0.962	**0.041**	**0.163**
PEF	0.345	0.378	0.539	0.768	0.806
Oxygen saturation	0.707	0.577	0.420	0.492	**0.050**
Systolic bp	0.391	0.499	0.646	0.313	**0.069**
Heart rate	0.368	0.320	0.398	0.317	0.756
Respiratory rate	0.452	0.332	0.666	**0.017**	**0.009**
Total cat score	**0.001**	**0.177**	**0.057**	0.875	**0.007**
dyspnoea	0.391	0.795	**0.077**	0.905	**0.043**
cough	**0.069**	0.401	0.701	**0.119**	**0.102**
Sputum production	0.941	0.688	**0.200**	0.684	0.704
Chest tightness	0.535	0.590	0.706	0.706	0.922
Wheeze	0.706	**0.058**	0.961	0.943	0.793
Fatigue	**0.001**	0.258	0.454	0.608	**0.031**
Recent hospitalization	0.815	0.335	0.828	**0.024**	**0.118**
Allergy	**0.086**	**0.043**	0.493	0.542	0.254
Comorbidities	**0.199**	0.327	**0.019**	**0.153**	0.785

Variables with $p < 0.2$ were included in the model

Table 3.11 Multivariate analysis for patients with spirometrically-defined COPD

Outcome variables	**Female sex (male=ref) Adjusted OR (95% CI)**	**P-value**
Physician-diagnosed COPD (correct diagnosis) [a]	0.862 (0.514-1.444)	0.573
Physician-diagnosed asthma (misdiagnosis) [b]	1.184 (0.486-2.887)	0.710
Referral to a specialist [c]	1.265 (0.428-3.738)	0.671
Referral for spirometry [d]	0.565 (0.160-1.994)	0.375
Referral for chest x-ray [e]	0.625 (0.191-2.051)	0.438

Explanatory variable is sex (male=ref)
[a]**Adjusted for:** age, smoking history, cough, fatigue, total catscore.
[b]**Adjusted for:** educational status, wheeze.
[c]**Adjusted for:** age, total cat score, comorbidities.
[d]**Adjusted for:** age, respiratory rate, comorbidities.
[e]**Adjusted for:** respiratory rate, fatigue.

Table 3.12 Univariate analysis for patients with spirometrically-defined asthma (Only p-values are presented in the table, see appendix c for output summary)

Independent Variable	**Outcome variables (p-value)**				
	Physician-diagnosed Asthma	Physician-diagnosed COPD	Referral to a specialist	Referral for spirometry	Referral for chest x-ray
Sex	**0.205**	**0.131**	0.809	**0.063**	**0.016**
Age	**0.092**	**0.007**	**0.021**	**0.006**	0.815
BMI	0.796	0.466	0.526	0.785	**0.021**
Weight	0.382	**0.185**	0.949	0.626	0.561
Race	0.292	0.880	0.545	0.404	**0.097**
Marital status	0.926	0.664	0.390	**0.028**	**0.148**
Educational status	**0.046**	**0.126**	**0.046**	0.701	0.312
Smoking history	0.486	**0.131**	0.706	0.327	0.465
Pack years	**0.130**	0.264	**0.052**	**0.081**	0.277
Second hand exposure to cigarette smoke	0.890	0.730	0.410	0.906	**0.118**
FEV_1% predicted	0.887	**0.009**	0.797	**0.107**	0.437
FEV_1/FVC	**0.012**	**0.015**	**0.186**	0.229	0.381

PEF	0.298	0.217	0.722	0.441	0.469
Oxygen saturation	0.281	0.354	0.739	**0.001**	0.312
Systolic bp	0.403	0.542	**0.174**	0.422	0.509
Heart rate	0.555	0.941	0.467	0.325	**0.116**
Respiratory rate	0.365	0.346	**0.017**	**0.194**	**0.100**
Total ACQ score	0.566	**0.020**	0.800	0.614	0.318
MRC dyspnoea	0.518	**0.006**	0.489	**0.008**	0.530
cough	0.405	0.478	0.967	**0.052**	0.767
Sputum production	0.664	0.346	0.872	0.967	**0.059**
Chest tightness	0.410	0.962	0.869	0.695	0.533
Wheeze	0.663	0.318	0.370	0.840	0.484
Fatigue	**0.031**	0.669	0.232	0.608	0.260
Recent hospitalization	0.945	0.531	0.536	0.345	**0.054**
allergy	**0.011**	**0.009**	0.247	0.484	0.763
comorbidities	**0.006**	**0.019**	**0.034**	**0.017**	**0.014**

Variables with $p < 0.2$ were included in the model

Table 3.13 Multivariate analysis for patients with spirometrically-defined asthma

Outcome variables	**Female sex (male=ref) Adjusted OR (95% CI)**	**P-value**
Physician-diagnosed asthma (correct diagnosis)[a]	0.535 (0.295-0.969)	0.039*
Physician-diagnosed COPD (misdiagnosis) [b]	0.343 (0.067-1.756)	0.199
Referral to a specialist [c]	0.871 (0.352-2.155)	0.765
Referral for spirometry [d]	0.446 (0.200-0.994)	0.048*
Referral for chest x-ray [e]	2.062 (1.030-4.128)	0.041*

Explanatory variable is sex (male=ref)
[a]**Adjusted for:** FEV1/FVC ratio, fatigue, allergy, comorbidities.
[b]**Adjusted for:** FEV1/FVC ratio, dyspnea, allergy.
[c]**Adjusted for:** packyears, respiratory rate, comorbidities.
[d]**Adjusted for:** age, oxygen saturation, cough, dyspnea.
[e]**Adjusted for:** BMI, heart rate, hospitalization, comorbidities.
***Significant**

