An Epidemiologic Study of Chronic Obstructive Pulmonary Disease in the United States

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Sara Chesnee Howard

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality in the United States (US), and its risk increases with age resulting in higher prevalence in aging populations like Florida. Understanding geographic disparities and predictors of COPD in such populations is useful for guiding intervention strategies. Occupational exposures increase COPD risk implying that Department of Energy (DOE) workers may have different risk profiles and comorbidity clusters than the general population. However, little is known about the disparities and these differences and yet this information may be important for guiding screening, prevention, and control programs. Therefore, the objectives of this study were to identify: (i) county-level geographic disparities and predictors of COPD in Florida, (ii) predictors of COPD occurrence and severity among DOE former workers, and (iii) comorbidity clusters and predictors of lung function changes and decline among DOE former workers.

Retrospective data were obtained from the Florida Department of Health, US Census Bureau, County Health Rankings and Roadmaps, and the National Supplemental Screening Program. High-prevalence geographic clusters were identified using Tango's flexible scan statistics. Predictors of COPD prevalence, occurrence, and severity were identified using ordinary least squares, ordinary logistic, and multinomial logistic regression, respectively. Comorbidity clusters were identified using hierarchical clustering, and predictors of lung function change and decline were identified using random forest models.

High-prevalence clusters of COPD were identified in the panhandle, north-central, and south-central counties. Counties with high percentages of smokers and asthma patients tended to have high COPD prevalence. At the individual level, smoking, asthma, age, and body mass index

were significant predictors of both COPD occurrence and severity. However, silica exposure was a significant predictor of occurrence only while diesel exhaust exposure was a significant predictor of severity only. Significant predictors of lung function were age, forced expiratory volume per second, age at hire, welding fume exposure, and silica exposure. Characteristics of the comorbidity clusters were: low prevalence of comorbidities (cluster 1), high cardiovascular disease prevalence (cluster 2), high lung cancer prevalence (cluster 3), and high prevalence of multiple comorbidities (cluster 4). Study findings are important for informing disease management programs and ultimately decreasing COPD burden.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AAT: Alpha-1 Antitrypsin

AQI: Air Quality Index

BMI: Body Mass Index

BOLD: Burden of Obstructive Lung Disease

CAT: Chronic Obstructive Pulmonary Disease Assessment Test

CI: Confidence Interval

COPD: Chronic Obstructive Pulmonary Disease

DALY: Disability Adjusted Life Years

DOE: Department of Energy

EPA: Environmental Protection Agency

FEV_1: Forced Expiratory Volume in One Second

FSSS: Flexible Spatial Scan Statistic

FWP: Former Worker Medical Screening Program

FVC: Forced Vital Capacity

GOLD: Global Initiative of Chronic Obstructive Lung Disease

ICS: Inhaled Corticosteroid

IQR: Interquartile Range

IRB: Institutional Review Board

LABA: Long-Acting Beta-Agonists

LAMA: Long-Acting Muscarinic Antagonists

LISE: Local Indicators of Spatial Associations

LLN: Lower Limit of Normal

LLR: Log Likelihood Ratio

MICE: Multivariate Imputation by Chained Equation

mMRC: Modified Medical Research Council

NSSP: National Supplemental Screening Program

OLS: Ordinary Least Squares

OR: Odds Ratio

$PM_{2.5}$: Particulate Matter 2.5

PM_{10}: Particulate Matter 10

RMSE: Root Mean Square Error

RRR: Relative Risk Ratios

RSV: Respiratory Syncytial Virus

UTK: University of Tennessee, Knoxville

US: United States

VIF: Variance Inflation Factor

ZCTA: Zip Code Tabulation Area

CHAPTER 1

Introduction and Literature Review

1.1 Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health concern with high morbidity and mortality. The condition is ranked as the third leading cause of death globally and in the top 10 causes of death in the United States (US) [1,2]. The prevalence is estimated at 2,638 cases per 100,000 persons globally [1,3] and 6.2% in the US [2,4]. The prevalence of COPD increases with advancing age from 2.7% among those 18-44 years old to 12.8% among those ≥ 65 years old [4,5]. Advancing age tends to increase the frequency of co-morbid conditions, which further complicates disease management [5]. In the US, the combined direct and indirect economic cost of COPD is estimated at $52 billion annually [6].

Several sociodemographic, environmental, and occupational factors are reported to be associated with increased COPD risk. Identifying how these factors increase the risk of COPD within aging populations may be helpful in guiding disease management and preventive strategies [7]. Approximately 4.5 million Florida residents are >65 years old, which makes it the state with one of the oldest populations in the country [8]. The state experiences one of the highest economic burdens of COPD within the US. The reported cost of the disease in the state is $3.1 billion annually [9]. Healthcare utilization due to COPD is also high with the state reporting 32.8 emergency department visits per 10,000 persons and 10.2 hospitalizations per 10,000 persons [10]. However, no studies have investigated the geographic disparities nor area-level predictors of COPD prevalence in Florida and yet this information is useful in developing intervention strategies for reducing COPD burden.

Previous studies have reported positive associations between COPD and several occupational exposures [11–13]. Occupational exposures account for 14% of all COPD cases and 31% of COPD cases in non-smokers [11]. However, studies investigating the role of occupational exposures in causing COPD remain under-recognized. Therefore, limited information is available on how these exposures impact specific disease attributes such as comorbidities or lung function changes [11]. In the general population, at least one comorbidity is reported for 80% of COPD patients. Moreover, the frequency of conditions increases with age [5,14]. Comorbidities are associated with worsening health outcomes including lung function decline, which makes comorbidities an important aspect for disease management [15]. The Department of Energy (DOE) workers are exposed to respiratory irritants (such as diesel exhaust, welding fumes, cadmium, and silica) in the course of their routine job duties. These exposures may produce differences in the risk of COPD occurrence, severity, disease progression, or comorbidities among these workers compared to the general population [16]. Thus, understanding the associations between occupational exposures and COPD among the DOE former workers may provide helpful information for preventing COPD, managing comorbidities, and controlling disease progression. Therefore, the objectives of this study were to identify: (i) county-level geographic disparities and predictors of COPD in Florida, (ii) predictors of COPD occurrence and severity among DOE former workers, and (iii) comorbidity clusters and predictors of lung function changes and decline among DOE former workers.

This dissertation includes five chapters. Chapter 1 includes a brief introduction and literature review. Chapters 2, 3, and 4 describe the methods and findings of studies addressing objectives 1, 2, and 3, respectively. Chapter 5 provides a summary of the conclusions and recommendations.

1.2 Literature Review

1.2.1 Chronic Obstructive Pulmonary Disease Overview

1.2.1.1 Definition

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease, characterized by persistent inflammation resulting in air flow limitations and ultimately reducing lung function [17]. Historically, the chronic bronchitis and emphysema components of COPD were considered separate conditions until the1960s when they were recognized as phenotypes of COPD [18,19]. Clinically, COPD is defined by spirometry, or lung function tests, that are interpreted using two different criteria. The first criterion is the Global Initiative of Chronic Obstructive Lung Disease (GOLD) criterion which uses a fixed ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) to define COPD. A ratio less than 0.70 (i.e., $FEV_1/FVC < 0.7$) is considered indicative of COPD [6]. The second criterion, referred to as the lower limit of normal (LLN) standard, identifies COPD when the ratio of FEV_1/FVC is less than the 5^{th} percentile of the normal population [20]. In clinical practice, the LLN method is often preferred because the GOLD criterion may underestimate COPD in younger populations but overestimate it in elderly populations [20]. In contrast, the LLN definition of COPD may underestimate the disease in populations where smoking is not the primary risk factor [21]. Thus, the GOLD criterion is still used in some clinical trials and epidemiologic studies [20,21].

1.2.1.2 Etiology

Chronic obstructive pulmonary disease (COPD) arises from a complex combination of genetic factors, personal behaviors, and environmental factors, and as such, both the etiology and pathogenesis are currently still areas of ongoing research [22]. Fundamentally, COPD is recognized as an accelerated lung function decline [22]. Historically, the Fletcher and Peto model

of COPD focused on rapid decline produced by physiological changes induced from exposure to respiratory irritants such as tobacco smoke, air pollution, or other fine particle exposures [23–25]. However, recent developments have recognized possible new etiological contributions to COPD including contributions from early life exposures and genetic predispositions [22,26]. Alpha-1 antitrypsin is the most widely recognized genetic marker for COPD, and it has also been associated with decreased pulmonary function and emphysema [22,23]. However, other genetic markers are still being evaluated with more than 50 genetic markers for COPD and accelerated pulmonary decline identified in a recent review [7]. Additionally, early life exposures also appear to be important for disease initiation. Pulmonary function and lung development is an intricate process that begins in utero and continues for approximately the first 20 years of life [22,23]. Thus, exposures which influence lung development may subsequently impair pulmonary function later in life leading to COPD [23]. Common factors under consideration for these early life predictors of COPD include premature birth, maternal smoking, respiratory infections, and asthma [23,27]. These newly recognized COPD etiologies suggest a time-dependent element in the interplay of genetics and external exposures that accumulate over a lifespan ultimately culminating in disease [23].

1.2.1.3 Symptoms and Disease Complications

The primary symptoms of COPD are dyspnea and chronic cough accompanied by sputum production [24,25,28,29]. Dyspnea in COPD may manifest as chest tightness, wheezing, or shortness of breath [26,28]. Patients may experience other physical manifestations of the disease that include fatigue, unintentional weight loss, swelling in extremities, sleep disturbances, and decreased physical activity [28,30]. Symptoms may have a pronounced impact on a patient's ability to perform routine tasks and as well as their quality of life. Approximately 33-50% of

COPD patients report that symptoms impair their routine daily activities, and 92.5% of patients experience at least 1 COPD symptom per week [30]. However, occurrence and severity of symptoms vary, with studies reporting seasonal and daily variability [30]. The review by Miravitilles and Ribera reports that patients experience greater respiratory symptoms in winter months due to greater risk of respiratory infections and weather conditions [30]. In clinical practice, several questionnaires for assessing the severity of COPD symptoms have been developed [29]. Some questionnaires like the COPD Assessment Test (CAT) measure the impact of symptoms on quality of while others like the modified medical Research Council dyspnea scale (mMRC) classify dyspnea impairment during routine actives [29]. The Clinical COPD questionnaire combines both symptom severity and impairment during routine activities to classify patients[29].

1.2.1.3.1 Exacerbations

During the course of the disease, patients may experience exacerbations of COPD symptoms, which are broadly defined as acute periods of worsening symptoms of dyspnea, coughing, and sputum production [31]. The GOLD report extends the definition to include a period of worsening of symptoms that require additional treatment or hospitalization [24,31]. Exacerbations may impact the general health of an individual, and they are reported to increase hospitalization and mortality risks [31]. Recent updates to the GOLD report treatment recommendations incorporated the exacerbations into the treatment planning schema, which reflects the importance of preventing these events [24]. Etiologically, the majority of exacerbations are due to bacterial or viral infections which are detected in approximately 78% of exacerbations [31]. Other possible causes for exacerbations include increased exposure to air pollution or worsening of comorbid condition(s) [31].

1.2.1.4 Diagnosis

Spirometry is used to diagnose COPD using either the GOLD criterion or the LLN standard [24]. The GOLD criterion identifies COPD when $FEV_1/FVC < 0.70$ whereas the LLN standard identifies COPD when FEV_1/FVC is less than the fifth percentile of the normal population [24,25]. In clinical practice, however, spirometry testing is only recommended for symptomatic individuals [22,29]. Clinicians may also use additional clinical tests such as chest x-rays for differential diagnosis [32].

The severity of COPD can be graded through two possible measurements: the level of obstruction and the level of dyspnea. Obstruction level is classified as mild ($FEV_1 \geq 80\%$ of predicted), moderate (FEV_1 50-79% of predicted), severe (FEV_1 30-49% of predicted), and very severe (FEV_1 <30% of predicted) [24]. The level of dyspnea can be classified using a dyspnea scale like the COPD Assessment Test (CAT) or modified Medical Research Council (mMRC) scales [24]. Both the CAT and mMRC dyspnea scales measure the impact of dyspnea on patient lives [33]. The CAT scale identifies dyspnea levels as low daily impact (score<10), medium (score 10-20), high (score 21-30), or very high (score >30) [34]. The mMRC dyspnea scale grades the level of dyspnea as 0, which indicates no dyspnea unless undertaking strenuous activity, to 5, which indicates dyspnea levels when completing daily tasks like dressing [35]. In 2024, the GOLD report proposed including the frequency and severity of exacerbations as part of the grading for COPD severity, but this proposal is still under evaluation [24].

1.2.1.5 Treatment

The treatment goals for COPD are to improve symptoms, prevent progression, improve general health status, and reduce the risk of death [6]. Thus, treatment plans may involve broader

strategies for treating comorbidities and improving general health [25,29]. These strategies may include immunizations to prevent respiratory infections, physical activity to improve general health, or other pharmacological interventions for managing specific comorbid conditions [25]. Treatments specific to COPD are recommended based on dyspnea level and exacerbations [24,25].

For patients who experience ≤1 symptom exacerbation per year that did not require hospitalization, a bronchodilator is recommended for those with low levels of dyspnea. However, both long-acting beta-agonists (LABA) and long-acting muscarinic antagonists (LAMA) are recommended for higher levels of dyspnea [24]. The combination of LAMA and LABA treatment is also recommended for patients who experience ≥2 symptom exacerbations per year or patients who are hospitalized from an exacerbation [24]. Additionally, triple combination treatment of LAMA, LABA, and an inhaled corticosteroid (ICS) is recommended for patients with increased levels of eosinophils [24]. For patients with persistent exacerbations even after the triple combination treatment of LAMA, LABAM, & ICS, macrolide or roflumilast are other treatment options. Macrolide and roflumilast are also possible treatment options for those with low eosinophil counts [24]. The roflumilast is suggested when FEV_1 <50% of predicted while the macrolide is most effective in non-smokers [24]. As the disease progresses towards end-of-life care, additional support for oxygenation may be required through oxygen therapy or non-invasive ventilation support [24].

1.2.2 Burden of Disease

1.2.2.1 Prevalence of COPD

The global prevalence of COPD is difficult to estimate due to differences in disease definitions and diagnostic criteria [36]. The most recent estimate of global age-standardized

COPD prevalence is 2,512.9 cases per 100,000 persons in 2021 [37]. Overall, the regions with the highest prevalence estimates of COPD were North America and South Asia with prevalence estimates of 3,298.9 and 3,019.1 per 100,000 persons, respectively [37]. Males and females had similar prevalence estimates at 44,027.7 per 100,000 and 41,728.0 per 100,000 persons, which Wang et al suggest could reflect changes in global smoking trends particularly in women [37]. A separate analysis in adults 30-79 years old reported the global prevalence as 10.3% using the GOLD criterion and 7.8% using the LLN standard in 2019 [38]. This equates to approximately 391.9 million and 292.0 million active cases when defined using the GOLD criterion and LLN standard, respectively [38]. Even with the restricted age range, COPD prevalence increased with advancing age based on both the GOLD criterion and the LLN standard [38]. Using the GOLD criterion, the prevalence of COPD increased from 3.8% among those 30-34 years old to 27.8% among those 75-79 years old whereas the prevalence increased from 3.6% among those 30-34 years old to 17.9% among 75-79 years old using the LLN standard [38]. The difference in GOLD criterion and LLN standard prevalence estimates for 75-79 year olds possibly reflect the potential for overclassification in elderly populations by the GOLD criterion [20]. By sex, COPD prevalence was higher in males (14.1%) compared to females (6.5%) when using the GOLD criterion [38]. However, the LLN standard produced similar prevalence estimates between the sexes with prevalence estimates of 7.8% among males and 7.5% among females [38]. Adeloye et al suggests that smoking and occupational exposure to respiratory irritants may explain the higher prevalence estimate in males compared to females using the GOLD criterion [38]. Globally, the prevalence estimates are higher in high-income countries compared to low-income countries, which Adeloye et al attributes to the generally young population in low-income countries [38]. However, they hypothesize that the prevalence estimates low-income countries

may grow as the younger population ages and experiences continued exposure to respiratory irritants like smoke from tobacco or biomass fuels [38]. By 2050, the projected global prevalence is estimated at 9.5% and represents a total of 592 million cases [39]. Low and middle income-countries and females are projected to have the highest estimated prevalence changes by 2050 [39]. These projected prevalence estimates changes reflect the population growth in low and middle-income countries as well as the exposures to both smoking and environmental exposures like biomass fuel smoke [39]. Females, especially in low and middle-income countries, are more likely to be exposed to biomass fuel smoke during cooking, which contributes to projected prevalence estimates [39].

In the US, the National Health Interview Survey reports the crude prevalence of COPD to be 4.3% in adults ≥18 years [40]. Higher crude prevalence was reported among females (4.8%) compared to males (3.8%) [40]. The overall COPD prevalence increased with age from 0.6% among those 18-34 years old, 2.1% among 35-39 years old, 6.1% among 50-64 years old, and 9.6% among those ≥65 years old [40]. Approximately 8.6% of the US unemployed population suffered from COPD compared to only 1.9% in the working population [40]. Similarly, the COPD prevalence had an inverse relationship with educational attainment. Approximately 8.8% of individuals without a high school diploma suffered from COPD compared to only 1.9% among those with college degrees [40]. In a separate analysis by Liu et al, the crude COPD prevalence within the US adult population was 6.5% and the age standardized prevalence was 6.0% [41]. Females (6.5%) also had a higher prevalence compared to males (5.5%) [41]. The employed (3.7%) population had a lower prevalence estimate compared to unemployed (7.7%), retired (11.0%), and disabled population (19.3%), which likely reflects a combination of age, smoking patterns, and other environmental exposures [41].

1.2.2.2 Economic Burden

Chronic obstructive pulmonary disease (COPD) represents a substantial challenge to the global economy, and its impact can be observed in both direct and indirect cost [42–45]. Globally, the economic cost of COPD is estimated to be $2.1 trillion annually [43,46]. However, economic costs are projected to increase to $4.236 trillion by 2050 [42]. North America, East and Central Asia, and the Pacific regions are projected to incur approximately 82.4% of the total economic burden during this time period [42]. In a meta-analysis and review of COPD cost in eleven European countries, the annual mean direct cost per person ranged from €1,715 in Spain to €10,701 in Norway [44]. Indirect costs also varied across countries which Rehman et al attributed to differences social programs and country characteristics. The annual indirect costs due to lost productivity per person ranged from €998 in Greece to € 5,735 in Germany, and the annual cost per person due to early retirements ranged from €3,695 in Sweeden to €19,031 in Germany [44]. Separately, Iheanacho et al found the direct cost of COPD to differ widely by country, likely reflecting the differences in patient characteristics, comorbidities, severity level, exacerbation frequency, healthcare systems, and social policies [43].