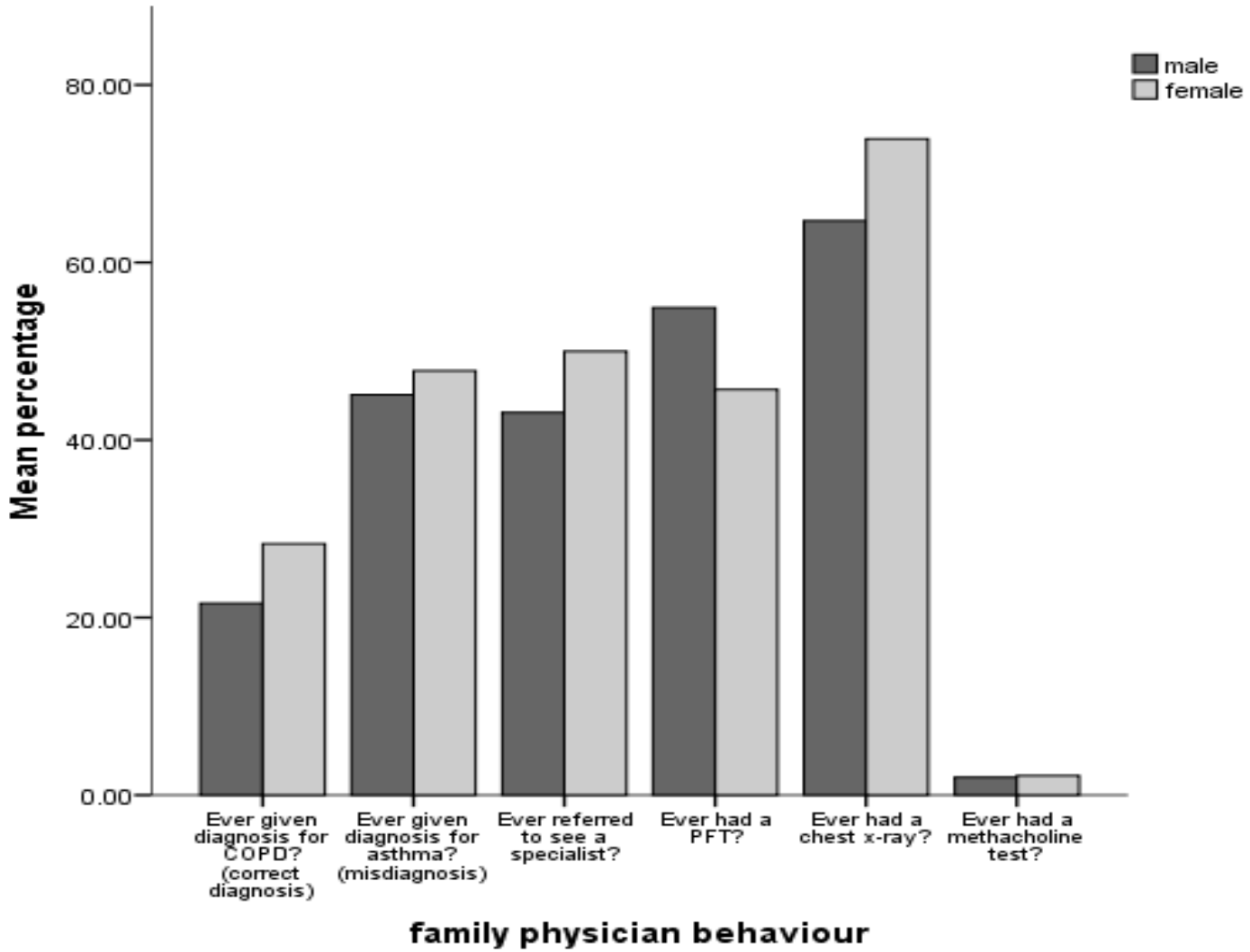


Figure 3.1 Unadjusted frequencies for patients with spirometrically-defined COPD

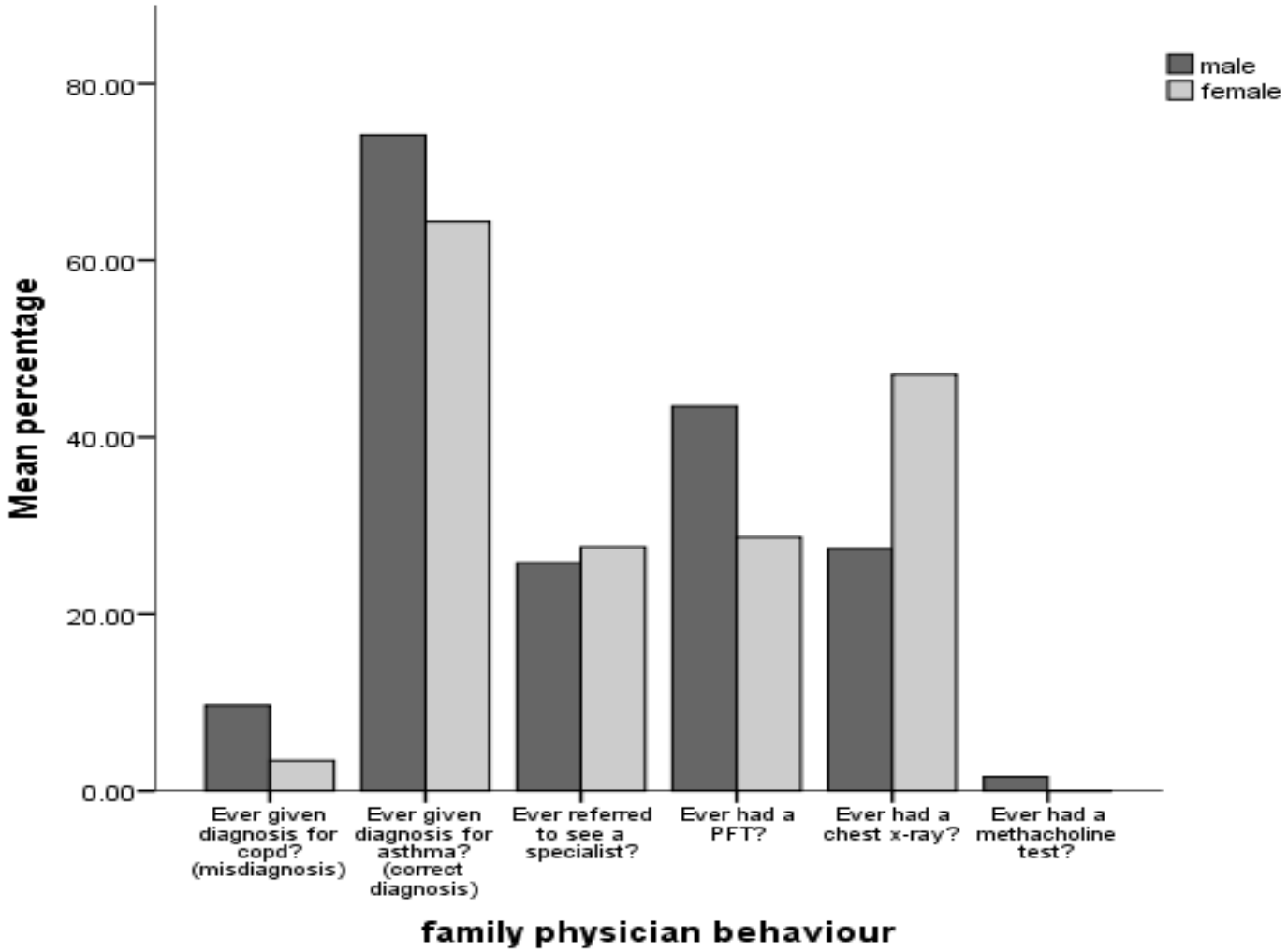
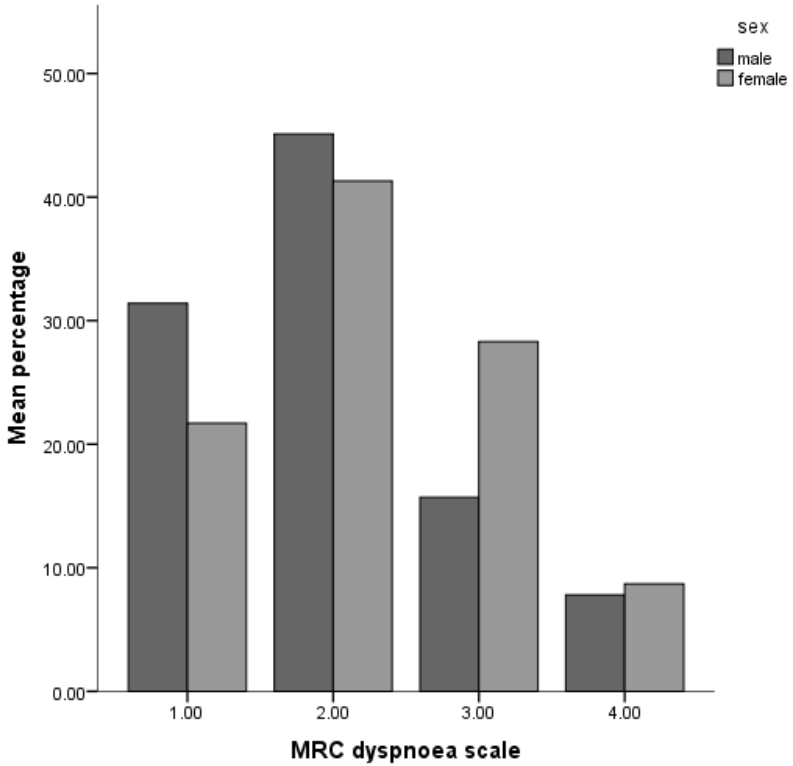


Figure 3.2 Unadjusted frequencies for patients with spirometrically-defined asthma



KEY

1-not troubled by breathlessness except on strenuous exercise.

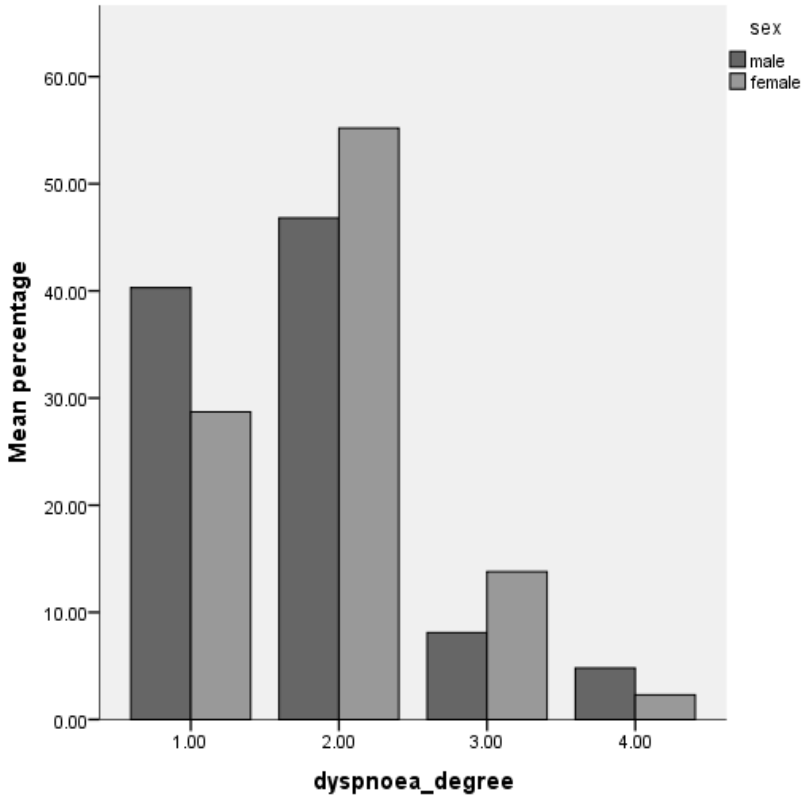
2- short of breath when hurrying or walking up a slight hill.

3- walks slower(than contemporaries) on level ground because of breathlessness or has to stop for breath when walking at own pace.

4- stops for breath after walking about 100 meters or after a few minutes on level ground.

5- too breathless to leave the house, or breathless when dressing/undressing .

Figure 3.3 MRC Degree of dyspnoea for men and women with spirometrically-defined COPD.



KEY

1-not troubled by breathlessness except on strenuous exercise.

2- short of breath when hurrying or walking up a slight hill.

3- walks slower(than contemporaries) on level ground because of breathlessness or has to stop for breath when walking at own pace.

4- stops for breath after walking about 100 meters or after a few minutes on level ground.

5- too breathless to leave the house, or breathless when dressing/undressing .

Figure 3.4 MRC Degree of dyspnoea for men and women with spirometrically-defined asthma

CHAPTER FOUR

Overall Discussion

4.1 Summary of findings and discussion

The aim of this research was to investigate gender disparities in the diagnosis of COPD and asthma from family physicians. To achieve this aim, we first conducted a systematic review and meta-analysis to objectively synthesize all the available evidence on this question. Based on the evidence provided by the review, we then investigated the presence or absence of gender disparities in a Canadian population, while addressing existing literature gaps.