For the US, Guarascio et al estimated the annual direct and indirect costs of COPD to be $30 billion and $20 billion, respectively [47]. A separate analysis by Mannino et al reported a similar estimate of $31.3 billion for the annual direct cost of COPD in the US [9]. The annual direct cost estimates varied across the US with Florida incurring the highest annual direct cost of any state ($3.1 billion) [9]. Approximately 54.6% of the US annual direct costs of COPD were accounted for by females while 55.6% of the annual direct costs were incurred by patients ≥65 years old [9]. By insurance type, the public insurance programs constituted nearly $14 billion in COPD costs, with $10.8 billion attributed to Medicare claims and $3.0 billion in Medicaid

claims [9]. In comparison, private insurance companies covered $11.4 billion in COPD medical expenditure claims [9]. At the individual level, the mean annual cost for medical care was approximately $16,086 for COPD patients compared to $6,283 for general medical care cost among individuals without COPD [9]. However, this cost estimate varies by age, sex, and location [9]. Within the US working population, the total annual of COPD is approximately $5 billion, of which 59% were paid by private insurance [48]. In-patient hospital visits constituted the highest COPD-related medical cost for US workers at $27,597 per person annually [48].

Future projections anticipate a continued increase in the economic burden of COPD in the US. By 2029, Mannino et al estimates the annual cost of COPD to be $60.5 billion compared to only $33.5 billion in 2020 [9]. In a separate study, Zafari et al projected $800.9 billion in direct and $101.3 billion in indirect costs from 2019-2038 [49]. The projections varied by both age and sex. Males are estimated to account for $337.1 billion in direct costs during the same 20-year period while females are projected to contribute $463.8 billion [49]. For both males and females, the age group with the highest projected economic cost was 60-69 years at $95.1 billion for males and $125.9 billion for females [49].

1.2.2.3 Workforce Impacts

Although the burden of COPD is often measured in monetary terms, the impacts to the workforce can be measured through other standards such as absenteeism, early retirement, and physical impairment that interferes with daily tasks. In a multi-country study of working age COPD patients, 70% of the cohort were unemployed, and approximately 40% of the cohort reported early retirement due to COPD [50]. In the Burden of Obstructive Lung Disease (BOLD) study, only 36.7% of those <65 years old with obstructive pulmonary disease were employed in the past year compared 53.2% employment in those without obstructive pulmonary disease [51].

Regarding absenteeism, individuals with COPD miss a mean of 12 workdays per year compared to a mean of only 7.2 days for those without COPD [52].

In country-specific studies, comorbidities, length of disease, and higher dyspnea levels were associated with lower productivity and higher daily activity impairment in a cohort of Egyptian COPD patients [53]. After 18 months of follow-up, 78.5% of a United Kingdom cohort of COPD patients remained in full time employment while 10.6% and 10.9% transitioned to part-time or full unemployment, respectively [54]. Only 30% of working age adults (ages 35-59 years) in the Netherlands were actively employed one year after first hospitalization for COPD exacerbation [55]. In the same period, 51% reported early retirement [55]. Compared to those still actively working, cohort members who received early retirement had higher odds of hospital readmittance and mortality over the follow-up period [55]. A similar study in Denmark reported an increase in disability retirements after first hospitalization for COPD exacerbation in those with advanced, comorbidities, lower educational attainment, solo living, and advanced treatment regiments [56].

Specific to the United States (US), Blanc et al reported the population attributable fraction of COPD from occupational exposures to be 14% for all US workers, and for non-smoking US workers at 31% [13]. In a recent update from the National Health Interview Survey, approximately 27.3% of COPD cases in all workers can be attributed to occupational causes [57]. Regarding productivity, 24.3% of individuals with COPD were unable to work due to physical impairment, and nearly 50% of individuals with COPD experienced health-related activity limitation [58]. However, Patel et al reported the likelihood of absenteeism to be the same in the workforce regardless of COPD status [59]. However, workers with COPD had 2.6 times higher odds of short-term disability compared to those without COPD [59].

1.2.3 Geographic Patterns of COPD

1.2.3.1 Global Patterns

Differences in geographic distribution of COPD prevalence estimates exist [38,60–64]. Globally, the prevalence of COPD is approximately 10.3% using the GOLD criterion, and 7.6% using the LLN standard [38]. The geographic distribution is similar for high-income (10.1%) and low-to-middle income countries (10.3%) when prevalence is defined using the GOLD criterion. However, the prevalence estimates calculated with the LLN standard is higher at 9.3% in high-income countries compared to low-to-middle income countries where the prevalence is 7.3% [38]. A separate study reported that high-income countries in North America had the highest prevalence of COPD at 3,558.4 cases per 100,000 followed by countries in South Asia at 3,298.8 per 100,000 [3]. The regions with the lowest prevalence of COPD were Andean Latin America (1,382.6 per 100,000), Asia Pacific high-income countries (1,500.7 per 100,000), and eastern sub-Saharan Africa (1,503.7 per 100,000) [3]. However, Safiri et al suggests that access to healthcare services, particularly diagnostic equipment, may limit the ability to classify COPD in low-income countries and therefore it is potentially under reported [3].

Spatial variations of COPD prevalence were also reported across China with the highest prevalence occurring in Deyang City at 21.8% [65]. Three high prevalence clusters in the Sichuan, Gansu, and Shaanxi areas of China were also geographic areas with high proportions of smokers and older adults [65]. In Australia, the prevalence of COPD within the Canberra community was estimated to be 2.2%[66]. The eastern suburbs of Canberra tended to have the highest prevalence of COPD while the lowest prevalence estimates were estimated in the southeastern areas [66]. High COPD prevalence tended to occur in areas with low socioeconomic status and older residents.

In Europe, the overall COPD prevalence was estimated to be 12.3%, but regional geographic variations were not observed by Blanco et al [63]. However, Blanco et al attributed the lack of geographic variation to the limited data on COPD prevalence in some regions of Europe [63]. Within specific countries, high COPD prevalence clusters were identified in eastern, southern, and northern Norway while western Norway reported low COPD prevalence clusters [67]. The geographic distribution of COPD reflects the general pattern of most health conditions in Norway, with the western portion of the country generally having better health outcomes [67]. In northern Germany, Kauhl et al reported the prevalence to be 6.5%, and the geographic clusters of high COPD prevalence to be in west Berlin, the communities surrounding Berlin, northern Brandenberg, and northwestern Mecklenburg-West-Pomerania [68]. A separate study of COPD prevalence within Hamberg City found the prevalence to be 7.0% with high prevalence clusters in urban and socioeconomically depressed areas of east Hamberg [69].

A global review of COPD prevalence by Aaron et al reported that both Latin America and North America had higher COPD prevalence estimates compared to Northern Europe [60]. However, the study was limited by the lack of COPD prevalence information from some regions, including Latin America [60]. Similarly, a review of COPD prevalence across the Americas found the prevalence to be generally high across all regions [64]. The study reported the highest prevalence areas to be in northeastern North America and the South American areas bordering the South Atlantic Ocean [64]. However, the study suffered from limited COPD prevalence data in many South American countries and Central America, which impacted the studies ability calculate adequate prevalence estimates in these areas [64].

1.2.3.2 Pattern in the United States

Geographic variations in COPD prevalence are reported across the US with the Southeast and Appalachian regions reporting the highest regional prevalence estimates [4]. Specifically, West Virgina (13.8%), Kentucky (11.3%), and Alabama (10.1%) had the highest state-level COPD prevalence estimates [4]. At the county-level, rural counties (8.2%) tended to have higher COPD prevalence than urban counties (4.7%) across the US [70]. McDaniel et al compared the county-level geographic distribution of COPD prevalence and reported that many of the highest prevalent areas were located in Appalachian counties [71].

For studies within individual states, Lipton et al found geographic variations of COPD hospitalization rates at the zip code tabulation area (ZCTAs) level in California. Areas with the highest COPD hospitalization rates occurred in the central valley and northern California [72]. Hotspots of COPD hospital claims were also identified in Los Angeles region, and these areas tended to have lower socioeconomic status, higher proportions of Hispanic residents, and higher proportions of immigrants [72]. In a separate study, high COPD hospitalization rates were found in central valley, southern, and northern regions of California, and areas of high hospitalization tended to occur in areas of high socioeconomic depression and high minority populations[73]. In Texas, the central east region had the highest COPD hospitalization rates while non-metropolitan counties tended to have higher COPD hospitalization rates in comparison to metropolitan counties [74]. Farah et al identified both hot and cold spots of COPD hospitalizations in Maine. The coastal areas between Portland and Rockport contained the majority of the cold-spots of COPD hospitalization while hotspots tended to occur primarily in areas of high population in Maine [75].

At the neighborhood level, areas of high COPD hospitalizations rates were identified in southern Illinois while areas of low COPD hospitalizations rates were reported in the northern Chicago suburbs and Springfield [76]. Hotspots of high COPD hospitalizations and high air pollution were identified in Peoria, Springfield, and Metro East [76]. In an analysis in Jefferson County, Alabama, neighborhoods with higher COPD prevalence tended to be located near toxic release facilities within the county [77].

1.2.3.3 Temporal Patterns

Overall, the temporal trends of COPD prevalence remained relatively stable. From 1990 to 2021, the global COPD prevalence decreased by 1.5% [37]. Regional changes in COPD prevalence were observed for several geographic locations. North Africa and the Middle East experienced 19.4% increase in COPD prevalence, which was the largest of any geographic region [37]. However, several regions reported declines in prevalence including Australasia with a decline of 23.1% followed by high-income Pacific Asia and Eastern Europe with declines of 12.7% and 11.4%, respectively [37]. Similar trends were reported by Safiri et al in their comparison of COPD prevalence from 1990 to 2019 which reported a global decrease of 8.7% [3]. North Africa and the Middle East reported the highest regional increase of COPD prevalence at 30.6% while Eastern Europe recorded the largest decrease in COPD prevalence at 29.5% [3]. Safiri et al hypothesize that the changes in COPD prevalence were likely due to multiple factors including widespread implementation of smoking restrictions, enhanced public awareness of prevention strategies, increased diagnostic availability, and enhanced safety practices for reducing exposure to respiratory irritants [3]. Conversely, a comparison of temporal trends from 1990 to 2017 by Sorinano et al reported an increase in COPD prevalence for high income countries with estimates increasing from 4.4% in 1990 to 5.9% in 2017. The largest regional

increases were reported for Latin America and the Caribbean followed by North Africa and the Middle East [61]. Sorinano et al attributed the observed increases in COPD prevalence to increased life expectancy, especially in high income countries, and improvements in diagnostic availability [61].

In the US, the COPD prevalence trends remained similar from 2011 to 2021 with estimated prevalences of 6.1% and 6.0%, respectively [41]. The prevalence by age category remained constant across the 10-year period while the prevalence in females decreased from 6.9% to 6.5% [41]. However, the COPD prevalence in both current and former smokers increased during the 10-year period. The prevalence of COPD in current smokers increased from 13.7% in 2011 to 16.2% in 2021 while the prevalence in former smokers increased from 7.0% to 7.7% [41]. The prevalence in retirees increased 8.5% to 11.0% in 2021 [41].

Seasonal variations, primarily related to symptom exacerbations, have also been reported with COPD [78]. In a study of COPD in 42 countries, the risk of exacerbation was nearly double during the winter months for non-tropical countries [79]. This trend was hypothesized to reflect the seasonal trends of infectious respiratory illnesses and lower temperatures compared to the summer month which typically leads physical activity reductions and increased indoor activities [79]. A separate study reported the monthly exacerbation rate to be >2 times higher in the winter compared to the summer and persisted regardless of patient demographics, disease severity, or comorbidities [80]. In tropical climates whose temperature fluctuations are minimal, the exacerbation seasonal trends tend to follow the patterns of the rainy season, which also coincides with higher risk of respiratory infection [78]. During the COVID-19 pandemic, however, the seasonal trends of COPD symptom exacerbation inverted with higher exacerbation hospitalizations occurring in the summer compared to the winter [81]. The authors attributed the

change in trend to the public health initiatives for reducing respiratory infections, specifically COVID, and the lessening of the public health restrictions in the summer months [81].

1.2.4 Risk factors of COPD

1.2.4.1 Non-modifiable Risk Factors

1.2.4.1.1 Age

Advanced age is widely recognized as an important factor in lung function. Regardless of the disease state, lung function is expected to change over a lifespan, with lung function increasing until early adulthood when a natural decline occurs [82]. Mechanistically, this decline is thought to be driven by declines in respiratory muscles, elasticity, and gas exchange produced by aging [83]. However, the natural lung function trajectory can be altered through other factors that can accelerate decline leading to COPD, which makes age a risk factor for COPD [83,84].

1.2.4.1.2 Genetic Risk Factors

For >25 years, genetic mutations have been assessed as possible risk factors for COPD, and alpha-1 antitrypsin (AAT) deficiency remains the most broadly recognized genetic risk factor [85]. The AAT inhibits leukocyte elastase in neutrophils, which results in a malformation to the AAT structure from a change in an amino acid [85]. Ultimately, this reduces the amount of AAT available for regulation of the leukocyte elastase, which increases the risk of COPD [85]. In the United States, severe AAT dysfunction occurs in only 1 per 3,000 persons [85]. Thus, active research into other genetic factors is ongoing, which one review listing >50 possible genetic risk factors [7].

1.2.4.1.3 Early Life Exposures

Before aging can occur, in-utero and early life exposures may impact COPD risk. Specifically, pre-mature birth and low birth weight have been identified as possible risk factors for COPD [86–89]. A meta-analysis reported the odds of COPD development for those with a low birth weight were 58% higher compared to those with a normal birth weight [86]. However, the same increase was not reported for pre-term birth in the same meta-analysis [86]. In individual studies, the odds of COPD development from age 30-50 years were 7.4 times higher in those born before 28 weeks gestation compared to those with full term birth and 3.2 times higher in those born between 28-31 weeks [89]. The risk of COPD in adulthood was 21% higher in individuals with a birthweight <2.86 kg compared to individuals with normal birth weights [87]. Moreover, the risk of COPD was higher in those exposed to maternal smoking as well as in individuals who passively smoked and were younger ages [87]. In a recent meta-analysis, the odds of COPD in adulthood increased by 42% in individuals exposed to maternal smoking either in-utero or post-natal [86]. Separately, the odds of COPD were higher after exposure to maternal tobacco smoke for both in-utero (36%) and post-natal (50%) exposure scenarios compared to individuals who were not exposed to maternal tobacco smoke [86]. Maternal smoking is an important indicator for lung development and can lead to deleterious health outcomes during pregnancy, including both pre-term birth and low birth weight [87,90]. In the US, 5.4% of women reported smoking during pregnancy while 12.0% and 7.2% reported smoking pre- and post-pregnancy, respectively [91]. Similarly, maternal smoking can increase the risk of childhood asthma which further increases the risk of adulthood COPD development [90,92]. A meta-analysis of childhood asthma and COPD reported the odds of COPD in individuals with childhood asthma to be 3 times higher than the odds in those without childhood asthma [92].

However, the odds of COPD were 7.8 times higher in those with a history of asthma, either childhood or adult onset, than those without a history of asthma in a separate meta-analysis [93].

1.2.4.1.4 Changes in Lung Function

Irrespective of COPD development, lung function is expected to change over the course of a normal lifespan as a natural consequence of aging due to the modification of pulmonary characteristics including reductions in respiratory strength, elasticity, or alveolar surface area [83]. The expected median annual decline in FEV_1 after reaching peak function is estimated to be 29.2 mL per year with a range of 9.9-56.0 mL per year [83]. Traditionally, an accelerated decline in lung function which deviates from the normal trajectory has been a characteristic of COPD [94,95]. However, only between 40% and 50% of COPD cases fit this lung function trajectory [82]. Recently, a second possible COPD lung function trajectory has emerged, which is hypothesized to be derived from in-utero or childhood exposures and inherited susceptibility [82,95]. In this trajectory, individuals fail to reach a normal peak lung function in early adulthood but experience a slower rate of lung function decline than the typical COPD trajectory [82,95]. Instead, these individuals experience a rate of decline more similar to that of normal aging [82]. Although both lung trajectories comprise COPD patients, rapid lung function decline is reported to be significantly associated with higher mortality compared to those with slower lung function decline [82].

1.2.4.2 Modifiable Risk Factors

1.2.4.2.1 Sociodemographic and Behavioral Factors

Smoking is widely recognized as a risk factor for COPD [6,95,96]. In a recent review, Holtjer et al reported the odds of COPD in smokers ranged from 2.89 to 5.50 times the odds in non-smokers [97]. However, it is estimated that between 25% and 45% of individuals with

COPD are non-smokers [98], and less than 50% of smokers develop COPD [6]. Sex differences in COPD are often observed with males generally having a higher risk of COPD compared to females [99]. Historically, the higher prevalence of COPD in males compared to females was attributed to sex-specific differences in smoking patterns [99]. However, females, especially in low- or middle-income countries, are more likely to be exposed to poor indoor air quality from burning biomass fuel for cooking, which increases the risk of COPD [100]. According to a review by DeMeo, females experience COPD earlier in life, suffer from different comorbidities, experience more severe COPD symptoms, and worse long-term outcomes than males [99].

Poor nutrition and body composition are also possible risk factors for COPD although the association appears to be paradoxical [96,101–103]. Nutrition deficiency and low body weight commonly occur among COPD patients [102]. At higher severity levels, the mortality risk is higher in COPD patients with low body weight compared to high body weight [103]. However, the mortality risk is higher for COPD patients with high body weight at less severe stages of COPD [103]. The nutritional value of dietary intakes is also important in COPD risk [101]. The risk of COPD is higher by approximately 40% for those with diets that include high intakes of red meat compared to those with normal dietary intakes of red meat [101]. Individuals with diets high in fruits and vegetables may have lower risk of COPD compared those with lower dietary intakes of fruits and vegetables [101]. The mechanism driving these associations is not well understood, but Beijers et al hypothesized that the paradoxical association between weight and mortality risk may be due to reduced muscle mass or distribution of body fat [103].