The findings from our first study (systematic review) revealed that women are less likely to be diagnosed with COPD by their family physicians and less likely to be referred for spirometry, even though they both may meet criteria for COPD. Our second study (secondary analysis) provided evidence that women with asthma are less likely to be given a diagnosis of asthma by their family physicians and less likely to be referred for spirometry, but more likely to be referred for chest x-rays. Comparing the two studies, referral for spirometry appears lower in women than men with obstructive airway diseases. Also, a correct diagnosis of COPD or of asthma appeared to have occurred more often in men than in women.

Despite the growing cognizance of gender differences in health care, disparate treatment between men and women still exists for many chronic conditions (1). Even though some of these contrasts could be due to differences in disease presentation, prevalence and therapeutic response, a considerable number of studies have also shown evidence of gender bias leading to

systemic mistreatment (1, 2). In order to overcome gender bias, identifying the presence or otherwise of gender differences in patient care is imperative.

While the systematic review presuppose that gender differences exist in primary care for COPD, the secondary analysis of data corroborates the possible existence of gender disparities in the diagnosis of asthma as well, as we found women as less likely to be diagnosed with the condition and less likely to have had spirometry, but more likely to have had chest x-rays. It must be noted that gender biases may take different forms and may be consciously or unconsciously endorsed (3). Unconscious prejudices among physicians, coupled with social stereotyping have been identified as one of the stimuli for gender bias (2, 3). Also, when physicians underestimate or misunderstand a woman's risk for health problems or complications, it may lead to biases (4). Moreover, there could be overt discrimination based on sex. For instance, when women's symptoms are taken less seriously by physicians and attributed to emotional rather than physical causes, it may lead to less referrals for diagnostic tests and to gender bias (4). No one knows for sure which of these factor(s) leads to situations that appear to be gender bias. Different factors or combination of factors may influence different clinical scenarios.

Not everyone agrees that gender bias exists in health care. A physician once said that although "it is commonly believed that American health-care delivery and research benefit men at the expense of women, the truth appears to be exactly the opposite" (4, 5). He cited the longer life expectancy of women than men as evidence that "women receive more medical care and benefit more from medical research. The net result is the most important gap of all: seven years, 10 percent of life" (4, 5). On the contrary, many more recent studies continue to provide evidence of gender bias in health care, which cuts across a wide spectrum of clinical practice

areas including cardiovascular diseases, airway diseases, surgery, orthopedics, behavioral health, as well as acute and critical care (6-11). It has been echoed that gender bias "need not be intentional to be detrimental, and in fact, the more insidious its existence, the more readily gender bias can invade, fester, and infect patient care in subtle and undetected ways"- JoAnn Grif Alspach, RN (4). Consequently, a bias in clinical diagnosis can hugely impact the health outcomes of patients (12). Results of the meta-analysis provided evidence of greater impairment in health-related quality of life and more dyspnoea in women than in men. However, the extent to which differences in symptoms and health outcomes of patients is reflected by gender bias in diagnosis and management was beyond the scope of our research.

Besides issues of gender disparities, our research supports findings of other studies that:

1. Underdiagnoses of both COPD and asthma is relatively high but higher for COPD than for asthma.

2. A considerable number of people who meet spirometry criteria for COPD are often wrongly diagnosed as asthma by their family physicians.

3. Spirometry -the recommended guidelines approved method of COPD and asthma diagnosis- is rarely used in primary care.

4. Chest x-rays are performed more often than spirometry.

There could be many reasons why underdiagnosis and misdiagnosis seem to be a major problem in primary care (13-15). The most apparent of all is diagnosis based mainly on patient history and clinical symptoms, without the use of spirometry (16-18). In a study by Herrera et al, underdiagnosis and misdiagnosis were less prevalent in those with previous spirometry (13). A

number of studies have shown evidence of spirometry underuse by general practitioners in establishing COPD diagnosis (19). In one of those studies, family physicians' diagnosis of COPD was compared to that of chest physicians. The authors found that family physicians classified 29.3% of the patients correctly while chest physicians diagnosed 84.8% correctly (20). Lack of familiarity and lack of access or availability of the equipment could be determining factors for spirometry underuse in primary care.

4.2 Strengths and limitations of the studies

The systematic review included in this thesis has several strengths and limitations. The strengths include a comprehensive, systematic, and highly sensitive literature search conducted without restriction for language. To the best of our knowledge, the review represents the first meta-analysis of the association between gender and COPD diagnosis. We used standardized criteria to identify relevant articles and abstract pertinent data. To minimize error and study selection bias, two reviewers selected studies independently, with high interrater agreement. Included studies were rigorously evaluated using the USPSTF Quality Rating. We identified studies from America, Europe, and Asia, which increased the generalizability for most outcomes.

The systematic review also has several important limitations. There is a possibility of publication bias for some of the outcomes, as funnel plots demonstrated possible existence of unpublished studies with negative results, which compromises findings of the systematic review. Also, including studies of "fair quality" in the analysis may have introduced bias and compromised findings of the study. Again, relatively few studies were identified for some primary outcomes at the meta-analysis stage, making it impractical to explore heterogeneity for those outcomes. A further shortcoming of the systematic review is reduced generalizability for

the outcome ‘physician-diagnosed COPD’, as all four studies that qualified for the meta-analysis were conducted in Spain.

The second study presents with its own strengths and limitations. To the best of our knowledge, we investigated more outcomes than have ever been published by a single study on gender differences in obstructive airway diseases. Also, to the best of our knowledge, this is the first study to dissect gender bias in the diagnosis of asthma, and the first study to consider gender disparities in a Canadian setting, using real life population. The findings of the study have provided valuable information that could be used to develop hypothesis for further research.

Findings from this study may however be limited in several ways. Participants were adults, and as such, results from the study may not be applicable to children and people under 40years of age. The cohort may also not be representative of the entire COPD/asthma population at large. Our cohort of patients appeared to have mild disease, and this may have impacted the findings of the study. Also, there were considerable differences between men and women at baseline. Although variables that were found to be strongly associated with the outcomes were controlled for in multivariate analysis, there could be some other unknown physiological and environmental factors causing residual confounding. Moreover, some sub-analyses recorded very small numbers of respondents and that may have impacted the results. Again, the many statistical tests increase the probability of a type I error. Another limitation of the study is the self-response nature of primary outcomes. Even though outcomes were crosschecked with patients’ records, we cannot rule out recall bias.

4.3 Clinical Implications

Discrepancies in care between men and women mean that necessary diagnostic procedures may not be performed, specialty referrals may not be made, and medications not prescribed, all of which can impact outcomes. Evidence obtained from this research can increase awareness of a possible existence of differences in care given to men and women, which is an important step in reducing gender bias and facilitating early recognition of disease in men and women. Our findings also highlight the importance of encouraging the use of objective methods of diagnosis in primary care, as this may greatly reduce discrepancies and bias.

4.4. Conclusion

Available guidelines for COPD and asthma care and management do not differ for men and women. Results of the meta-analysis however provided evidence of differences in diagnostic procedures for men and women with COPD, with less appropriate diagnostic work-up for women. Discrepancies between men and women were also identified for some diagnostic procedures for asthma. These differences persisted after accounting for potential confounders, and may imply an underlying gender bias in COPD/asthma care. Nonetheless, due to considerable number of study limitations and inability to corroborate results for COPD in a Canadian setting, the findings of this project should be interpreted cautiously. We still require more well-conducted studies of higher quality and with larger sample sizes to draw more meaningful conclusions. Also, more studies need to be conducted across jurisdictions to increase generalizability and precision. Future studies may subsequently explore the reasons behind these observed differences in order to make corrective measures more targeted. As healthcare systems

continue to explore various means to improve patient care, attention should also be channeled towards promoting equal care for men and women.

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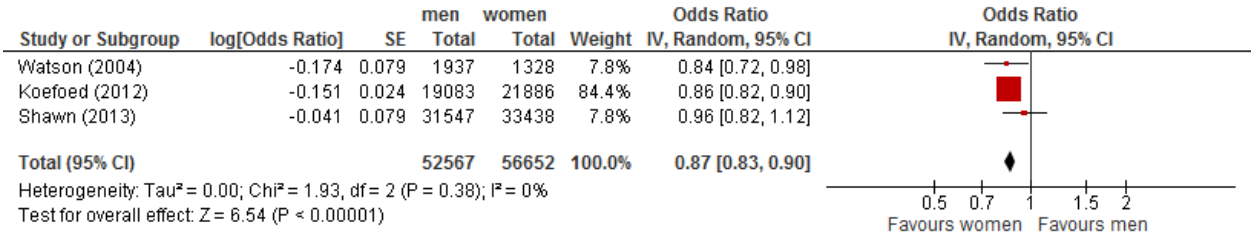
APPENDIX A: Detailed search strategy for systematic review and meta-analysis and sensitivity analysis

Database	Search string
PubMed	("Pulmonary Disease, Chronic Obstructive"[Mesh] OR COPD[tiab] OR "chronic obstructive pulmonary disease"[tiab]) AND ("Sexism"[Mesh] OR "gender difference"[tiab] OR "gender differences"[tiab] OR "gender factor"[tiab] OR "gender factors"[tiab] OR "gender bias"[tiab] OR "sex bias"[tiab]) "[Mesh] OR "risk factor"[tiab] OR "risk factors"[tiab])
Embase	('chronic obstructive lung disease'/de OR copd:ab,ti OR 'chronic obstructive pulmonary disease':ab,ti) AND ('sexism'/exp OR 'gender difference':ab,ti OR 'gender differences':ab,ti OR 'gender factor':ab,ti OR 'gender factors':ab,ti OR 'gender bias':ab,ti OR 'sex bias':ab,ti)
Cinahl	(MH "Pulmonary Disease, Chronic Obstructive+" OR TI COPD OR AB COPD OR TI "chronic obstructive pulmonary disease" OR AB "chronic obstructive pulmonary disease") AND (MH "Sexism" OR MH "Gender Bias" OR MH "Gender Specific Care" OR MH "Sex Factors" OR TI "gender difference" OR AB "gender difference" OR TI "gender differences" OR AB "gender differences" OR TI "gender factor" OR AB "gender factor" OR TI "gender factors" OR AB "gender factors" OR TI "gender bias" OR AB "gender bias" OR TI "sex bias" OR AB "sex bias")



Sensitivity analysis for forest plot assessing whether women are less likely than men to be referred for spirometry.

APPENDIX B: HREB approval letter

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

June 23, 2017

82 Larkhall street
A1B 2C6
St. John's
Canada

Dear Miss Acheampong:

Researcher Portal File # 20180403
Reference # 2017.138

RE: "Examing gender bias in the diagnosis, treatment and management of Obstructive Airway Diseases(OADs)"

Your application received a delegated review by a sub-committee of the Health Research Ethics Board (HREB). ***Full approval*** of this research study is granted for one year effective **June 23, 2017**.

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

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

- Application, approved
- Letter of request, approved
- Episob variable list, approved
- Chart audit Episob, approved
- Sample consent form, approved

MARK THE DATE

This approval will lapse on June 23, 2018. It is your responsibility to ensure that the Ethics Renewal form is submitted prior to the renewal date; you may not receive a reminder. The Ethics

Renewal form can be found on the Researcher Portal as an Event form.

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

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

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

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

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

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

We wish you every success with your study.

Sincerely,

Patricia Grainger

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

CC: Dr. William Midodzi

APPENDIX C: Spss output summary for univariate analysis

a. Univariate analysis for patients with spirometrically-defined COPD

i. Dependent variable: Physician-diagnosed COPD (correct diagnosis)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	.359	.472	.579	1	.447	1.433	.568	3.616
	Constant	-1.291	.340	14.379	1	.000	.275		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Age	.028	.018	2.407	1	.121	1.029	.993	1.066
	Constant	-2.908	1.207	5.808	1	.016	.055		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nweight	-.013	.010	1.690	1	.200	.987	.967	.993
	Constant	-.054	.965	.003	1	.955	.947		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	d_nmarital	-.578	.312	3.436	1	.064	.561	.304	1.034
	Constant	.215	.734	.086	1	.770	1.240		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsmoking	-.603	.334	3.251	1	.071	.547	.284	1.054
	Constant	.037	.656	.003	1	.955	1.038		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	tff_pr2	-.015	.012	1.563	1	.200	.985	.963	.992
	Constant	-.023	1.280	.000	1	.986	.977		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	ncough_n	-.463	.254	3.311	1	.069	.629	.382	1.036
	Constant	.429	.863	.248	1	.619	1.536		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nfatigue	-1.012	.317	10.176	1	.001	.363	.195	.677
	Constant	2.132	1.013	4.429	1	.035	8.432		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nallergy	.856	.498	2.951	1	.086	2.353	.886	6.246
	Constant	-2.242	.718	9.742	1	.002	.106		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Comorbidities	-.134	.104	1.653	1	.199	.875	.713	1.073
	Constant	2.360	2.694	.767	1	.381	10.586		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	dtotal	.115	.036	10.321	1	.001	1.121	1.046	1.203
	Constant	-3.048	.722	17.819	1	.000	.047		