1.2.4.2.2 Environmental

1.2.4.2.2.1 Occupational Exposures

Occupational exposures have been identified as possible risk factors for obstructive pulmonary dysfunction from as early as the nineteenth century [11]. Common occupational exposures include particulate matter, silica, cadmium, welding fumes, deiseal exhaust, pesticides, chemical cleaners, biomass fuels, cement dust, general dust, and the combined exposure of vapors, dusts, and gases [11,13,104–107]. Regardless of the source, an estimated 143.02 DAILYs per 100,000 persons and 6.61 deaths per 100,000 persons are attributed to occupationally related COPD [108]. In total, occupational exposures are estimated to account for approximately 14% of all COPD cases [13,108]. A recent review of meta-analyses of COPD risk factors reported the meta-analysis derived odds ratios from all occupational exposure to range from 0.97 to 1.79 [97]. Within the US, the odds of COPD were higher after exposure to several occupational exposures including mineral dust, sensitizers, diesel exhaust, and general vapors and gases [109]. The US Health and Retirement Study reported increased risk of COPD in retirement age populations across multiple occupations including laborers, famers, maids, mechanics, and equipment operators [110].

Regardless of the possible exposure agent, the biological mechanism linking occupational exposures and COPD remains unclear. In fact, occupationally related COPD is still considered to be an under-recognized aspect of the disease [11–13,111]. De Matteis attributes this under recognition to a lack of centralized surveillance of occupational respiratory hazards as well as the general under-reporting of occupational conditions [12]. Additionally, the lack of standardized measurements for occupational exposures across epidemiologic studies likely contributes to the under-recognition of the disease as well [98,111].

1.2.4.2.2.2 Air Quality

Studies investigating the role of air quality in COPD have produced inconsistent results [89,92,104–110]. Sin et al attributes the inconsistency to the limited agreement on the definition of poor air quality or pollution used across studies [112]. The primary source of exposure for poor indoor air quality is thought to be biomass fuel combustion for cooking or heating residential areas although other common household products like chemicals found in cleaning supplies may also contribute to poor air quality [97,100,113,114]. Women, particularly in low- and middle-income countries, are the most affected by this source of exposure [115,116]. This potentially explains why low- and middle-income countries account for over 90% of COPD mortality, and more than 75% of these deaths are women [100]. Overall, Pathak et al reported a pooled risk of COPD from biomass exposure to be 2.38 times higher than that of the pooled controls in a meta-analysis of 24 studies. [100]. The review by Raju et al also reported increases in COPD in low- and middle-income countries from indoor air pollution, but they suggested more evidence was needed before confirming a causative relationship [113].

As for poor outdoor air quality, traffic patterns, weather conditions, and wildfires contribute to ambient air conditions through the release of particulate matter or other noxious substances that can impact respiratory health [117]. However, the association between outdoor air pollution and COPD risk is less well defined [115,117,118]. In a report produced by the American Thoracic Society, Thurston et al concluded that the evidence of an association between COPD and traffic induced air pollution is inadequate as the strongest support is provided from meta-analyses [118]. However, they noted that the few published animal studies simulating ambient air pollution produced pulmonary damage consistent with COPD development, which is suggestive of a possible risk factor [118]. Additionally, Sin et al reported an 18% increase in

COPD after particulate matter 2.5 ($PM_{2.5}$) exposures increased by 10 $\mu g/m^3$ [112,117]. However, they also concluded that the causal association between air pollution and COPD lacked sufficient evidence due to the presence of confounding and biases inherent in observational studies [112]. Thus, air quality, both indoor and outdoor, represents areas of further COPD research.

1.2.4.2.3 Respiratory Infections

Serious childhood respiratory infections increase the odds of COPD development. In a recent meta-analysis, the odds of COPD development are 2.2 times higher in those who experience serious childhood respiratory illnesses like pneumonia or bronchitis than individuals with no serious childhood respiratory illness [86]. Although the mechanism for this association is unknown, Duan et al provide two possible hypotheses [86]. First, an inherited lung function abnormality increases both the risk of acute respiratory illness and COPD [86]. In the second hypothesis, COPD develops from inflammation resulting from serious respiratory infections [86]. In adulthood, respiratory illnesses also increase the risk of exacerbations in those with COPD. Estimates of exacerbations attributed to either viral or bacterial respiratory infections can be as high as 80% [119]. More conservative estimates suggest that viral infections account for approximately 30% of exacerbations while bacterial infections account for 5-10% [120].

1.2.4.2.4 Comorbidities

Co-occurring conditions, or comorbidities, are common among those suffering from COPD, regardless of severity level [24]. An accurate prevalence of comorbidities is difficult to ascertain due to overlapping risk factors, underdiagnosis of both COPD and comorbidities, and shared clinical characteristics between the disease [121]. However, the estimated prevalence of at least one comorbid condition is estimated to be around 80% or higher [14,25,121]. In a survey of COPD patients in the United States (US), approximately 46% of women and 48% of men

suffered from 6-10 comorbid conditions, and only 15% of women and 24% of men suffered from <6 comorbidities [122]. The prevalence and types of commodities tend to increase with advancing age [5]. The most common types of comorbidities include metabolic disorders like diabetes, cardiovascular diseases including hypertension, cognitive impairment, anxiety, depression, skeletal and muscle dysfunction such as osteoporosis, gastrointestinal diseases, lung cancer, and other respiratory conditions including asthma and pulmonary fibrosis [123]. Although the biological mechanism for comorbidity development is still unclear, leading theories suggest a combination of chronic systemic inflammation, genetic susceptibility, or shared risk factors [123]. The presence of comorbidities has been associated with poor health outcomes in COPD patients regardless of the type of co-occurring condition. Overall, COPD patients with comorbid conditions experience lower quality of life, more frequent hospitalizations, and higher mortality risk than those without comorbidities [121,123].

1.2.5 Prevention and Control

Prevention and control efforts for COPD are multifaceted reflecting the complex nature of the disease and the variety of risk factors [24]. Prevention and control efforts should focus on risk factors which are modifiable to prevent both the initiation and progression of the disease. One of the best recognized ways to prevent COPD and its progression is the removal of airway irritants, specifically, smoking cession for current smokers, and the avoidance of occupational related hazards or air pollution where possible [24]. Additionally, ensuring vaccination against respiratory illnesses could help prevent severe disease or exacerbations in those with COPD [24]. The influenza and pneumococcal vaccinations are specifically recommended by GOLD report, but they also suggest following country and physician guidelines for other respiratory illnesses including respiratory syncytial virus (RSV) and COVID-19 [24]. Other control activities involve

physical activity and pulmonary rehabilitation as needed. Both can aid in improving lung function and preventing further decline [24].

CHAPTER 2

Spatial patterns and sociodemographic predictors of chronic obstructive pulmonary disease in Florida

Spatial patterns and sociodemographic predictors of chronic obstructive pulmonary disease in Florida

Sara C Howard[1], Agricola Odoi[1]

[1]Department of Biomedical and Diagnostic Sciences, University of Tennessee, Knoxville, TN, United States

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My contribution to this research includes conceptual design, data analysis, and manuscript writing.

2.1 Abstract

Background. Chronic Obstructive Pulmonary Disease (COPD) is a chronic, inflammatory respiratory disease that obstructs airflow and decreases lung function and is a leading cause death globally. In the United States (US), the prevalence among adults is 6.2%, but increases with age to 12.8% among those 65 years or older. Florida has one of the largest populations of older adults in the US, accounting for 4.5 million adults 65 years or older. This makes Florida an ideal geographic location for investigating COPD as disease prevalence increases with age. Understanding the geographic disparities in COPD and potential associations between its disparities and environmental factors as well as population characteristics is useful in guiding intervention strategies. Thus, the objectives of this study are to investigate county-level geographic disparities of COPD prevalence in Florida and identify county-level socio-demographic predictors of COPD prevalence.

Methods. This ecological study was performed in Florida using data obtained from the US Census Bureau, Florida Health CHARTS, and County Health Rankings and Roadmaps. County-level COPD prevalence for 2019 was age-standardized using the direct method and 2020 US population as the standard population. High-prevalence spatial clusters of COPD were identified using Tango's flexible spatial scan statistics. Predictors of county-level COPD prevalence were investigated using multivariable ordinary least squares model built using backwards elimination approach. Multicollinearity of regression coefficients was assessed using variance inflation factor. Shapiro-Wilks, Breusch Pagan, and Robust Lagrange Multiplier tests were used to assess for normality, homoskedasticity, and spatial autocorrelation of model residuals, respectively.

Results. County-level age-adjusted COPD prevalence ranged from 4.7% (Miami-Dade) to 16.9% (Baker and Bradford) with a median prevalence of 9.6%. A total of 6 high-prevalence

clusters with prevalence ratios >1.2 were identified. The primary cluster, which was also the largest geographic cluster that included 13 counties, stretched from Nassau County in north-central Florida to Charlotte County in south-central Florida. However, cluster 2 had the highest prevalence ratio (1.68) and included 10 counties in north-central Florida. Together, the primary cluster and cluster 2 covered most of the counties in north-central Florida. Significant predictors of county-level COPD prevalence were county-level percentage of residents with asthma and the percentage of current smokers.

Conclusions. There is evidence of spatial clusters of COPD prevalence in Florida. These patterns are explained, in part, by differences in distribution of some health behaviors (smoking) and co-morbidities (asthma). This information is important for guiding intervention efforts to address the condition, reduce health disparities, and improve population health.

2.2 Background

Chronic Obstructive Pulmonary Disease (COPD) is a chronic respiratory condition in which inflammation obstructs airflow and decreases lung function [17]. Globally, COPD was ranked as the third leading cause of death in 2019 [1] and had a prevalence of 2,638.2 cases per 100,000 people in 2019 [3]. In the United States (US), the prevalence among adults is 6.2%, but increases with age to 12.8% among those 65 years or older [4]. The condition is ranked among the top 10 causes of death in the US [2]. Economically, the financial costs of COPD are steadily increasing. From 2002 to 2010, the annual direct cost of COPD in the US increased from $18 billion to $29.5 billion [15], and more recent calculations estimate the annual direct cost at $32 billion [47].

Several environmental and sociodemographic factors have been shown to be associated with COPD including air pollutants [7], rurality [70,124], and poverty [7,124]. Chronic exposure

to outdoor air pollutants including particulate matter 2.5 ($PM_{2.5}$) have been shown to reduce lung function and increase COPD risk [7]. Interestingly, COPD prevalence is reportedly higher in rural areas (8.2%) compared to metropolitan areas (4.7%) [70]. This is surprising because rural areas tend to have better air quality with the mean total number of $PM_{2.5}$ days greater than the US Environmental Protection Agency's National Ambient Air Quality Standard at 0.95 days compared to 11.21 days in metropolitan areas [125]. However, rural communities often suffer from poor indoor air quality, including exposure to second-hand smoke and solid fuels used as heating sources. Populations in rural areas may also participate in occupations such as mining that increase risk of harmful respiratory exposures that may contribute to higher COPD prevalence [70,124,126]. Other sociodemographic characteristics such as poverty have been reported to be associated with higher COPD prevalence including both community-level poverty (OR: 1.12, 95% CI: 1.03-1.32) and household poverty (OR: 1.08, 95% CI: 1.06-1.10) [124].

In the US, Florida has one of the largest populations of older adult residents, accounting for 4.5 million adults 65 years or older [8], which makes Florida an ideal geographic location for investigating COPD since disease prevalence increases with age [4]. In 2021, COPD resulted in 77,506 emergency department visits and 25,405 hospitalizations in Florida [10]. These frequencies equate to an age-adjusted prevalence of 32.8 COPD related emergency room visits per 10,000 persons, and 10.2 COPD related hospitalizations per 10,000 persons [10]. However, even with an older state population and the reported burden of COPD in Florida, there is limited information on the association between COPD and environmental factors and population characteristics in Florida. No studies have examined the association between COPD and area-level characteristics such as environmental and sociodemographic factors in the state. These types of area-level studies are useful for not only identifying predictors of COPD risk but also in

identifying possible geographic disparities. The information gleaned from such studies can be helpful in the creation of targeted public health prevention and control efforts. Thus, the objectives of this study were to investigate county-level spatial patterns of COPD prevalence in Florida and identify county-level sociodemographic predictors of the identified spatial patterns of COPD prevalence.

2.3 Materials & Methods

2.3.1 Ethical Statement

This study was reviewed by the University of Tennessee, Knoxville Institutional Review Board which determined that it was not human subjects' research (IRB Number: UTK IRB-23-07928-XM). Therefore, it determined that IRB oversight was not required.

2.3.2 Study Area

This ecological study was performed in Florida, which has an estimated population of 21.2 million people [127] spread across 67 counties, 44.7% of which are considered rural [128]. The most populated county is Miami-Dade with 2,830,500 residents, and the least populated is Lafayette County with 8,613 residents [129]. Approximately 80.1% of the Florida residents are at least 18 years old [127]. Of these, 41.6% are 18-44 years old, 32.8% are 45-64 years old, and 25.6% are ≥65 years old [127]. Florida has a slightly lower percentage of males (48.9%) compared to females (51.1%) [129]. Individuals of white race account for 76.9% of the population whereas those who are black account for 17.0% and other races account for 6.0% [127]. Residents of Hispanic or Latino ethnicity comprise 26.8% of the population [127].

2.3.3 Data Sources

The 2019 county-level crude prevalence of COPD for each age group (18-44 years old, 45-64 years old, and ≥65 years old) were obtained from Florida Health CHARTS [129].

Sociodemographic variables investigated for possible association with county-level COPD prevalence were also downloaded from Florida Health CHARTS [129] and County Health Rankings and Roadmaps (**Table 2.1**) [130]. Cartographic boundary files, for map generation, were obtained from the United States Census Bureau TIGER Geodatabase [131].

Table 2.1. Potential Predictors of Chronic Obstructive Pulmonary Disease Prevalence

Variable Theme	Variable
Health	% Asthma Diagnosis
Smoking	% Current Smokers
	% Former Smokers
	% Never Smokers
Economic	% Individuals Below Poverty Line
	% Families Below Poverty Line
	Median Household Income
Sex	% Male
	% Female
Race and Ethnicity	% White Hispanic
	% White Non-Hispanic
	% Non-White Hispanic
	% Non-White Non-Hispanic
Geographic	% Rural
	Mean Daily Particulate Matter 2.5 ($PM_{2.5}$)

2.3.4 Descriptive Analyses and Data Preparation

All descriptive analyses and data preparation were performed using RStudio 2021.09.2 [132] interface of R version 4.0.4 [133]. County-level COPD prevalence was age-standardized using the direct method [134] and 2020 United States population as the standard population [135]. The normality distribution of continuous variables was assessed using the Shapiro-Wilks test [136]. Since the majority of the continuous variables were not normally distributed, medians and interquartile ranges were reported for all continuous variables.

2.3.5 Cluster Identification and Investigation

Tango's flexible spatial scan statistic (FSSS) was used to detect and identify high-prevalence spatial clusters of COPD using FleXScan [137]. Specification of FSSS included maximum scanning window of 15 counties and Poisson probability models with a restricted log likelihood ratio (LLR) tests and an alpha of 0.2. Significance testing was performed using 999 Monte Carlo permutations and a critical p-value of 0.05. Only statistically significant clusters (p-value < 0.05) with a relative risk >1.2 were reported to avoid reporting clusters with very low relative risks. The choice of 1.2 cut-off was based on similar interpretations from previous published studies [138–140].

2.3.6 Assessment of Correlations among Potential Predictors

Spearman's rank correlation coefficient was used to identify highly correlated ($|r| \geq 0.7$) potential predictors of COPD prevalence. Only one of a pair of highly correlated variables was retained for assessment in the subsequent multivariable model. The decision of which of a pair of highly correlated variables to retain was based on biological and statistical considerations.

2.3.7 Predictors Investigation of Geographic Distribution of COPD Prevalence

Ordinary least squares (OLS) regression was used to identify county-level predictors of age-adjusted COPD prevalence using RStudio 2021.09.2 [132] interface of R version 4.0.4 [133]. A conceptual model was developed and used to guide model development and selection of variables to include in the investigation (**Figures. 2.1**). The multivariable OLS model was built in two steps. In the first step, univariable models identified potential predictors that had univariable associations with age-adjusted COPD prevalence at a relaxed critical p-value of 0.2. Only potential predictors with a p-value <0.2 were considered for investigation in the multivariable model. In the second step, a multivariable OLS model was built using manual backwards selection and a critical p-value of 0.05. A variable was considered a confounder if its removal from the OLS model resulted in a >20% change in the OLS regression coefficient of at least one of the other variables in the model. The above approach of identification was used in conjunction with the conceptual diagram shown in **Figure 2.1**. Multicollinearity was assessed using variance inflation factor (VIF) with values >10 considered indicative of multicollinearity. The Shapiro-Wilks test [136] and the Breusch Pagan tests [141] were used to assess normality of residuals and heteroskedasticity, respectively [134]. The VIF, Shapiro-Wilks test, and Breusch Pagan test were all implemented in R version 4.0.4 [133] with the RStudio version 2021.09.2 [132] interface. Robust Lagrange Multiplier test, implemented in GeoDa [142], using queen weights was used to assess spatial autocorrelation of model residuals.