ii. Dependent variable: Physician-diagnosed asthma (misdiagnosis)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	.110	.408	.072	1	.788	1.116	.502	2.482
	Constant	-.197	.281	.489	1	.485	.821		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Age	-.041	.016	6.849	1	.009	.960	.931	.990
	Constant	2.411	1.001	5.804	1	.016	11.148		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	d_neducat	-1.404	.436	10.356	1	.001	.246	.104	.578
	Constant	2.061	.718	8.234	1	.004	7.852		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsmoking	.501	.284	3.105	1	.078	1.650	.945	2.879
	Constant	-1.145	.607	3.560	1	.059	.318		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	n2ndhand	1.262	.711	3.148	1	.076	3.532	.876	14.234
	Constant	-1.543	.805	3.672	1	.055	.214		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nwheeze	-.489	.258	3.598	1	.058	.613	.370	1.016

	Constant	1.349	.814	2.749	1	.097	3.854		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nallergy	-.979	.485	4.083	1	.043	.376	.145	.971
	Constant	1.094	.638	2.940	1	.086	2.986		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	dtotal	-.038	.028	1.820	1	.177	.963	.911	1.017
	Constant	.303	.476	.405	1	.524	1.354		

iii. Dependent variable: Referral to a specialist

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	.276	.409	.457	1	.499	1.318	.592	2.936
	Constant	-.276	.283	.955	1	.329	.759		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Age	.037	.016	5.574	1	.018	1.038	1.006	1.070
	Constant	-2.468	1.015	5.917	1	.015	.085		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nweight	-.012	.010	1.524	1	.200	.988	.969	1.007
	Constant	.843	.822	1.051	1	.305	2.323		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	dtotal	.054	.028	3.613	1	.057	1.055	.998	1.115
	Constant	-1.034	.495	4.359	1	.037	.355		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	d_nmrc_c	.417	.236	3.135	1	.077	1.518	.956	2.410
	Constant	-1.030	.542	3.614	1	.057	.357		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsputum	.315	.248	1.618	1	.200	1.370	.843	2.227
	Constant	-1.169	.834	1.962	1	.161	.311		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	comorbidities	-.225	.096	5.465	1	.019	.798	.661	.964
	Constant	5.730	2.521	5.168	1	.023	308.085		

iv. Dependent variable: Referral for spirometry

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	-.371	.408	.825	1	.364	.690	.310	1.536
	Constant	.197	.281	.489	1	.485	1.217		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Age	.050	.017	9.185	1	.002	1.051	1.018	1.086
	Constant	-3.106	1.061	8.576	1	.003	.045		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	ncough_n	.381	.244	2.436	1	.119	1.463	.907	2.359
	Constant	-1.281	.863	2.203	1	.138	.278		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	n2ndhand	1.074	.711	2.284	1	.131	2.927	.727	11.783
	Constant	-1.167	.803	2.112	1	.146	.311		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nhosp	.428	.190	5.100	1	.024	1.535	1.058	2.226
	Constant	-1.369	.656	4.352	1	.037	.254		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nresprt	-.209	.088	5.667	1	.017	.812	.684	.964
	Constant	3.700	1.742	4.512	1	.034	40.463		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	comorbidities	-.132	.092	2.038	1	.153	.877	.732	1.050
	Constant	3.456	2.416	2.046	1	.153	31.679		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	tfev_pr2	-.027	.012	5.025	1	.025	.974	.951	.997
	Constant	1.766	.814	4.705	1	.030	5.849		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	tff_pr2	-.019	.009	4.185	1	.041	.982	.964	.999
	Constant	1.494	.760	3.867	1	.049	4.454		

v. Dependent variable: Referral for chest x-ray

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	.435	.446	.954	1	.329	1.545	.645	3.702
	Constant	.606	.293	4.279	1	.039	1.833		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	BMI	.062	.036	3.016	1	.082	1.064	.992	1.141
	Constant	-.998	1.036	.927	1	.336	.369		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	tfev_pr2	-.023	.013	3.479	1	.062	.977	.953	1.001
	Constant	2.422	.896	7.302	1	.007	11.265		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	tff_pr2	-.025	.018	1.945	1	.163	.975	.942	1.010

	Constant	2.648	1.333	3.949	1	.047	14.129		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	no2sat	-.223	.114	3.839	1	.050	.800	.640	1.000
	Constant	21.957	10.824	4.115	1	.042	5.849		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nbpsys	.024	.013	3.316	1	.069	1.025	.998	1.052
	Constant	-2.281	1.706	1.788	1	.181	.102		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nresprt	.244	.093	6.880	1	.009	1.277	1.064	1.533
	Constant	-4.180	1.830	5.220	1	.022	.015		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	dtotal	.091	.034	7.398	1	.007	1.096	1.026	1.170
	Constant	-.757	.511	2.195	1	.138	.469		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	d_nmrc_c	.551	.273	4.078	1	.043	1.734	1.016	2.960
	Constant	-.313	.575	.296	1	.587	.731		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	ncough_n	-.487	.298	2.667	1	.102	.614	.342	1.102

	Constant	2.503	1.087	5.301	1	.021	12.219		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nfatigue	-.725	.336	4.652	1	.031	.485	.251	.936
	Constant	3.287	1.202	7.474	1	.006	26.761		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nhosp	-.337	.216	2.437	1	.118	.714	.468	1.090
	Constant	1.920	.768	6.248	1	.012	6.821		

b. Univariate analysis for patients with spirometrically-defined asthma

i. Dependent variable: Physician-diagnosed asthma (correct diagnosis)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	-.465	.367	1.607	1	.205	.628	.306	1.289
	Constant	1.056	.290	13.239	1	.000	2.875		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Age	-.024	.014	2.939	1	.092	.976	.976	1.004
	Constant	1.856	.510	13.235	1	.000	6.398		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	d_neducat	-.725	.363	3.996	1	.046	.484	.238	.986
	Constant	1.899	.602	9.948	1	.002	6.681		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	packyears	-.056	.037	2.291	1	.130	.945	.878	.983
	Constant	1.021	.222	21.237	1	.000	2.776		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	tff_pr2	-.020	.015	1.777	1	.012	.980	.965	.996
	Constant	2.482	1.314	3.568	1	.059	11.963		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nfatigue	-.282	.131	4.634	1	.031	.754	.583	.974
	Constant	1.708	.761	5.034	1	.025	5.520		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nallergy	-1.278	.504	6.424	1	.011	.279	.104	.748
	Constant	2.238	.608	13.553	1	.000	9.375		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Comorbidities	.207	.075	7.618	1	.006	1.230	1.061	1.4
	Constant	-4.967	2.702	3.380	1	.066	.007		

ii. Dependent variable: Physician-diagnosed COPD (misdiagnosis)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	-1.099	.728	2.278	1	.131	.333	.080	1.388
	Constant	-2.234	.430	27.037	1	.000	.107		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Age	.062	.023	7.172	1	.007	1.064	1.017	1.114
	Constant	-5.924	1.400	17.911	1	.000	.003		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nweight	.020	.015	1.759	1	.185	1.020	.991	1.050
	Constant	-4.456	1.394	10.216	1	.001	.012		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	d_neducat	1.253	.819	2.337	1	.126	3.500	.702	17.440
	Constant	-4.808	1.488	10.440	1	.001	.008		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsmoking	-.670	.444	2.277	1	.131	.512	.215	1.221
	Constant	-1.343	.919	2.136	1	.144	.261		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	tfev_pr2	-.047	.018	6.754	1	.009	.954	.920	.988
	Constant	1.090	1.407	.601	1	.438	2.975		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	tff_pr2	-.049	.020	5.928	1	.015	.952	.916	.991
	Constant	1.195	1.566	.582	1	.445	3.303		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	totalacqscore	.184	.079	5.386	1	.020	1.202	1.029	1.404
	Constant	-4.576	1.010	20.517	1	.000	.010		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	d_nmrc_c	1.128	.412	7.490	1	.006	3.089	1.377	6.926
	Constant	-5.166	1.069	23.349	1	.000	.006		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nallergy	1.897	.724	6.860	1	.009	6.667	1.612	27.572
	Constant	-5.116	1.072	22.786	1	.000	.006		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for E	
								Lower	
Step 1[a]	comorbidities	-.412	.176	5.481	1	.019	.662	.469	
	Constant	8.483	4.694	3.267	1	.071	4831.818		

Dependent variable: Referral to a specialist

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nweight	.020	.015	1.759	1	.185	1.020	.991	1.050
	Constant	-4.456	1.394	10.216	1	.001	.012		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	d_neducat	1.253	.819	2.337	1	.126	3.500	.702	17.440
	Constant	-4.808	1.488	10.440	1	.001	.008		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsmoking	-.670	.444	2.277	1	.131	.512	.215	1.221
	Constant	-1.343	.919	2.136	1	.144	.261		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	tfev_pr2	-.047	.018	6.754	1	.009	.954	.920	.988
	Constant	1.090	1.407	.601	1	.438	2.975		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	tff_pr2	-.049	.020	5.928	1	.015	.952	.916	.991
	Constant	1.195	1.566	.582	1	.445	3.303		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	totalacqscore	.184	.079	5.386	1	.020	1.202	1.029	1.404

	Constant	-4.576	1.010	20.517	1	.000	.010		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	d_nmrc_c	1.128	.412	7.490	1	.006	3.089	1.377	6.926
	Constant	-5.166	1.069	23.349	1	.000	.006		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nallergy	1.897	.724	6.860	1	.009	6.667	1.612	27.572
	Constant	-5.116	1.072	22.786	1	.000	.006		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	comorbidities	-.412	.176	5.481	1	.019	.662	.469	.935
	Constant	8.483	4.694	3.267	1	.071	4831.818		

iii. Dependent variable: Referral to a specialist

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	.091	.377	.058	1	.809	1.095	.524	2.291
	Constant	-1.056	.290	13.239	1	.000	.348		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Age	-.024	.011	5.397	1	.021	.976	.956	.996
	Constant	1.856	.510	13.235	1	.000	6.398		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	d_neducat	-.725	.363	3.996	1	.046	.484	.238	.986
	Constant	1.899	.602	9.948	1	.002	6.681		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	packyears	-.056	.029	3.768	1	.052	.945	.893	1.001
	Constant	1.021	.222	21.237	1	.000	2.776		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	tff_pr2	-.020	.015	1.747	1	.186	.980	.952	1.010
	Constant	2.482	1.314	3.568	1	.059	11.963		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nbpsys	.135	.099	1.847	1	.174	1.144	.942	1.389
	Constant	-1.504	1.858	.655	1	.418	.222		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nresprt	-.028	.012	5.700	1	.017	.972	.950	.995
	Constant	4.240	1.468	8.340	1	.004	69.397		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	comorbidities	.207	.097	4.505	1	.034	1.230	1.016	1.488

	Constant	-4.967	2.702	3.380	1	.066	.007		

iv. Dependent variable: Referral for spirometry

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	-.649	.349	3.457	1	.063	.523	.264	1.036
	Constant	-.260	.256	1.026	1	.311	.771		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Age	.047	.011	17.566	1	.006	1.048	1.025	1.071
	Constant	-2.727	.550	24.601	1	.000	.065		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	d_nmarital	.449	.204	4.848	1	.028	1.566	1.051	2.336
	Constant	-1.697	.531	10.209	1	.001	.183		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	packyears	.050	.029	3.050	1	.081	1.051	.994	1.112
	Constant	-.837	.214	15.319	1	.000	.433		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	tfev_pr2	-.011	.007	2.593	1	.107	.989	.975	1.002
	Constant	.517	.724	.511	1	.475	1.678		

Variables in the Equation

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper

Step 1[a]	no2sat	-.351	.108	10.507	1	.001	.704	.569	.870
	Constant	.260	.256	1.026	1	.311	.771	-.260	.256