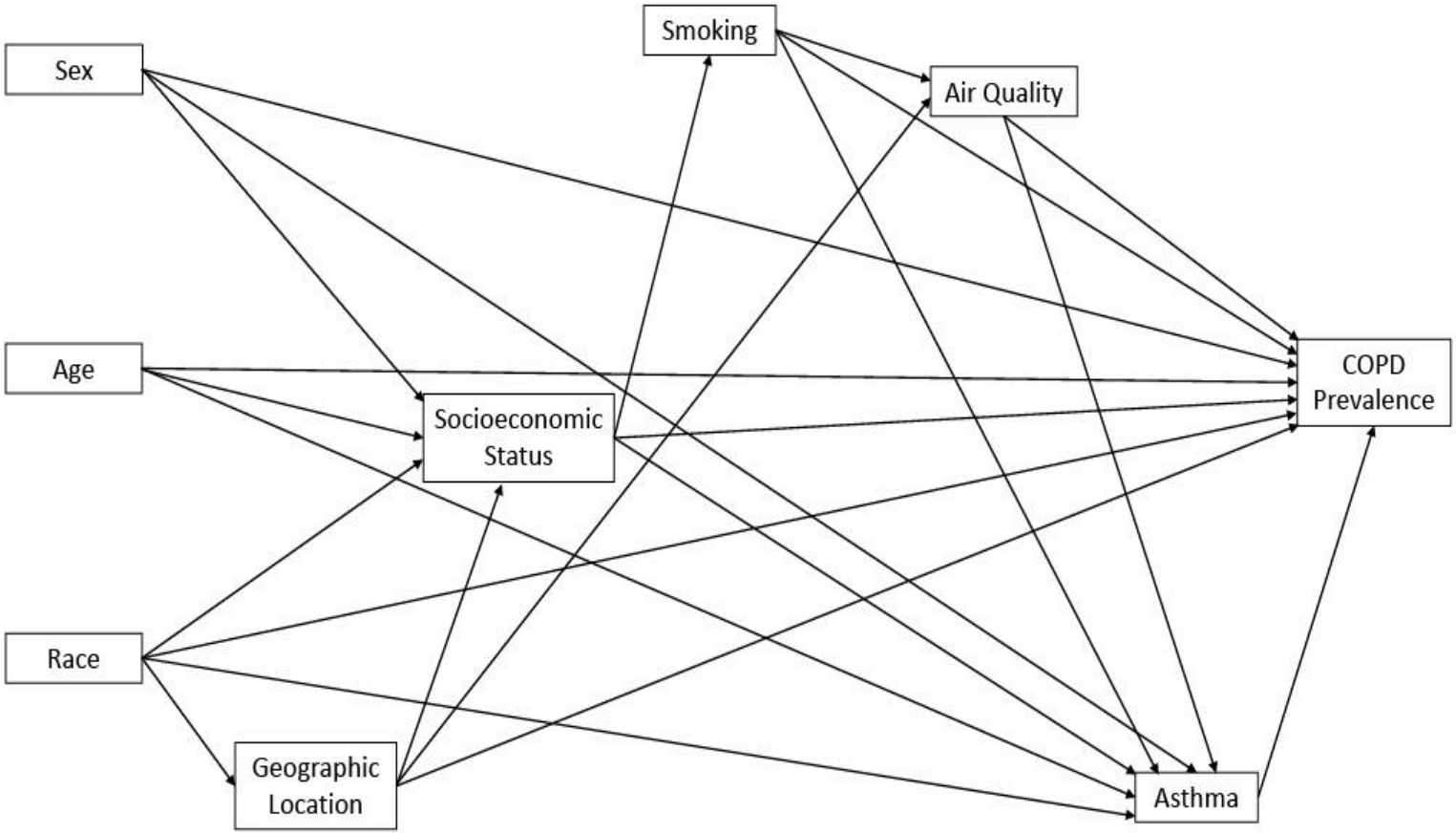

Figure 2.1 Conceptual model representing predictors of chronic obstructive pulmonary disease in Florida.

2.3.8 Cartographic displays

All cartographic displays were generated in ArGIS [143]. The spatial distribution of county-level age-adjusted COPD prevalence as well as its significant county-level predictors were displayed in choropleth maps. The critical intervals of the choropleth maps were determined using Jenk's optimization classification scheme [144]. Spatial distribution of the identified significant high-prevalence clusters of COPD were also displayed in a map.

2.4 Results

2.4.1 Geographic Distribution of COPD Prevalence

The county-level age-adjusted COPD prevalence ranged from 4.7% (Miami-Dade) to 16.9% (Baker and Bradford) (**Figures. 2.2** and **2.3**) with a median prevalence of 9.6%. The highest prevalence proportions were observed in seven counties, six of which (Baker, Bradford, Citrus, Dixie, Lafayette, and Suwannee) were located near north-central Florida. The remaining county, Walton, was in the panhandle. The lowest prevalence was observed among seven counties, four of which (Collier, Miami-Dade, Pasco, and Sarasota) were located in the south and south-central portions of the state. Two counties (Alachua and Seminole) were in the north-central Florida, and the other county (Wakulla) was located in the panhandle area **(Figures. 2.2** and **2.3**).

2.4.2 High-prevalence Clusters of COPD

A total of 6 high-prevalence clusters with prevalence ratios >1.2 were identified (**Table 2.2** and **Figure. 2.4**). The primary cluster, which was also the largest geographic cluster with 13 counties, stretched from Nassau County in north-central Florida to Charlotte County in south-central Florida (**Figures. 2.2** and **2.4**).

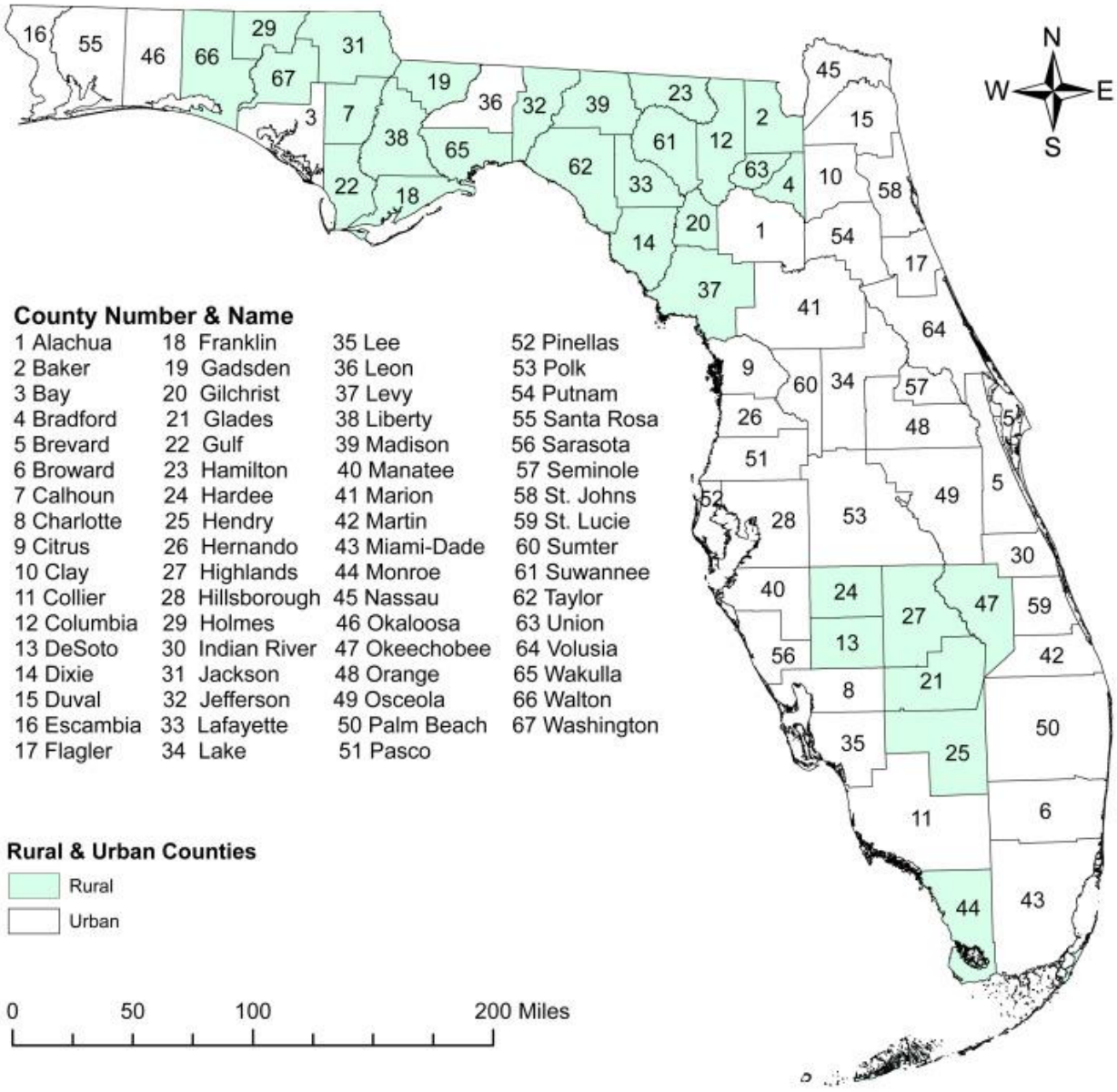

Figure 2.2 Geographic distribution of rural and urban counties in Florida.

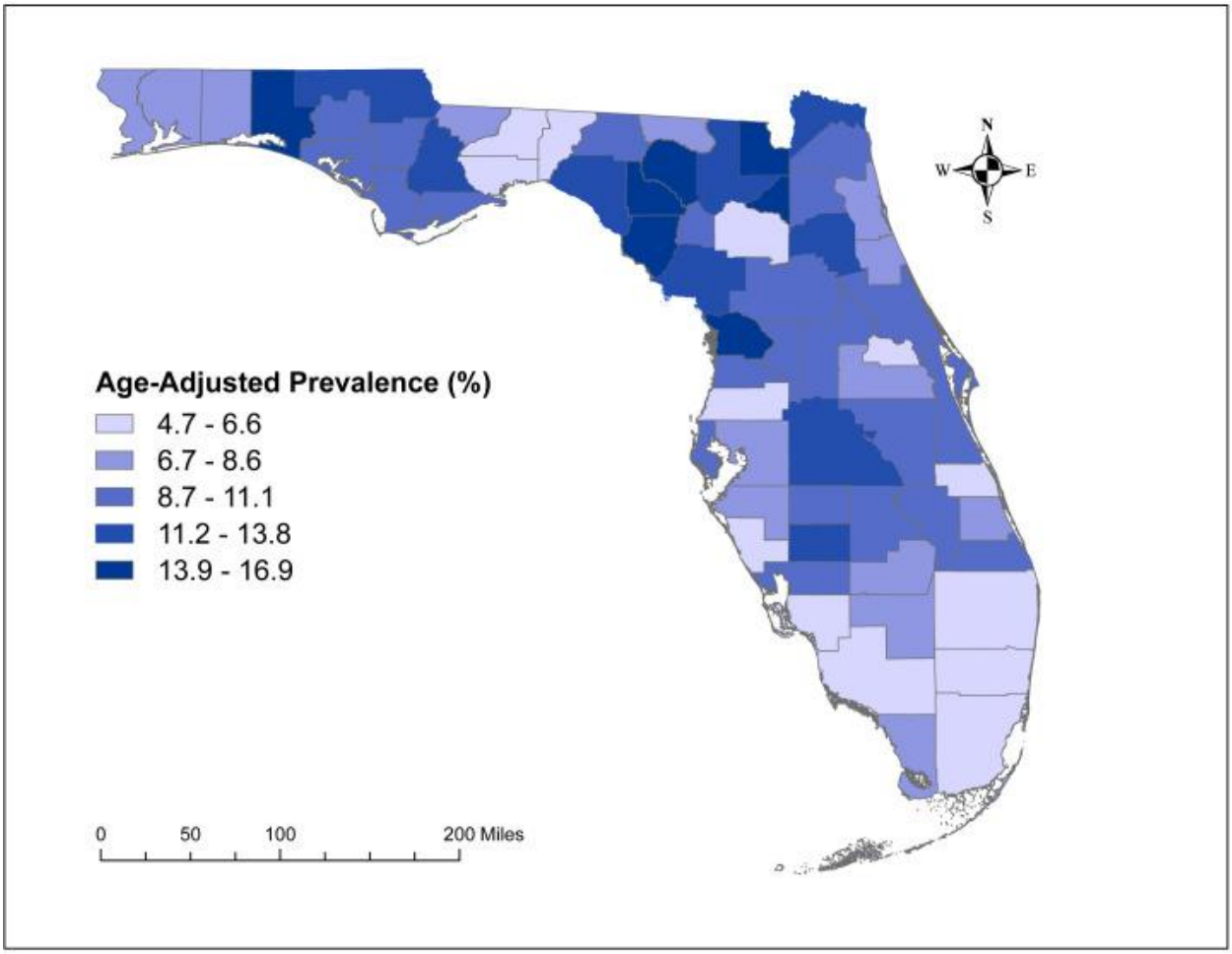

Figure 2.3 Geographic distribution of age-adjusted chronic obstructive pulmonary disease prevalence per 100 in Florida, 2019.

Table 2.2. Significant High-Prevalence Clusters of Age-Adjusted Chronic Obstructive Pulmonary Disease in Florida, 2019

Cluster	Observed Number of Cases	Expected Number of Cases	Number of Counties	Prevalence Ratio	p-value
1	334,202	243,935	13	1.37	0.001
2	74,174	44,165.7	10	1.68	0.001
3	200,116	161,968	7	1.24	0.001
4	47,200	30,564.2	7	1.54	0.001
5	94,887	75,070.9	1	1.26	0.001
6	1,914	1,496.96	1	1.28	0.001

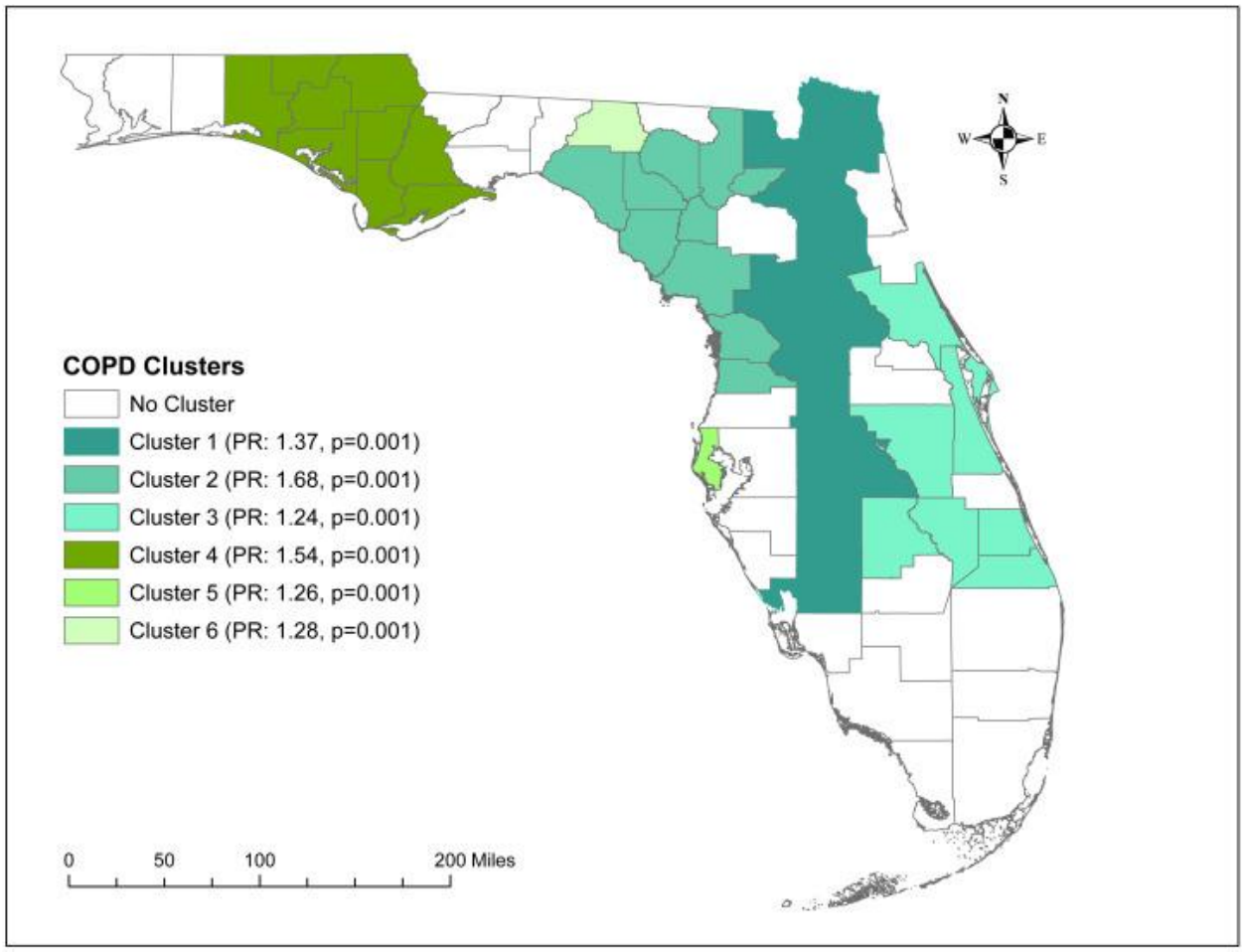

Figure 2.4 Significant clusters of age-adjusted chronic obstructive pulmonary disease Prevalence in Florida, 2019.

However, cluster 2 had the highest prevalence ratio (1.68) and included 10 counties in north-central Florida. Together, the primary cluster and cluster 2 covered most of the counties in north-central Florida (**Figures. 2.2** and **2.4**). Additionally, two other clusters (clusters 3 & 4) covering large geographic areas were identified. Cluster 3 covered 7 counties in south and south-central Florida and had a prevalence ratio of 1.24 whereas cluster 4 had a prevalence ratio of 1.54 and included 7 counties in the panhandle area.

2.4.3 Predictors of COPD Prevalence

All investigated potential predictors, except percentage of former smokers and mean daily $PM_{2.5}$, had univariable associations ($p<0.2$) with county-level COPD prevalence (**Table 2.3**) and were assessed in the multivariable model. Based on the results of the final multivariable model, only percentage of residents with asthma and percentage of current smokers were significant predictors of county-level COPD prevalence (**Table 2.4**). The percentage of non-White non-Hispanic residents was included in the final model as a confounder for the association between percentage of residents with asthma and COPD prevalence. The final multivariable OLS model accounted for 62.1% (adjusted $R^2=0.621$) of the variation in COPD prevalence and showed no evidence of non-normally of residuals (Shapiro-Wilks test $p=0.805$), multicollinearity (all VIFs<5), or heteroscedasticity of residuals (Breusch Pagan test $p=0.191$). There was also no evidence of spatial dependence of residuals based on both the robust Lagrange Multiplier tests for error (LM_{error} $p=0.646$) and lag (LM_{lag} $p=0.221$). This indicates that spatial autocorrelation is not violating model assumptions, which suggests the OLS model is appropriate for analyzing the county level data.

2.4.4 Geographic Distribution of Significant Predictors

The geographic distributions of both the percentage of individuals with asthma (**Figure. 2.5A**) and those who are current smokers (**Figure. 2.5B**) are similar to that of age-adjusted COPD prevalence (**Figure. 2.3**). Counties with the highest percentage of current smokers were primarily located in north-central Florida as well as the panhandle. However, the percentage of current smokers was fairly high across the state, with 29 counties having at least 20% current smokers. Of the counties with the seven highest COPD prevalence (Baker, Bradford, Citrus, Dixie, Lafayette, Suwannee, and Walton), all but Citrus County had more that 25% of current smokers. The similarity in the geographic distribution in the prevalence of asthma and that of COPD was less pronounced. The panhandle and north-central Florida generally had high prevalence of both asthma and COPD.

Table 2.3 Descriptive Statistics & Univariable associations between Age-Adjusted Chronic Obstructive Pulmonary Disease Prevalence and socioeconomic factors in Florida, 2019

Variable	Median	25th Quartile	75th Quartile	Unadjusted Parameter Estimate	95% Confidence Interval	p-value
% Asthma Diagnosed	13.3	11.3	14.8	0.455	0.213, 0.697	0.000372
% Current Smokers	19.3	15.7	22.3	0.465	0.373, 0.558	<0.0001
% Former Smokers	26.8	24.4	30.1	0.002	-0.142, 0.147	0.9750
% Never Smokers	52.2	48.3	57.2	-0.251	-0.340, -0.162	<0.0001
Mean Daily PM 2.5	14.6	12.1	20.0	0.4645	-0.366, 1.295	0.2679
% Individuals Below the Poverty Line	10.2	8.3	14.2	0.129	-0.016, 0.274	0.0805
% Families Below the Poverty Line	49.4	48.7	53.2	0.214	0.045, 0.382	0.0137
% Male	50.6	46.8	51.3	0.356	0.163, 0.548	0.0005
% Female	8.6	5.0	18.1	-0.356	-0.548, -0.163	0.0005
% White Hispanic	71.3	59.8	77.5	-0.092	-0.149, -0.036	0.0018
% White Non-Hispanic	1.2	0.9	1.8	0.085	0.041, 0.123	0.0003
% Non-White Hispanic	16.2	11.7	22.0	-1.089	-1.807, -0.372	0.0035
% Non-White Non-Hispanic	23.8	8.5	67.5	-0.057	-0.135, 0.022	0.1560
% Median Household Income	53,023.0	43,644.0	60,264.5	-0.0001	-0.0002, -3.121	0.0042
% Rural Population	7.7	7.0	9.1	0.023	0.0001, 0.046	0.0493

Table 2.4 Significant Predictors Age-Adjusted Chronic Obstructive Pulmonary Disease Prevalence in Florida, 2019

Variable	Adjusted Parameter Estimate	95% Confidence Interval	p-value
% Asthma Diagnosis	0.200	0.004, 0.396	0.0457
% Current Smoker	0.408	0.305, 0.512	<0.0001
% Non-White Non-Hispanic*	-0.047	-0.101, 0.007	0.0858

* Included as a confounder for % of asthma diagnosis

2.4.5 Geographic Distribution of Significant Predictors

The geographic distributions of both the percentage of individuals with asthma (**Figure. 2.5A**) and those who are current smokers (**Figure. 2.5B**) are similar to that of age-adjusted COPD prevalence (**Figure. 2.3**). Counties with the highest percentage of current smokers were primarily located in north-central Florida as well as the panhandle. However, the percentage of current smokers was fairly high across the state, with 29 counties having at least 20% current smokers. Of the counties with the seven highest COPD prevalence (Baker, Bradford, Citrus, Dixie, Lafayette, Suwannee, and Walton), all but Citrus County had more that 25% of current smokers. The similarity in the geographic distribution in the prevalence of asthma and that of COPD was less pronounced. The panhandle and north-central Florida generally had high prevalence of both asthma and COPD.

2.5 Discussion

This study investigated geographic clusters and county-level predictors of COPD prevalence in Florida. The results suggest that COPD prevalence varies across geographic areas, which is consistent with the results from other ecological studies of COPD in the US [4,64,70,72,73,75].

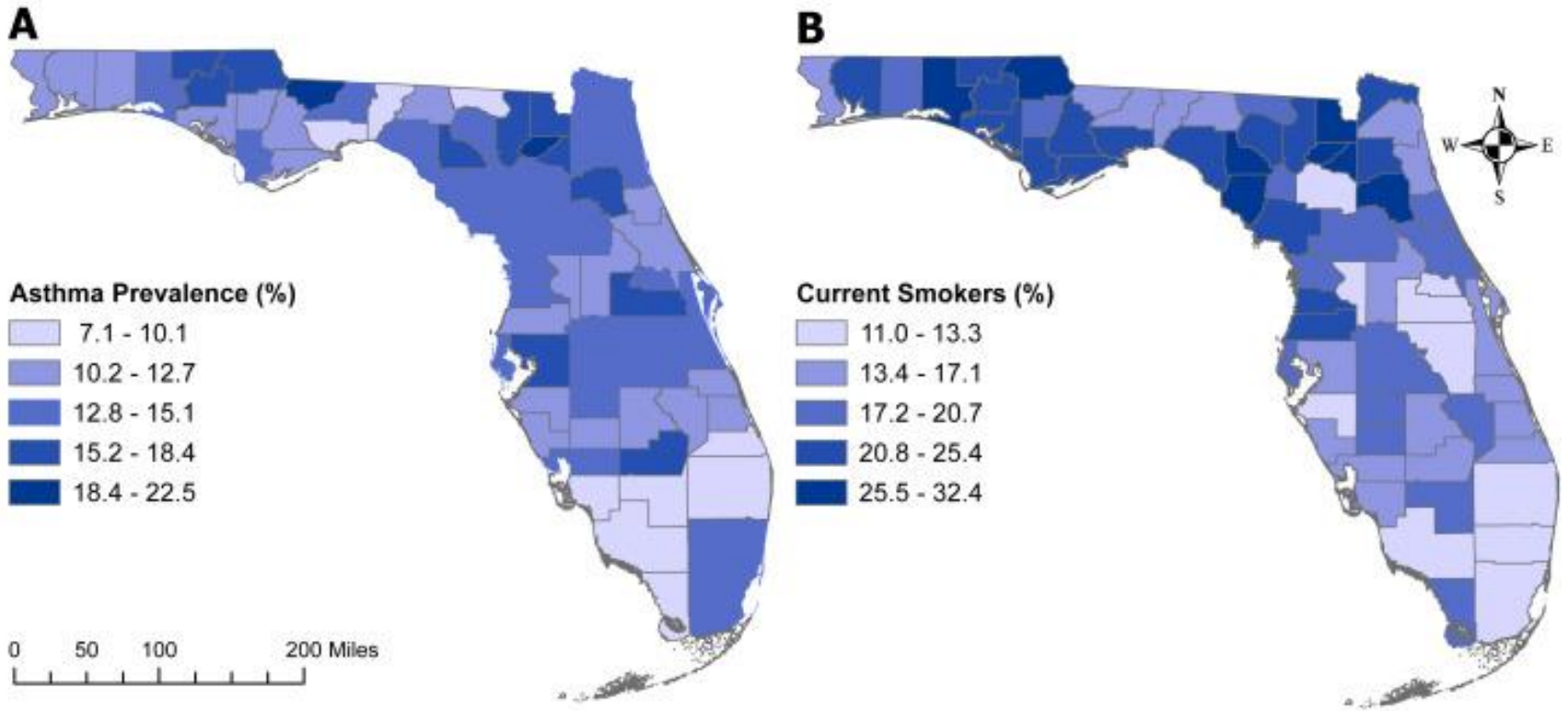

Figure 2.5 Geographic distributions of the percentages of Florida population with asthma (2.5A) or are current smokers (2.5B)

In a state-level study of COPD prevalence, the geographic distribution of COPD was similar to that of current smokers, which is similar to the results of the current analysis [4]. A study in Maine reported an overlap between areas of high COPD risk and high asthma risk at the Zip Code Tabulation Area (ZCTA)-level [75]. However, that study excluded any non-white cases of COPD from the analysis [75], which may limit the generalizability of the results especially to a more racially or ethnically diverse population. In a study of state-level prevalence, the geographic distribution of COPD prevalence was similar in current smokers and non-smokers, which the authors hypothesized was due to possible exposure to second-hand smoke among non-smokers [4]. Other studies of geographic distributions of COPD have primarily focused on hospitalizations [72,73]. A California study of COPD hospitalizations showed that the COPD hospitalization rates varied across ZCTAs, particularly across urban and rural areas or areas with varying socioeconomic status [72].

In this study, COPD prevalence was associated with the county-level percentage of current smokers and percentage of population with asthma. Although the association between smoking and COPD in individual-level studies is well documented [4,6,145], previous ecological studies are limited in their assessment of area-level risk factors, including smoking status [66,68,75,146,147]. Previous studies assessing area-level smoking reported no associations with COPD prevalence. The authors hypothesized that the lack of association may be due to methodological limitations [75,147]. At the individual-level, however, smoking is recognized as a primary risk factor for COPD [6], which is similar to the results of the current study although not directly comparable. The results of the current ecological study taken together with the results in the individual-level study suggest that targeting areas with high percentages of current

smokers for smoking cessation or prevention campaigns may help reduce the burden of COPD in these areas.

The association between COPD prevalence and asthma is less clear as the mechanism of COPD development among individuals with asthma is not well understood. Only a few individual-level studies have studied the risk of COPD development in those with asthma, both of which found an increase in risk of COPD [148,149]. In ecological studies, asthma prevalence is typically not included in the area-level risk factor investigation [68,146,147]. Only one ecological study reported overlap in high prevalence locations of COPD and asthma, which they suggested could be the result of shared risk factors or co-occurring diseases [75]. Although traditionally identified as two distinct diseases, both asthma and COPD are consequences of airway inflammation. A recent review comparing risk factors of COPD and adult-onset asthma identified several risk-factor overlaps between the two conditions. The risk factors common to both conditions included early-life factors (such as low-birth weight and pre-term births), smoking, air pollution, and a number of occupational exposures including dust, pesticides, and other chemical respiratory irritants[97]. In recent years, however, the overlap of asthma and COPD within the same individual has been recognized as a separate syndrome, referred to as the asthma-COPD overlap syndrome [150,151]. Thus, it may be possible that the association between county-level percentage of asthma and prevalence of COPD may be the result of the asthma-COPD overlap syndrome. However, the reported prevalence of asthma-COPD overlap syndrome is highly variable across studies primarily due to lack of consensus on the definition of the syndrome, but the reported estimate in the United States general population is approximately 3.7% [150]. Regardless, the current results suggest that efforts targeted at reducing asthma prevalence may also be beneficial for reducing COPD prevalence. However, whether these

strategies should be focused on shared risk factors or asthma-COPD overlap syndrome is still unclear. Further investigation is needed to elucidate the nature of the association between asthma and COPD in order to better attune prevention efforts.

The percentage of non-white non-Hispanic residents was a confounder for the association between COPD prevalence and percentage of asthma. In the United States, asthma prevalence is higher in the non-white non-Hispanic population compared to the white population [152]. It is suggested that the higher prevalence of asthma among non-white non-Hispanic populations may be due to differences in socioeconomic determinants of health [153] some of which are also associated with COPD.

Perhaps, the most surprising result from the study is the lack of association between COPD prevalence and poor air quality and poverty. Previous studies of socioeconomic status have reported significant associations between poverty or lower socioeconomic status and higher COPD prevalence [38,124,154]. Unfortunately, the variables used as measures of socioeconomic status vary widely across studies and some of these measures may not completely capture the socioeconomic status within an area, particularly for areas undergoing dynamic changes [154]. Thus, it is possible that a different measure of socioeconomic status or a smaller unit of analysis, such as census tract might be worth considering for future investigations. Although not directly comparable with the findings of this county-level study, previous individual-level studies have provided some evidence of association between poor air quality and COPD [155,156]. Moreover, poor air quality has been reported to have strong associations with some severe outcomes such as hospitalizations and mortality [118]. A recent review stated that more evidence is required before poor air quality could be considered a universal risk factor for the onset of COPD [118].

2.5.1 Strengths and Limitations

This study used rigorous spatial statistical methods to identify spatial clusters of COPD in Florida. The strength of Tango's Flexible Scan Statistic (FSSS) is its ability to identify irregularly shaped clusters, unlike other methods such as Kulldorff's Spatial Scan Statistics that are better at identifying circular clusters. Additionally, FSSS does not suffer from multiple comparisons that may be associated with other cluster identification methods such as Moran's Local Indicators of Spatial Associations (LISA) [137].

A limitation of this study is that the estimates of COPD prevalence, smoking status, and asthma are all based on self-reporting from health surveys [129]. Self-reported measures may be biased [157]. Additionally, due to unavailability of data, this study could not investigate the association between COPD prevalence and occupational exposures such as welding fumes or diesel exhaust [158,159]. Although the findings of this study are directly valid for Florida, similar study approaches can be used in other geographic locations to help improve our understanding of these disparities and their predictors. Suffice it to say that this study provides important information on the geographic distribution of COPD prevalence and on area-level predictors of COPD prevalence that are imperative for local health planning and resource allocation to address the condition.

2.6 Conclusion

There is evidence of spatial clusters of COPD prevalence in Florida. These patterns are explained, in part, by differences in distribution of some health behaviors (smoking) and co-morbidities (asthma). This information is important for guiding intervention efforts to address the condition, reduce health disparities, and improve health for all.

CHAPTER 3

Burden and predictors of chronic obstructive pulmonary disease occurrence and severity among an occupational cohort of United States Department of Energy former workers

Burden and predictors of chronic obstructive pulmonary disease occurrence and severity among an occupational cohort of United States Department of Energy former workers

Sara C. Howard[1,2,], Louis Rocconi[3], Agricola Odoi[1,]

[1]Department of Biomedical and Diagnostic Sciences, The University of Tennessee, Knoxville, Tennessee, United States of America

[2]Epidemiology and Exposure Science, Oak Ridge Associated Universities, Oak Ridge, Tennessee, United States of America

[3]Department of Educational Leadership and Policy Studies, The University of Tennessee, Knoxville, Tennessee, United States of America

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My contributions to this work included conceptual design, data analysis, and manuscript preparation.

3.1 Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is a chronic inflammatory lung disease that reduces lung function and primarily affects older adults. Evidence suggests that occupational exposures like diesel exhaust, cadmium, welding fumes, and silica increase the risk of COPD. Some United States Department of Energy (DOE) workers may be exposed to these noxious substances as they execute their job responsibilities. Assessment of the burden of COPD among these workers and identification of the potential associations between the condition and the above occupational exposures is important for guiding screening, prevention, and control programs. Therefore, the objectives of this study are to: (a) estimate the burden of COPD among former workers of the DOE in the United States and (b) investigate the association between occupational exposures and COPD occurrence and severity among these workers while controlling for environmental, behavioral, and socio-demographic factors.

Methods: Retrospective data containing health screening records of former DOE workers, covering the time period 2006-2019, were obtained from the National Supplemental Screening Program. Multivariate imputation by chained equation was used to impute missing values. Binary and multinomial logistic regression models were used to investigate predictors of COPD occurrence and severity, respectively.

Results: Of the 17,376 participants included in the study, 20.8% had COPD. History of asthma, age at exam, body mass index, and smoking were significant predictors of both COPD occurrence and severity. Individuals exposed to silica had higher odds of COPD compared to those that were not exposed to silica. Similarly, diesel exhaust exposure was significantly associated with risk of more severe COPD.

Conclusions: The findings of this study demonstrate the importance of considering occupational experience in the assessment of both COPD occurrence and severity. This information may be important for occupational screening programs as well as aiding in identifying modifiable risk factors to guide prevention and control efforts.

3.2 Background

Chronic Obstructive Pulmonary Disease (COPD) is an inflammatory disease of the lungs, which obstructs airflow and reduces lung function [17]. Although the prevalence of the condition in the United States is only 6.2%[4], its annual economic burden is high and results in $32 billion in direct costs and $20.4 billion in indirect costs[6]. The prevalence of COPD increases with age, and hence older adults experience a higher burden of the condition. In the United States, approximately 10.6% of adults 55-64 years old and 12.8% of those ≥65 years old suffer from the condition [2]. Thus, COPD represents a significant challenge during aging.

Evidence suggests that occupational exposures to substances such as cadmium [160], diesel exhaust [158], welding fumes [161], and silica [162] increase the risk of COPD. Approximately 31% (95% CI: 18-43%) of the COPD cases among non-smokers and 14% (95% CI: 10-18%) of cases among smokers are attributed to occupational exposures [13]. Historically, the United States Department of Energy (DOE) workers have been tasked with activities such as energy production, weapons design and production, and environmental cleanup, which may have resulted in occupational exposures of noxious substances [16]. As a result, the DOE instituted the Former Worker Medical Screening Program (FWP), which is comprised of six individual surveillance programs, for screening and early identification of diseases, such as COPD [16].

Understanding the association between occupational exposures and risk of COPD while controlling for environmental (e.g. air quality) [6], socio-demographic, and behavioral (e.g.

smoking) factors[163], among aging DOE former workers is important for guiding disease prevention/control and reduction of healthcare costs associated with the condition. Therefore, the objectives of this study were to: (a) estimate the burden of COPD among former workers of the DOE in the United States and (b) investigate occupational predictors of COPD among these former workers while controlling for environmental, behavioral, and socio-demographic factors.

3.3 Methods

3.3.1 Ethics approval

This study was reviewed and approved by the United States Central Department of Energy Institutional Review Board (DOE ID: DOE000645). The need for consent was waived by the Institutional Review Board. No minors were included in the study since it involved only DOE former workers.

3.3.2 Study population

This retrospective study used data collected as part of the National Supplemental Screening Program (NSSP), which is one of the six surveillance programs under the Former Worker Program (FWP), and is the only national program for non-construction former workers. These data were accessed for research purposes on August 26, 2021 in an anonymized form to ensure that the investigators could not identify participants during or after data collection. The NSSP provides free, voluntary medical screening to DOE former workers, contractors, and subcontractors across all 50 states of the United States. Repeated screening exams are offered to participants every three years [16,164]. Only participants who completed an initial screening exam that included a spirometry test from January 1, 2006, to December 31, 2019, were included in this study (n=17,960). Individuals who reported a history of restrictive lung disease including silicosis, asbestosis, and chronic beryllium disease at the time of the initial exam (n=584) were

excluded to avoid false positives since obstructive lung function patterns, similar to COPD, have been reported among individuals with restrictive lung diseases [165]. In some instances, participants had some aspects of their initial screening exams repeated (n=2,230). When this occurred, the most recent exam results were used. The final study cohort included 17,376 participants.