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nresprt	.122	.094	1.684	1	.194	1.129	.940	1.357
	Constant	-3.250	1.813	3.213	1	.073	.039		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	d_nmrc_c	.641	.240	7.143	1	.008	1.899	1.187	3.040
	Constant	-1.836	.494	13.807	1	.000	.160		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	ncough_n	-.352	.181	3.787	1	.052	.703	.493	1.003
	Constant	.532	.614	.752	1	.386	1.703		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	comorbidities	-.230	.096	5.699	1	.017	.794	.658	.960
	Constant	5.777	2.680	4.648	1	.031	322.819		

v. Dependent variable: Referral for chest x-ray

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	.858	.357	5.794	1	.016	2.359	1.173	4.746
	Constant	-.973	.285	11.692	1	.001	.378		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	BMI	.055	.024	5.364	1	.021	1.056	1.008	1.106
	Constant	-2.094	.727	8.295	1	.004	.123		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	race	-.980	.590	2.757	1	.097	.375	.118	1.193
	Constant	.638	.666	.919	1	.338	1.893		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	d_nmarital	.275	.190	2.096	1	.148	1.316	.907	1.908
	Constant	-1.098	.484	5.153	1	.023	.334		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	n2ndhand	-1.240	.794	2.441	1	.118	.289	.061	1.371
	Constant	.871	.849	1.053	1	.305	2.390		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nheartrt	-.024	.015	2.476	1	.116	.976	.948	1.006
	Constant	1.358	1.144	1.409	1	.235	3.888		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nresprt	.149	.090	2.699	1	.100	1.160	.972	1.385
	Constant	-3.290	1.740	3.576	1	.059	.037		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsputum	-.333	.176	3.578	1	.059	.717	.508	1.012
	Constant	.600	.577	1.081	1	.298	1.823		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nhosp	-.273	.142	3.703	1	.054	.761	.577	1.005
	Constant	.422	.481	.770	1	.380	1.526		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	comorbidities	-.235	.096	6.035	1	.014	.791	.655	.954
	Constant	6.092	2.664	5.228	1	.022	442.088		

APPENDIX D: Spss output summary for multivariate analysis using the backward elimination method for final models

a. Final models for patients with spirometrically-defined COPD

i. Dependent variable: Physician-diagnosed COPD (correct diagnosis)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	-.149	.263	.321	1	.573	.862	.514	1.444
	Age	.068	.027	6.395	1	.011	1.071	1.015	1.129
	nsmoking	-.766	.391	3.838	1	.050	.465	.216	1.000
	ncough_n	-.493	.311	2.505	1	.049	.611	.332	.978
	nfatigue	-1.277	.362	12.408	1	.000	.279	.137	.568
	dtotal	.110	.043	6.419	1	.011	1.116	1.025	1.216
	Constant	2.816	2.157	1.705	1	.192	16.711		

ii. Dependent variable: Physician-diagnosed asthma (misdiagnosis)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	.169	.455	.138	1	.710	1.184	.486	2.887
	d_neducat	-1.691	.479	12.475	1	.001	.184	.072	.471
	nwheeze	-.698	.287	5.919	1	.015	.497	.283	.873
	Constant	4.552	1.334	11.648	1	.001	94.799		

iii. Dependent variable: Referral to a specialist

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	.235	.553	.180	1	.671	1.265	.428	3.738
	Age	.045	.021	4.620	1	.032	1.046	1.004	1.090
	dtotal	.062	.032	3.754	1	.050	1.064	1.000	1.132
	comorbidities	-.256	.131	3.819	1	.050	.774	.599	1.000
	Constant	2.556	3.954	.418	1	.518	12.889		

iv. Dependent variable: Referral for spirometry

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	-.572	.644	.788	1	.375	.565	.160	1.994
	Age	.055	.024	5.105	1	.024	1.056	1.007	1.108
	nresprt	-.236	.105	5.026	1	.025	.790	.642	.971
	comorbidities	-.335	.151	4.932	1	.026	.715	.532	.961
	Constant	.462	2.120	.048	1	.827	1.588		

v. Dependent variable: Referral for chest x-ray

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	-.470	.606	.601	1	.438	.625	.191	2.051
	nresprt	.268	.102	6.922	1	.009	1.307	1.071	1.596
	nfatigue	-.814	.414	3.876	1	.049	.443	.197	.996
	Constant	-1.542	2.345	.433	1	.511	.214		

b. Final models for patients with spirometrically-defined asthma

i. Dependent variable: Physician-diagnosed asthma (correct diagnosis)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	-.625	.303	4.255	1	.039	.535	.295	.969
	tff_pr2	-.576	.294	3.838	1	.050	.562	.3158	1.000
	nfatigue	-.470	.239	3.867	1	.049	.625	.391	.998
	nallergy	-1.177	.552	4.546	1	.033	.308	.104	.909
	comorbidities	.223	.072	9.593	1	.002	1.250	1.085	1.4399
	Constant	-1.275	3.115	.168	1	.682	.279		

ii. Dependent variable: Physician-diagnosed COPD (misdiagnosis)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	-1.070	.833	1.649	1	.199	.343	.067	1.756
	tff_pr2	-.062	.025	5.911	1	.015	.940	.894	.988
	d_nmrc_c	1.074	.489	4.819	1	.028	2.928	1.122	7.639
	nallergy	2.557	.959	7.102	1	.008	12.894	1.967	84.530
	Constant	-2.840	2.111	1.809	1	.179	.058		

iii. Dependent variable: Referral to a specialist

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	-.138	.462	.090	1	.765	.871	.352	2.155
	packyears	-.767	.407	3.554	1	.050	.465	.209	1.000
	nresprt	-.236	.096	6.006	1	.014	.790	.654	.954

	comorbidities	-.230	.103	4.986	1	.026	.795	.650	.973
	Constant	2.312	4.534	.260	1	.610	10.099		

iv. Dependent variable: Referral for spirometry

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	-.807	.409	3.904	1	.048	.446	.200	.994
	Age	.062	.019	10.648	1	.001	1.064	1.025	1.104
	no2sat	-.034	.015	5.138	1	.025	.966	.938	.996
	ncough_n	-.357	.182	3.848	1	.050	.700	.490	.700
	d_nmrc_c	.436	.216	4.074	1	.043	1.547	1.014	2.361
	Constant	1.721	1.931	.794	1	.373	5.588		

v. Dependent variable: Referral for chest x-ray

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	nsexn(1)	.724	.354	4.183	1	.041	2.062	1.030	4.128
	BMI	.056	.025	4.993	1	.025	1.058	1.007	1.111
	nheartrt	-.036	.017	4.457	1	.035	.965	.933	.997
	nhosp	-.334	.158	4.487	1	.034	.716	.526	.975
	comorbidities	-.241	.110	4.827	1	.028	.785	.633	.974
	Constant	7.900	3.751	4.435	1	.035	26.451		