3.3.3 Data sources, description, preparation, and management

3.3.3.1 Chronic Obstructive Pulmonary Disease (COPD) data

Spirometry measurements, which assess lung function, were used to identify COPD based on the **G**lobal Initiative for Chronic **O**bstructive **L**ung **D**isease (GOLD) criterion [6]. Using this criterion, participants with COPD were identified as those with forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio less than 0.7 (i.e. FEV_1/FVC <0.7). The severity of the condition was also graded using the GOLD criterion as mild ($FEV_1 \geq$ 80% of predicted), moderate (FEV_1 50-79% of predicted), severe (FEV_1 30-49% of predicted), and very severe (FEV_1 < 30% of predicted)[6,21]. For investigation of predictors of COPD, two outcome variables were used: COPD occurrence (yes/no) and COPD severity (very severe, severe, moderate, mild). Due to the small number of NSSP participants with very severe COPD, this category was combined with the severe category to avoid the small number problem resulting in unreliable/unstable estimates during statistical analysis.

3.3.3.2 Occupational exposures data

Occupational exposures to cadmium, diesel exhaust, welding fumes, and silica were assessed using the exposure history available in the NSSP at the time of initial screening exams. Participants were asked if they were exposed to each of the substances as a normal part of their job duties. Response options were dichotomous (yes/no). Job title for each participant was

provided by the NSSP as one of twelve standardized job titles: administrative support, biohazard, crafts, field professionals, guests, in-house professionals, line operators, management, security/fire protection, service, technical support, and unknown. For participants who had more than one job title, the longest held title was recorded as the job title. The twelve standardized job titles were classified into three occupational exposure categories (low, medium, and high) based on potential level of occupational hazards as described in a previous DOE surveillance program which used the same standardized job titles [166] . The low exposure category included individuals involved in administrative support, management, and in-house professionals while the medium exposure category included field-professionals, biohazard, security/fire protection, and guests. Line operators, crafts, service, and technical support job titles were categorized in the high exposure risk category. The DOE facility where the worker spent most of their career was recorded as their primary site. The facilities were categorized as weapons production, uranium processing, or science and laboratory facilities. Hire and termination dates were provided as month/year and were used to calculate duration of employment, which was then categorized into 5-year time periods.

3.3.3.3 Smoking data

Data on lifetime smoking habits were captured at the time of the initial exams. Participants were categorized as ever smokers or never smokers based on whether they ever smoked more than 20 packs of cigarettes or if they were smokers at the time of the screening.

3.3.3.4 Air quality data

Air quality data were downloaded from the Environmental Protection Agency (EPA) website [167]. Data on mean concentration of air pollutants were used to calculate the EPA's air quality index (AQI) per zip code per year. To calculate AQI, the mean concentrations for ozone,

carbon monoxide, sulfur dioxide, nitrogen dioxide, and particulate matter ($PM_{2.5}$ and PM_{10}) were calculated per zip code. Using EPA's technical basis document for air quality, the mean values were converted to AQI values and categorized as good (AQI: <51), moderate (AQI: 51-100), unhealthy for sensitive groups (AQI: 101-150), unhealthy (AQI: 151-200), very unhealthy (AQI: 201-300), and hazardous (AQI: 301-500) [168].

Study participants were matched to AQI based on their zip code of residence and year of their initial exam. If a participant's zip code did not contain air quality data, then AQI of the closest zip code was assigned. To find the nearest zip code, the zip codes were first converted to zip code tabulation areas (ZCTAs) using the crosswalk developed by USA Mapper [169] and then matched to the US Census Bureau's TIGER/Line shapefiles [170]. The centroid of the ZCTAs were then used to calculate the distance to the nearest ZCTA.

3.3.4 Statistical analyses

3.3.4.1 Descriptive analysis

All statistical analyses were performed in SAS 9.4 [171] and R version 4.0.3 [172] using RStudio version 2021.09.2 interface[132]. Frequencies and 95% confidence intervals were computed for categorical variables.

3.3.4.2 Multiple imputation

Due to the high proportion of missing values for race (22.3%) as well as smaller proportion of missing data in potential predictors of COPD occurrence and severity, multivariate imputation by chained equation (MICE) was performed on the dataset using the MICE package [173] in RStudio version 2021.09.2 [132] interface of R [172] . The MICE procedure used logistic regression for binary variables and multinomial logistic regression for categorical variables with more than two categories [173]. Since the outcome variable of interest should be

included in the multiple imputation model [174], multiple imputed (or MICE) datasets were created separately for the two outcome variables of interest: COPD occurrence (yes/no) and COPD severity (very severe, severe, moderate, mild). Multiple imputation by chained equations was conducted for all potential predictors of COPD occurrence and COPD severity separately. For both the COPD occurrence and COPD severity imputations, the number of imputed datasets was 20 and the maximum number of iterations for the imputation was 30. The choice of the number of imputations was based on the fraction of missing data and on limiting the decrease in power as outlined by Graham et al. [175]. The results of the statistical models performed on the multiple imputed datasets were pooled in accordance with Rubin's rules for pooling, which accounts for the additional variability produced by multiple imputation [176].

3.3.4.3 Identification of highly correlated potential predictors

To avoid multicollinearity, pairwise Spearman's rank correlation coefficients were computed to identify highly correlated ($|r|>0.70$) potential predictors. If a pair of variables was highly correlated, only one of them was included for assessment in the multivariable models. However, none of the variables were highly correlated (**Table 3.1**).

3.3.4.4 Predictors of COPD occurrence

To identify potential predictors of COPD occurrence (yes/no), logistic regression models were fit using RStudio version 2021.09.2 [132] interface of R [172] for multiple imputation data. Initially, univariable logistic regression models were fit, and the independent variables with a $p < 0.20$ were considered for the multivariable logistic regression model. The reference categories for the logistic regression models were chosen with apriori knowledge of the data and the possible direction of association with COPD. Backwards elimination was used to build the multivariable logistic model using an alpha of 0.05. An independent variable was considered a

confounder if its removal from the model resulted in at least a 20% change in the regression coefficients of any of the variables still in the model [134]. Goodness of fit of the final model was assessed using the Hosmer-Lemeshow test [177].

Table 3.1. Spearman rank correlation coefficients for potential predictors of chronic obstructive pulmonary disease among the National Supplemental Screening Program participants, 2006-2019

	Body Mass Index	Air Quality Index	Sex	Race	Smoking Status	DOE Site	Asthma	Cadmium	Diesel Exhaust	Silica	Welding Fumes	Exposure Potential	Work Duration	Age
Body Mass Index	1.000	-0.016	0.007	0.090	0.036	0.097	0.062	0.047	0.082	0.056	0.083	0.074	0.035	-0.073
Air Quality Index	-0.016	1.000	-0.011	-0.049	0.066	0.036	0.009	0.084	-0.011	0.046	0.050	0.103	0.005	-0.034
Sex	0.007	-0.011	1.000	0.014	0.000	0.013	0.000	0.006	0.006	0.002	0.002	0.004	0.002	-0.011
Race	0.090	-0.049	0.014	1.000	-0.069	0.116	0.023	0.013	0.074	-0.001	0.027	0.081	0.045	-0.108
Smoking Status	0.036	0.066	0.000	-0.069	1.000	0.077	-0.021	0.068	0.066	0.066	0.116	0.135	0.094	0.179
DOE Site	0.097	0.036	0.013	0.116	0.077	1.000	0.008	0.111	0.132	0.081	0.126	0.165	0.143	0.063
Asthma	0.062	0.009	0.000	0.023	-0.021	0.008	1.000	0.002	0.013	0.004	0.003	-0.023	-0.018	-0.053
Cadmium	0.047	0.084	0.006	0.013	0.068	0.111	0.002	1.000	0.230	0.370	0.328	0.166	0.197	0.008
Diesel Exhaust	0.082	-0.011	0.006	0.074	0.066	0.132	0.013	0.230	1.000	0.303	0.361	0.132	0.168	-0.040
Silica	0.056	0.046	0.002	-0.001	0.066	0.081	0.004	0.370	0.303	1.000	0.364	0.133	0.160	-0.029
Welding Fumes	0.083	0.050	0.002	0.027	0.116	0.126	0.003	0.328	0.361	0.364	1.000	0.193	0.218	0.008
Exposure Potential	0.074	0.103	0.004	0.081	0.135	0.165	-0.023	0.166	0.132	0.133	0.193	1.000	0.135	0.004
Work Duration	0.035	0.005	0.002	0.045	0.094	0.143	-0.018	0.197	0.168	0.160	0.218	0.135	1.000	0.239
Age	-0.073	-0.034	-0.011	-0.108	0.179	0.063	-0.053	0.008	-0.040	-0.029	0.008	0.004	0.239	1.000

3.3.4.5 Predictors of COPD severity

For COPD severity, only participants with COPD were included in the model. Due to the small number of participants with very severe COPD, the severity variable was re-coded from a 4-categeory variable (very severe, severe, moderate, mild) to a 3-category (severe, moderate, mild) variable by combining the very severe and severe categories. Multinomial logistic regression models were used to identify potential predictors of COPD severity in RStudio 2021.09.2 interface [132] of R [172] for analyses with MICE data. As with the ordinary logistic regression models, a relaxed critical value of $p < 0.20$ was used to determine which independent variables from the univariable multinomial logistic regression models would be included in the multivariable multinomial logistic regression model. Variables were removed from the multivariable multinomial logistic regression model using backwards elimination when the $p > 0.05$. An independent variable was considered a confounder if its removal from the model resulted in at least a 20% change in the regression coefficients of any of the variables still in the model [134]. The exponentiated regression coefficients of the multinomial logistic regression models are Relative Risk Ratios (RRR) which are similar to odds ratios in interpretation [178]. Thus, the RRR is a ratio of the relative risks produced by the multinomial model for each level of the outcome compared to the baseline outcome level [134,178]. The reference categories for each variable were selected based on apriori knowledge of the data and the hypothesized/plausible association with COPD. For example, advanced age tends to be associated with higher risk of COPD [6]. Therefore, the reference category for the age variable would be the lowest age category.

3.4 Results

3.4.1 Descriptive statistics

The study included 17,376 DOE former workers who participated in the NSSP from 2006 through 2019. Based on the GOLD criteria, 20.8% of the study participants had COPD (**Table 3.2**). A total of 43.0% of the COPD cases were classified as mild, 42.8% as moderate, and 14.2% as severe or very severe. The study population was predominantly non-black (88.1%) and male (74.7%). There was a fairly even spread across age categories with 17.9% less than 55 years old, 12.0% 55-59 years old, 16.5% 60-64 years old, 17.3% 65-69 years old, 14.3% 70-74 years old, and 21.5% ≥ 75 years old. The majority of the study cohort were overweight (39.9%) or obese (39.8%) while only 19.9% had normal weight and an additional 0.5% were underweight. Less than a half (43.5%) were ever smokers, and 13.2% reported a history of asthma. The majority (85.7%) of the study population lived in areas where the air quality index (AQI) was considered good whereas 14.3% lived in areas where the AQI was moderate or unhealthy for sensitive groups.

Most of the study population were employed at weapons production facilities (72.8%), followed by science and laboratory facilities (20.7%), and uranium processing facilities (6.5%). The majority were employed at DOE facility for less than 15 years (<5 years: 32.2%, 5-9 years: 16.6%, 10-14 years: 11.5%) although 16.0% were employed for at least 30 years. Regarding potential for occupational exposures, 26.7% of the study participants were classified as having low potential for exposure, 28.9% were classified as medium potential, and 44.5% were classified as high potential. Welding fumes and cadmium were the most commonly reported occupational exposures at 47.0% of the cohort each, with silica at 34.8% and diesel exhaust at 29.0%.

Table 3.2. Summary Statistics of the characteristics of National Supplemental Screening Program participants at initial examination, 2006-2019

Characteristics	Frequency	Percentage	95% Confidence Interval
Chronic Obstructive Pulmonary Disease Occurrence (COPD)	**n = 17,376**		
No	13,755	79.2	78.6, 79.8
Yes	3,621	20.8	20.2, 21.44
Chronic Obstructive Pulmonary Disease Severity	**n = 3,621**		
Mild	1,557	43.0	41.4, 44.6
Moderate	1,549	42.8	41.2, 44.4
Severe or Very Severe	515	14.2	13.1, 15.4
Race	**n = 13,515**		
Black	1,612	11.9	11.4, 12.5
Non-Black	11,903	88.1	87.5, 66.6
Sex	**n=17,376**		
Male	12,978	74.7	74.0, 75.3
Female	4,398	25.3	24.7, 26.0
Age Categories	**n = 17,376**		
< 55 years old	3,112	17.9	17.3, 18.5
55-59 years old	2,085	12.0	11.5, 12.5
60-64 years old	2,871	16.5	16.0, 17.1
65-69 years old	3,010	17.3	16.8, 17.9
70-74 years old	2,562	14.7	14.2, 15.3
≥ 75 years old	3,736	21.5	20.9, 22.1
Body Mass Index (BMI) Category	**n = 17,333**		
Underweight	82	0.47	0.37, 0.59
Normal	3,442	19.9	19.3, 20.5
Overweight	6,910	39.9	39.1, 40.6
Obese & Extremely Obese	6,899	39.8	39.1, 40.5

Table 3.2 Continued

Characteristics	Frequency	Percentage	95% Confidence Interval
Smoking Status	**n = 17,376**		
Non-Smoker	9,825	56.5	55.8, 57.3
Ever Smoker	7,551	43.5	42.7, 44.2
History of Asthma	**n = 16,932**		
No	14,697	86.8	86.3, 87.3
Yes	2,235	13.2	12.7, 13.71
Air Quality Index (AQI) Category	**n = 17,338**		
Good	14,862	85.7	85.2, 86.2
Moderate or Unhealthy for Sensitive Groups	2,476	14.3	13.8, 14.8
Department of Energy Site Category	**n = 17,376**		
Science and Laboratory Facilities	3,600	20.7	20.1, 21.3
Uranium Processing Facilities	1,125	6.5	6.1, 6.8
Weapons Production Facilities	12,651	72.8	72.2, 73.5
Working Duration	**n = 17,376**		
< 5 years	5,594	32.2	31.5, 32.9
5-9 years	2,879	16.6	16.0, 17.1
10-14 years	1,998	11.5	11.0, 12.0
15-19 years	1,547	8.9	8.5, 9.3
20-24 years	1,368	7.9	7.5, 8.3
25-29 years	1,212	7.0	6.6, 7.4
≥ 30 years	2,778	16.0	15.4, 16.5
Exposure Potential	**n = 17,140**		
Low	4,568	26.7	26.0, 27.3
Medium	4,946	28.9	28.2, 29.5
High	7,626	44.5	43.8, 45.2

Table 3.2 Continued

Characteristics	Frequency	Percentage	95% Confidence Interval
Occupational Exposure to Cadmium	**n= 17,343**		
No	9,188	53.0	64.5, 65.9
Yes	8,148	47.0	34.1, 35.5
Occupational Exposure to Welding Fumes	**n = 17,336**		
No	9,188	53.0	52.3, 53.7
Yes	8,148	47.0	46.3, 47.7
Occupational Exposure to Silica	**n= 17,340**		
No	11,308	65.2	52.3, 53.7
Yes	6,032	34.8	46.3, 47.7
Occupational Exposure to Diesel Exhaust	**n = 17,352**		
No	12,313	71.0	70.3, 71.6
Yes	5,039	29.0	28.4, 29.7

3.4.2 Predictors of COPD occurrence

Of the potential predictors investigated, only sex and AQI category did not have univariable associations ($p>0.2$) with COPD occurrence (**Table 3.3**). However, based on the multivariable model, significant ($p<0.05$) predictors of COPD occurrence were age category, BMI category, smoking, history of asthma, DOE facility, and occupational exposure to silica (**Table 3.4**). The odds of COPD were higher across all age categories compared to those < 55 years old, and the odds ratios steadily increased with each advancing age category, reaching its highest value of 3.184 (95% CI: 2.786, 3.638) among those ≥75 years old. Individuals who were underweight had higher odds of COPD (OR: 2.161; 95% CI: 1.355, 3.445) compared to normal weight individuals. However, those who were overweight (OR: 0.676; 95% CI: 0.612, 0.746) or obese (OR: 0.513: 95% CI: 0.463, 0.569) had lower odds of COPD compared to individuals with normal weight. The odds of COPD occurrence were 2.029 times (95% CI: 1.877, 2.193) higher among ever smokers than non-smokers. Individuals with a self-reported history of asthma had 2.259 times (95% CI: 2.035, 2.508) higher odds of COPD occurrence compared to those without history of asthma. Additionally, NSSP participants who were employed at uranium processing facilities (OR: 1.255; 95% CI: 1.057, 1.491) or weapons production facilities (OR: 1.173; 95% CI: 1.061, 1.296) had higher odds of COPD occurrence compared to participants employed at science and laboratory facilities. The Hosmer-Lemeshow goodness of fit test p-value was $p=0.0872$ implying a good model fit.

Table 3.3. Unadjusted logistic regression model results investigating predictors of chronic obstructive pulmonary disease occurrence among the National Supplemental Screening Program participants, 2006-2019

Characteristics	Odds Ratio	95% Confidence Interval	p-value	Overall p-value
Race				<0.001
Black	0.776	0.673, 0.894	<0.001	
Non-Black		*Reference*		
Sex				0.683
Female	0.983	0.903, 1.069	0.683	
Male		*Reference*		
Age Categories				<0.001
55-59 years old	1.295	1.010, 1.524	0.002	
60-64 years old	1.645	1.423, 1.902	<0.001	
65-69 years old	1.944	1.690, 2.238	<0.001	
70-74 years old	2.292	1.987, 2.642	<0.001	
≥ 75 years old	3.645	3.204, 4.146	<0.001	
< 55 years old		*Reference*		
Body Mass Index (BMI) Categories				<0.001
Underweight	2.21	1.421, 3.436	<0.001	
Overweight	0.724	0.658, 0.795	<0.001	
Obese & Extremely Obese	0.551	0.499, 0.608	<0.001	
Normal		*Reference*		
Smoking Status				<0.001
Ever Smoker	2.196	2.039, 2.366	<0.001	
Non-Smoker		*Reference*		
History of Asthma				<0.001
Yes	1.902	1.721, 2.101	<0.001	
No		*Reference*		

Table 3.3 Continued.

Characteristics	Odds Ratio	95% Confidence Interval	p-value	Overall p-value
Air Quality Index (AQI) Category				0.412
Moderate or Unhealthy for Sensitive Groups	1.044	0.941, 1.159	0.412	
Good	*Reference*			
Department of Energy Site Category				<0.001
Uranium Processing Facilities	1.296	1.099, 1.526	0.002	
Weapons Production	1.26	1.145, 1.285	<0.001	
Science and Laboratory Facilities		*Reference*		
Working Duration				<0.001
5-9 years	1.028	0.918, 1.152	0.629	
10-14 years	1.128	0.994, 1.280	0.061	
15-19 years	1.076	0.935, 1.238	0.306	
20-24 years	1.012	0.872, 1.175	0.871	
25-29 years	1.295	1.117, 1.502	<0.001	
≥ 30 years	1.34	1.201, 1.495	<0.001	
< 5 years		*Reference*		
Exposure Potential				0.024
Medium	0.917	0.829, 1.014	0.091	
High	1.038	0.948, 1.136	0.417	
Low		*Reference*		
Occupational Exposure to Cadmium				0.063
Yes	1.075	0.996, 1.160	0.063	
No		*Reference*		
Occupational Exposure to Welding Fumes				0.009
Yes	1.103	1.025, 1.187	0.009	
No		*Reference*		

Table 3.3 Continued.

Characteristics	Odds Ratio	95% Confidence Interval	p-value	Overall p-value
Occupational Exposure to Silica				<0.001
Yes	1.139	1.056, 1.229	<0.001	
No		*Reference*		
Occupational Exposure to Diesel Exhaust				0.090
Yes	1.072	0.989, 1.161	0.090	
No		*Reference*		

Table 3.4. Predictors of chronic obstructive pulmonary disease occurrence among National Supplemental Screening Program participants, 2006-2019

Characteristics	Odds Ratio	95% Confidence Interval	p-value	Overall p-value
Age Categories				<0.001
55-59 years old	1.249	1.057, 1.476	0.009	
60-64 years old	1.552	1.337, 1.800	<0.001	
65-69 years old	1.797	1.555, 2.076	<0.001	
70-74 years old	2.085	1.800, 2.415	<0.001	
≥ 75 years old	3.184	2.786, 3.638	<0.001	
< 55 years old		*Reference*		
Body Mass Index (BMI) Categories				<0.001
Underweight	2.161	1.355, 3.445	0.001	
Overweight	0.676	0.612, 0.746	<0.001	
Obese & Extremely Obese	0.513	0.463, 0.569	<0.001	
Normal		*Reference*		
Smoking Status				<0.001
Ever Smoker	2.029	1.877, 2.193	<0.001	
Non-Smoker		*Reference*		
History of Asthma				<0.001
Yes	2.259	2.035, 2.508	<0.001	
No		*Reference*		
Department of Energy Site Category				0.003
Uranium Processing Facilities	1.255	1.057, 1.491	0.009	
Weapons Production	1.173	1.061, 1.296	0.002	
Science and Laboratory Facilities		*Reference*		

Table 3.4 Continued.

Characteristics	Odds Ratio	95% Confidence Interval	p-value	Overall p-value
Occupational Exposure to Silica				<0.001
Yes	1.157	1.068, 1.253	<0.001	
No		*Reference*		

3.4.3 Predictors of COPD severity

With the exception of sex, race, and work duration, all assessed potential predictors had univariable associations ($p<0.2$) with COPD severity (**Table 3.5**). The final multivariable multinomial logistic model included age category, BMI category, smoking, history of asthma, DOE facility category, and occupational exposure to diesel exhaust as significant ($p<0.05$) predictors of COPD severity (**Table 3.6**). While most of the predictors had similar relative risk ratios (RRR) for moderate disease and severe or very severe disease, smoking status and history of asthma had higher RRRs for severe or very severe disease compared the RRRs for moderate disease. For instance, the risk of moderate COPD among ever smokers was 1.606 (95% CI: 1.385, 1.863) times higher than the risk in non-smokers, but the risk of severe or very severe COPD was 2.720 (95% CI: 2.163, 3.420) times higher among ever smokers than non-smokers. A similar difference in the association was observed among participants with asthma. The risk for moderate COPD among those with asthma was 1.991 (95% CI: 1.638, 2.420) times higher than among those without asthma. However, the risk of severe or very severe COPD among individuals with asthma was 3.362 (95% CI: 2.607, 4.336) times higher than that among those without asthma.

Table 3.5. Unadjusted multinomial regression model results investigating predictors of chronic obstructive pulmonary disease severity among the National Supplemental Screening Program participants, 2006-2019

	Moderate			Severe or Very Severe			Overall
Characteristics	**RRR**	**95% CI**	**p-value**	**RRR**	**95% CI**	**p-value**	**P-value**
Race							0.471
Black	0.811	0.620, 1.062	0.127	1.038	0.708, 1.521	0.848	
Non-Black			*Reference*				
Sex							0.6710
Female	1.060	0.901, 1.246	0.495	0.968	0.767, 1.221	0.782	
Male			*Reference*				
Age Categories							<0.001
55-59 years old	1.427	1.037, 1.964	0.029	1.316	0.739, 2.342	0.351	
60-64 years old	1.352	1.017, 1.798	0.038	2.028	1.253, 3.283	0.004	
65-69 years old	1.58	1.198, 2.085	0.001	2.884	1.822, 4.566	<0.001	
70-74 years old	1.267	0.958, 1.675	0.097	2.75	1.740, 4.345	<0.001	
≥ 75 years old	1.557	1.214, 1.998	<0.001	2.789	1.815, 4.296	<0.001	
< 55 years old			*Reference*				
Body Mass Index (BMI) Categories							<0.001
Underweight	3.049	1.240, 7.496	0.015	6.243	2.471, 15.772	<0.001	
Overweight	1.213	1.015, 1.450	0.034	0.799	0.621, 1.027	0.080	
Obese & Extremal Obese	1.837	1.521, 2.220	<0.001	1.361	1.053, 1.758	0.018	
Normal			*Reference*				
Smoking Status							<0.001
Ever Smoker	1.651	1.431, 1.905	<0.001	2.854	2.288, 3.560	<0.001	
Non-Smoker			*Reference*				

Table 3.5 Continued.

Characteristics	Moderate RRR	Moderate 95% CI	Moderate p-value	Severe or Very Severe RRR	Severe or Very Severe 95% CI	Severe or Very Severe p-value	Overall P-value
History of Asthma							<0.001
Yes	1.905	1.574, 2.306	<0.001	2.92	2.282, 3.737	<0.001	
No			*Reference*				
Air Quality Index (AQI) Category							0.0907
Moderate or Unhealthy for Sensitive Groups	1.239	1.014, 1.514	0.036	1.176	0.887, 1.559	0.259	
Good			*Reference*				
Department of Energy Site Category							<0.001
Uranium Processing Facilities	1.744	1.264, 2.407	<0.001	2.345	1.507, 3.650	<0.001	
Weapons Production	1.568	1.303, 1.887	<0.001	1.776	1.338, 2.356	<0.001	
Science and Laboratory Facilities			*Reference*				
Working Duration							0.279
5-9 years	1.11	0.893, 1.380	0.347	1.102	0.799, 1.518	0.554	
10-14 years	1.125	0.880, 1.439	0.347	1.617	1.163, 2.247	0.004	
15-19 years	1.09	0.866, 1.426	0.527	1.068	0.718, 1.589	0.745	
20-24 years	1.131	0.834, 1.504	0.399	0.962	0.620, 1.494	0.864	
25-29 years	1.168	0.850 1.551	0.283	1.459	0.989, 2.152	0.057	
≥ 30 years	1.045	0.880, 1.287	0.680	1.326	0.990, 1.776	0.058	
< 5 years			*Reference*				
Exposure Potential							<0.001
Medium	1.144	0.944, 1.386	0.171	0.88	0.662, 1.170	0.380	
High	1.333	1.121, 1.585	0.001	1.399	1.098, 1.782	0.007	
Low			*Reference*				

Table 3.5. Continued.

Characteristics	Moderate RRR	Moderate 95% CI	Moderate p-value	Severe or Very Severe RRR	Severe or Very Severe 95% CI	Severe or Very Severe p-value	Overall P-value
Occupational Exposure to Cadmium							0.130
Yes	1.126	0.972, 1.303	0.113	1.206	0.982, 1.482	0.074	
No			*Reference*				
Occupational Exposure to Welding Fumes							<0.001
Yes	1.193	1.036, 1.374	0.014	1.439	1.177, 1.759	<0.001	
No			*Reference*				
Occupational Exposure to Silica							0.008
Yes	1.102	0.952, 1.276	0.194	1.373	1.120, 1.682	0.002	
No			*Reference*				
Occupational Exposure to Diesel Exhaust						<0.001	
Yes	1.348	1.155, 1.574	<0.001	1.388	1.119, 1.721	0.003	
No			*Reference*				

Table 3.6. Predictors of chronic obstructive pulmonary disease severity among National Supplemental Screening Program participants, 2006-2019

Characteristics	Moderate			Severe or Very Severe			Overall
	RRR	95% CI	p-value	RRR	95% CI	p-value	p-value
Age Categories							<0.0001
55-59 years old	1.217	0.875, 1.692	0.2441	1.004	0.554, 1.818	0.9899	
60-64 years old	1.132	0.842, 1.520	0.4115	1.539	0.936, 2.532	0.0896	
65-69 years old	1.341	1.007, 1.787	0.0448	2.228	1.386, 3.582	0.0009	
70-74 years old	1.124	0.841, 1.501	0.4307	2.256	1.405, 3.623	0.0008	
≥ 75 years old	1.465	1.131, 1.898	0.0039	2.402	1.540, 3.746	0.0001	
< 55 years old			*Reference*				
Body Mass Index (BMI) Categories							<0.0001
Underweight	2.933	1.179, 7.297	0.0207	5.749	2.203, 15.008	0.0004	
Overweight	1.186	0.989, 1.423	0.0655	0.757	0.584, 0.982	0.0362	
Obese & Extremely Obese	1.751	1.442, 2.128	<0.0001	1.239	0.947, 1.620	0.1177	
Normal			*Reference*				
Smoking Status							<0.0001
Ever Smoker	1.606	1.385, 1.863	<0.0001	2.720	2.163, 3.420	<0.0001	
Non-Smoker			*Reference*				
History of Asthma							<0.0001
Yes	1.991	1.638, 2.420	<0.0001	3.362	2.607, 4.336	<0.0001	
No			*Reference*				
Department of Energy (DOE) Site Category							0.0002
Uranium Processing Facilities	1.584	1.139, 2.204	0.0063	2.185	1.379, 3.461	0.0009	
Weapons Production	1.432	1.183, 1.733	0.0002	1.578	1.177, 2.118	0.0023	
Science and Laboratory Facilities			*Reference*				

Table 3.6 Continued.

Characteristics	Moderate			Severe or Very Severe			Overall
	RRR	95% CI	p-value	RRR	95% CI	p-value	p-value
Occupational Exposure to Diesel Exhaust							0.0126
Yes	1.243	1.060, 1.460	0.0075	1.273	1.016, 1.594	0.0357	
No			*Reference*				

Conversely, the overweight RRR was 1.186 (95% CI: 0.989, 1.423) for moderate COPD and 0.757 (95% CI: 0.584, 0.982) for severe or very severe COPD while obese had similar RRRs across both moderate (RRR: 1.751 95% CI: 1.442, 2.128) and severe or very COPD (RRR: 1.239, 95% CI: 0.947, 1.620). The underweight RRR was higher for both moderate (RRR: 2.933, 95% CI: 1.179, 7.297) and severe or very severe COPD (RRR: 5.749, 95% CI: 2.203, 15.008) compared to normal BMI.

3.5 Discussion

This study investigated predictors of COPD occurrence and severity among an occupational cohort of DOE former workers in the United States. The findings from this study will be useful for improving screening guidelines for occupational screening programs such as the National Supplemental Screening Program (NSSP).

The results of this study show that predictors of COPD occurrence and severity are quite similar in the NSSP population. Similar to reports from other studies [4,6,17,38,95,163,179] this study found significant associations between COPD and both smoking and age. Moreover, consistent with findings from several other studies [38,97,180,181], this study found that, compared to normal BMI, low BMI (underweight) was associated with higher odds of COPD whereas high BMI (overweight/obese) was associated with lower odds of COPD. The associations between low BMI (vs normal BMI) and higher risks of both moderate and severe COPD, observed in this study, is consistent with reports from other studies [182,183]. However, this should be interpreted with caution due to potential reverse causation bias since severe COPD can lead to weight loss resulting in low BMI and therefore complicating interpretation [184]. Moreover, the cross-sectional nature of the study does not allow for assessment of temporality of events or causal inference [134]. Therefore, further investigation is required to fully understand

the association between BMI and COPD severity. It is worth noting that, in this study, there was no evidence of association between high BMI (overweight/obese) and lower risk of moderate or severe COPD, which has been reported by other studies [183].

The finding that history of asthma is a predictor of COPD occurrence and severity is consistent with results from a few other studies [148,149] although the underlying biological mechanism of the observed association between asthma and COPD is not well understood. Some studies have suggested that history of asthma, particularly in childhood, may impact lung function over a lifetime possibly leading to COPD and possibly declining lung function, which could be indicative of more severe COPD [149]. In recent years, asthma-COPD overlap syndrome, in which both asthma and COPD occur simultaneously in the same individual, has begun to be recognized as a distinct condition that may have different implications for disease progression than COPD or asthma alone [6,150,151]. While consensus definition of asthma and COPD overlap syndrome is limited, a broad definition of chronic respiratory disease with clinical features of both asthma and COPD is generally agreed [185]. However, other qualifications can include semi-reversible airflow limitation, increased eosinophil counts, a history of asthma, a history of smoking or atopy [185]. Since we could not investigate other clinical features and temporality in the current study, it remains unclear whether the identified association is the result of asthma-COPD overlap syndrome or historical asthma affecting long term lung function leading to the eventual development of COPD.

In this study, several occupational exposures had significant associations with COPD occurrence or severity. A study by Dement et al. reported that certain types of trades such as masons (cement, brick, plaster, etc.), mechanics, and carpenters had higher odds of COPD in older DOE construction workers compared to non-construction workers [186]. This is consistent

with the observed association between COPD occurrence and occupational exposure to silica dust in this study. Moreover, silica dust has also been reported to have an association with restrictive lung diseases such as silicosis [187]. Suffice it to say that the findings from the current study are consistent with those from several other studies [13,188,189] that reported associations between silica dust and occurrence of obstructive lung conditions, including COPD. Contrary to reports from other published literature [158,190–192], the current study observed an association between diesel exhaust exposure and higher COPD severity. However, a previous study by Zhang et al. did examine long-term effects of diesel exhaust on lung function and reported a significant association between decreased lung function and diesel exhaust exposure [191]. Since the severity level of COPD is based on grading lung function measurements, specifically the forced expiratory volume in one second (FEV_1), the results of the current study seem to support those of Zhang et al. [191].

3.5.1 Strengths and limitations

The use of records from a large nation-wide cohort of over 17,000 DOE former workers in this study allowed for the assessment of individual occupational exposures of interest including silica, diesel exhaust, and welding fumes. In many previous studies assessing occupational exposures and COPD [13,105,193,194], the exposures of interest were combined into single generic variable of vapors, dusts, or gases. However, the current study assessed each occupational exposure variable separately, which provides for a more refined analysis of the possible associations of these exposures with COPD occurrence and severity.

A limitation of the study is the limited ability to decipher temporality in the identified associations between COPD and its predictors, which is a factor of cross-sectional study designs, and as such, causal inferences cannot be drawn [134]. Additionally, the NSSP relies on self-

reported measures for medical histories and occupational exposures which may be subject to bias [157]. This limitation may be particularly applicable to association of history of asthma and COPD since the study relies on self-reported history of asthma, without clinical confirmation of disease, for the variable definition. For the outcome, however, the study relies on the application of GOLD criteria to clinical spirometry readings for identification of COPD. Although the GOLD criterion is an accepted standard for COPD, it may overestimate the prevalence especially in the elderly as well as underestimate the associations between risk factors and COPD [21]. Additionally, the investigation of air quality for a possible association with COPD prevalence and severity relied upon the annual mean air quality index in each participant's residential zip code, which may not accurately represent individual exposure [195]. Finally, the study does not incorporate quantitative measures of occupational exposure because this information is not available in the NSSP database. Therefore, residual confounding is possible since only self-reported occupational exposures were used instead of quantitative values (that were unavailable in the dataset). The exposure potential classification scheme for the twelve standardized job titles, initially developed by a Department of Energy (DOE) surveillance program, was based on the perceived potential for exposure to noxious agents based on the job requirements. However, this classification scheme has some level of subjectivity and hence may be prone to mis-classification bias. Finally, the retrospective data used in this study did not contain genetic information nor did the study include information on comorbidities. Hence, genetic factors and comorbidities were not assessed in this study, but they represent a possible extension in future studies. In addition, the generalizability of these results may be affected by the lack of diversity within the study population as the NSSP cohort is primarily non-Black males. Future studies will need to assess a more diverse population. Despite these limitations, this study provides valuable

information on predictors of COPD occurrence and severity in an occupational cohort and therefore the findings are useful for improving screening guidelines for occupational cohorts.

3.6 Conclusion

This study identified predictors of COPD occurrence and disease severity in the NSSP cohort. In addition to confirming the importance of historically prominent predictors of COPD such as smoking and age, this study demonstrates the importance of considering the occupational experience for both COPD occurrence and severity. This information may be important for occupational screening programs as well as aiding in identifying modifiable risk factors to guide prevention efforts.

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CHAPTER 4

Chronic obstructive pulmonary disease among former United States Department of Energy workers: comorbidities and lung function changes

Chronic obstructive pulmonary disease among former United States Department of Energy workers: comorbidities and lung function changes

Sara Howard[1,2], Louis Rocconi[3], Agricola Odoi[1]

[1]Department of Biomedical and Diagnostic Sciences, The University of Tennessee, Knoxville, TN, United States

[2]Epidemiology and Exposure Science, Oak Ridge Associated Universities, Oak Ridge, Tennessee, United States

[3]Evaluation, Statistics, & Methodology Program, Educational Leadership and Policy Studies Department, the University of Tennessee, Knoxville, TN, United States

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My contributions to study are conceptional design, data analyses, and manuscript preparation.

4.1 Abstract

Background. Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality in the United States and is frequently associated with multiple comorbidities which lead to poor COPD outcomes in the general population. However, little is known regarding COPD comorbidities in occupational cohorts whose exposure experiences could result in differences in comorbidities compared to the general population. These differences may also be important for assessing COPD outcomes such as lung function changes or decline. Therefore, the objectives of this study were to: (1) identify and describe clusters of COPD comorbidities among Department of Energy (DOE) former workers; (2) assess if the attributes of the identified clusters differ from those identified among the general population based on the published literature, and (3) identify predictors of lung function changes and decline among DOE former workers.

Methods. Clinical/medical, occupational, and sociodemographic data were obtained from the National Supplemental Screening Program. Imputation for missing values was performed using multiple imputation by chained equation. Comorbidity clusters were identified using hierarchical clustering. Regression and classification random forest models were used to identify predictors of changes in forced expiratory volume in one second (FEV_1) and FEV_1 decline. Variable importance scores were used to assess the predictive importance of the predictors.

Results. A total of 17,448 DOE former workers were included in this study, 20.9% of whom had COPD at their initial exam. Four comorbidity clusters were identified among those with COPD. Cluster 1 was composed of individuals with low prevalence of comorbidities, cluster 2 contained individuals with high prevalence of cardiovascular diseases, cluster 3 had those with high lung cancer prevalence, while cluster 4 had individuals with high prevalence of multiple comorbidities. There was no significant association between the clusters and either FEV_1 change

or decline. Age at hire, welding fume exposure, and silica exposure were significant predictors of both FEV_1 changes and decline. Age at initial exam and baseline FEV_1, which have been identified as significant predictors of these outcomes in the general population, were also significantly associated with the outcomes in the current study. By contrast, smoking, which is a common risk factor in the general population, was a weak predictor of FEV_1 change and decline in this cohort.

Conclusion. This study identified clusters of COPD related comorbidities and important predictors of lung function changes and decline within an occupational cohort. The findings suggest that the important predictors of lung function changes and decline in this occupational cohort are different from those reported in the general population. Study findings may be useful for guiding enhanced monitoring efforts and control programs.

4.2 Background

Chronic Obstructive Pulmonary Disease (COPD), a chronic inflammatory disease of the lungs, is a major cause of morbidity and mortality in the United States (US) and is frequently associated with multiple comorbidities [2,4,121]. Approximately 80% of individuals with COPD have at least one comorbidity [14]. Moreover, the prevalence and number of comorbidities tend to increase with age [5]. The mean number of comorbidities is estimated to be as high as five conditions, although this varies based on the population [196]. The most commonly reported comorbidities in the general population include multiple cardiovascular outcomes, stroke, hypertension, hyperlipidemia, diabetes, metabolic syndrome, chronic kidney disease, pulmonary and extra-pulmonary cancers, cachexia, skeletal muscle wasting, osteoporosis, gastro-esophageal reflux, anemia, arthritis, depression, sleep apnea, and other respiratory non-malignant respiratory diseases [14,122,123,196–198]. The presence of these comorbid conditions is associated with

poor health outcomes including lower quality of life as well as higher rates of dyspnea, hospitalizations, and mortality [15,94,121,199,200].

In clinical practice, comorbidities are important considerations when making disease management decisions [15,197]. Therefore, identifying common combinations or clusters of comorbidities and assessing if these disease combinations impact health outcomes is critically important for guiding clinical decisions and case management for improving health outcomes. Significant efforts have been taken to identify comorbid clusters in the general population as well as their impact on disease progression [201–205]. However, information on COPD comorbidities in occupational cohorts is limited. These comorbidities may differ from those in the general population due to differences in exposure experiences related to occupations. These differences, if identified, may be important for guiding clinical management. This is particularly critical among Department of Energy (DOE) workers who historically were exposed to respiratory hazards unique to the work they performed within the DOE complex. It is also possible that the effect of these comorbidities on the progression of COPD may differ in this occupational cohort compared to the general population. Thus, further investigation of COPD related comorbidities in this occupational cohort is warranted to better guide clinical decisions, disease management, and improvement of health outcomes. Therefore, the objectives of this study were to: (1) identify and describe clusters of COPD comorbidities among Department of Energy (DOE) former workers; (2) assess if the attributes of the identified clusters differ from those identified among the general population based on the published literature, and (3) identify predictors of lung function changes and decline among DOE former workers.

4.3 Methods

4.3.1 Ethical Statement

The United States Central Department of Energy Institutional Review Board (IRB) provided ethics approval and oversight of the study (DOE ID: DOE000645). A waiver of informed consent was granted by the IRB because this was a retrospective study involving analysis of secondary data.

4.3.2 Study Population

Data for this study were provided by the National Supplemental Screening Program (NSSP), which is a free medical screening program for DOE former workers, contractors, and subcontractors in the US. This voluntary program screens participants for occupational illnesses as well as general health conditions. Participants are eligible for rescreening every three years [16,206]. Eligibility for this study required participants to complete their initial exam, including spirometry results, before January 1, 2020 (n=18,075). A subset of participants (n=587) was excluded from the study due to their self-reported medical history of restrictive lung diseases such as chronic beryllium disease, silicosis, or asbestosis as these conditions may present with obstructive lung function patterns, potentially leading to misclassification as chronic obstructive pulmonary disease (COPD) (i.e. false positive) [165]. For individuals with repeated clinical tests, only the results from the initial and first rescreen exam were assessed in this study. The final full cohort for this study had 17,488 participants.

4.3.3 Data sources and preparation

4.3.3.1 Chronic obstructive pulmonary disease definition

Chronic obstructive pulmonary disease (COPD) was classified using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criterion, which compares the ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) with a fixed standard of 0.7 [6]. If the FEV_1/FVC ratio was less than the fixed standard (i.e. FEV_1/FVC <0.7), then the individual was considered to have COPD [6]. For descriptive purposes, COPD severity was also categorized as mild ($FEV_1 \geq 80\%$ of predicted), moderate (FEV_1 50-79% of predicted), severe (FEV_1 30-49% of predicted), and very severe ($FEV_1 < 30\%$ of predicted) [6,21].

4.3.3.2 Comorbidities Data

The comorbid conditions considered for investigation were identified from the scientific literature and the data extracted from participants' self-reported medical histories. The conditions assessed included: myocardial infarction, coronary artery disease, hypertension, stroke, underweight, overweight or obese, kidney problems, rheumatoid arthritis, asthma, diabetes, lung cancer, and non-pulmonary cancer. Participants who reported a diagnosis of diabetes or who reported routine insulin use were classified as having a history of diabetes. Additionally, participants who reported any indication of cancer occurring outside of the lungs were classified as having non-pulmonary cancers. The remaining comorbidities were extracted as binary indicators (Yes/No) from the medical histories (**Table 4.1**).

Table 4.1. Variables investigated for potential association with lung function changes.

Variable	Variable Definition
Demographic, Clinical, & Behavioral	
Age at Initial Exam (in Years)	Age of study participant at initial exam
Time between Exams (in Years)	Time from initial exam to rescreen exam
[1]FEV_1 at Initial Exam	Captured at initial exam
Race	Classified as black or non-Black
Sex	Categorized as male or female
Smoking Status	Self-reported at initial exam & classified as smoker/never smoker
Occupational History	
[2]DOE Site Category	Classified as uranium processing, weapons production, and science and laboratory facilities
Age at Hire (in Years)	Age of study participant at self-reported hire date
Duration of Employment	Self-reported and categorized into 5-year categories
Cadmium Exposure	Self-reported at initial exam (Yes/No)
Silica Exposure	Self-reported at initial exam (Yes/No)
Diesel Exhaust Exposure	Self-reported at initial exam (Yes/No)
Welding Fumes Exposure	Self-reported at initial exam (Yes/No)
Respiratory Symptoms	
Frequent cough	Self-reported at initial exam (Yes/No)
Shortness of breath	Self-reported at initial exam (Yes/No)
Wheezing	Self-reported at initial exam (Yes/No)
Other breathing problems	Self-reported at initial exam (Yes/No)
Medical History	
Comorbidity Cluster	Assigned after hierarchical clustering (Clusters 1-4)
Myocardial Infarction	Self-reported at initial exam (Yes/No)
Coronary Artery Disease	Self-reported at initial exam (Yes/No)
Hypertension	Self-reported at initial exam (Yes/No)
Stroke	Self-reported at initial exam (Yes/No)
Underweight	Self-reported at initial exam (Yes/No)
Overweight or Obese	Self-reported at initial exam (Yes/No)
Kidney Problems	Self-reported at initial exam (Yes/No)
Rheumatoid Arthritis	Self-reported at initial exam (Yes/No)
Lung Cancer	Self-reported at initial exam (Yes/No)
Non-Pulmonary Cancer	Self-reported at initial exam (Yes/No)
Asthma	Self-reported at initial exam (Yes/No)

[1]*Forced expiratory volume in one second is abbreviated as FEV_1.*
[2]*Department of Energy is abbreviated as DOE.*

4.3.3.3 Demographic, clinical, behavioral, and work history data

The demographic, clinical, and behavioral factors assessed in this study included age at initial exam, self-reported respiratory symptoms, FEV_1 value at initial exam, time between exams, sex (male/female), race (Black/non-Black), and self-reported smoking status (smoker/never smoker). For the occupational histories, the type of DOE facility where the participant spent the majority of their career was classified by the NSSP as uranium processing, weapons production, or science and laboratory facility. Duration of employment at a DOE facility was calculated from self-reported hire and termination dates. Age at hire was also computed from the self-reported hire dates and birth dates. The occupational exposures to silica, diesel exhaust, welding fumes, and cadmium were also self-reported and captured as dichotomous (Yes/No) variables.

4.3.4 Statistical & machine learning analyses

4.3.4.1 Descriptive statistics

All data management, statistical analyses, and machine learning were performed in SAS 9.4 [207] and RStudio version 2021.09.2 [132] interface of R version 4.0.3 [133]. Basic descriptive analyses for categorical variables included computation of frequencies and percentages as well as 95% confidence intervals of the percentages. Continuous variables were assessed for normality of distribution using the one-sample Kolmogorov-Smirnov test and a critical p-value of 0.05 [208]. Since most of the continuous variables were not normally distributed, summary statistics were presented as quartiles.

4.3.4.2 Multiple imputation

Imputation of missing values was performed using multivariate imputation by chained equation (MICE) through the mice R package [173]. Through this process, imputation was performed using predictive mean matching with a maximum of 30 iterations for 20 total imputations across all variables considered for comorbidity cluster identification as well as investigation of predictors of lung function changes [209].

4.3.4.3 Investigation of chronic obstructive pulmonary disease comorbidity clusters

Before performing the cluster analysis, univariable logistic regression models were used to identify comorbid conditions in the imputed datasets that had significant associations with COPD using a relaxed alpha of 0.2, and the results were combined using Rubin's rules for pooling [176]. Only comorbid conditions that had univariable logistic regression $p \leq 0.2$ were included in the cluster analysis.

To identify comorbidity clusters specific to COPD, hierarchical clustering using an agglomerative approach was applied only to participants with COPD. The cluster analysis used the complete linkage strategy for cluster merging and Gower's distance [210] as the distance measure. The multiple imputation pooling framework developed by Basagana et al was applied to the hierarchical clustering with the MICE datasets [211]. In this approach, Basagana et al. propose performing hierarchical cluster analysis on each imputed dataset individually to identify the optimal number of clusters for each dataset using an accepted method of optimizing the number of clusters [211]. Then, Basagana et al suggest using the median or mode of those values to find the overall optimal number of clusters across all the imputed datasets [211]. In this study, the "elbow" method was chosen for determining the optimal number of clusters in each imputed dataset. The point at which the smallest decrease in the within cluster sum of squares

occurs, creating an elbow on the graph, indicates the optimal number of clusters. After performing the elbow method for each data, the median of those optimal number of clusters was chosen for the overall optimal number of clusters. The imputed datasets were re-analyzed using the overall optimal number of clusters. Summary statistics on cluster membership and prevalence of comorbidities within each cluster were reported [211]. Kruskal Wallis, followed by Dunn's Test with a Bonferroni correction, was used to determine if the percentages of comorbidities varied across clusters. All cluster analyses were performed using the cluster R package [212].

4.3.4.4 Investigation of predictors of lung function changes and decline

Two approaches were used to predict lung function changes: a regression random forest model predicting the percent of FEV_1 change at the rescreen exam and a classification random forest model predicting whether the FEV_1 value declined at the rescreen exam. First, the regression random forest model was used to identify variables that had a significant association with the percentage change in FEV_1 using univariable ordinary least squares models and a relaxed alpha of 0.2. The results were then pooled using Rubin's rules for pooling [176], and only variables with a p-value ≤ 0.2 were included in the regression random forest. Each MICE dataset was split into 75% training data and 25% testing data. These data only included individuals with COPD who completed their initial exam and returned for their first rescreen exam. Model performance was assessed using root mean squared error. To identify which variables were most important for prediction, variable importance scores were calculated using the sum of squared errors.

As with the regression random forest models, the classification random forest models used univariable logistic regression with a relaxed alpha of 0.2 to identify variables associated with a decline in FEV_1 at the rescreen exam. The logistic regression model results were pooled

using Rubin's Rules [176]. Only variables with a p-value ≤ 0.2 were included in the classification random forest models. As before, the MICE datasets were split into training data (75%) and testing data (25%). As with the regression random forest models, the training and testing data included only individuals with COPD who completed both an initial and rescreen exam. Model performance assessment was based on the overall classification accuracy as well as the sensitivity and specificity. Variable importance scores were once again used for identifying the most important factors driving model performance. However, this time the classification variable importance scores were calculated using the Gini impurity index.

The full list of variables considered for both the regression and classification random forest models is provided in **Table 4.1** and includes the comorbidity clusters identified through the cluster analysis. If the comorbidity clusters were not selected for the random forest models, then the individual comorbidity components of the clusters were considered for possible inclusion in the random forest models. Descriptive statistics (i.e., median, minimum, maximum, interquartile range) were used to describe the performance metrics and variable importance scores across imputed datasets for both the regression and classification random forest models. All the random forest model building, variable selection, and descriptive statistics were performed using the caret R package [213].

4.4 Results

4.4.1 Descriptive statistics

A total of 17,488 NSSP participants completed their initial exams before 2020, and 20.9% of them had COPD (**Table 4.2**). The majority of COPD cases were mild (43.0%) or moderate (42.8%) and only 14.2% were severe or very severe. Most of the participants were male (74.7%) and non-black (88.2%).

Table 4.2. Descriptive statistics of work history, demographic, and clinical characteristics of Department of Energy former workers participating in the National Supplemental Screening Program, 2005-2019.

Categorical Characteristics	Frequency	Percentage	95% Confidence Interval
COPD	**n=17,488**		
Yes	3,647	20.9	20.3-21.5
No	13,841	79.2	78.5-79.7
GOLD Level	**n=3,647**		
Mild	1,569	43.0	41.4-44.6
Moderate	1,561	42.8	41.2-44.4
Severe or Very Severe	515	14.2	13.0-15.3
Sex	**n=17,488**		
Male	13,064	74.7	74.1-75.4
Female	4,424	25.3	24.7-25.9
Race	**n=13,525**		
Black	1,615	11.9	11.3-12.4
Non-Black	12,010	88.2	87.6-88.7
Smoking Status	**n=17,488**		
Ever Smoker	7,619	43.6	42.8-44.3
Never Smoker	9,869	56.4	55.7-57.2
Age	**n=17,488**		
< 55 years old	3,122	17.9	17.3-18.4
55-59 years old	2,095	12.0	11.5-12.5
60-64 years old	2,882	16.5	15.9-17.0
65-69 years old	3,015	17.3	16.7-17.9
70-74 years old	2,586	14.8	14.3-15.3
≥ 75 years old	3,778	21.6	21.0-22.2
[1]**DOE Category**	**n=17,488**		
Weapons Production	12,763	73.0	72.3-73.6
Science/Laboratory	3,600	20.6	20.0-21.2
Uranium Processing	1,125	6.4	6.1-6.8
Welding Fumes Exposure	**n= 17,448**		
Yes	8,221	47.1	46.4-47.9
No	9,227	52.9	52.1-53.6
Cadmium Exposure	**n=17,455**		
Yes	6,206	35.6	34.8-36.3
No	11,249	64.5	63.7-65.2
Silica Exposure	**n=17,452**		
Yes	6,077	34.8	34.1-35.5
No	11,375	65.2	64.4-65.9
Diesel Exhaust Exposure	**n=17,464**		
Yes	5,072	29.0	28.4-29.7
No	12,392	71.0	70.3-71.6

Table 4.2. Continued.

Categorical Characteristics	Frequency	Percentage	95% Confidence Interval
Duration of Employment	**n=17,488**		
< 5 years	5,605	32.1	31.4-32.8
5-9 years	2,886	16.5	16.0-17.1
10-14 years	2,008	11.5	11.0-12.0
15-19 years	1,551	8.9	8.5-9.3
20-24 years	1,375	7.9	7.5-8.3
25-29 years	1,229	7.0	6.7-7.4
≥ 30 years	2,834	16.2	15.7-16.8
Shortness of Breath	**n=17,465**		
Yes	7,618	43.6	42.9-44.4
No	9,847	56.4	55.7-57.1
Frequent Cough	**n=17,461**		
Yes	5,890	33.7	33.0-34.4
No	11,571	66.3	65.6-67.0
Wheezing	**n=17,437**		
Yes	4,643	26.6	26.0-27.3
No	12,794	73.4	72.7-74.0
Other Breathing Problems	**n=17,438**		
Yes	4,024	23.1	22.5-23.7
No	13,414	76.9	76.3-77.6
Overweight or Obese	**n=17,445**		
Yes	13,900	79.7	79.1-80.3
No	3,545	20.3	19.7-20.9
Hypertension	**n=17,032**		
Yes	6,312	37.1	36.3-37.8
No	10,720	62.9	62.2-63.7
Non-Pulmonary Cancer	**n=17,345**		
Yes	4,900	28.3	27.6-28.9
No	12,445	71.7	71.1-72.4
Diabetes	**n=17,247**		
Yes	3,008	17.4	16.9-18.0
No	14,239	82.6	82.0-83.1
Asthma	**n=17,044**		
Yes	2,247	13.2	12.7-13.7
No	14,797	86.8	86.3-87.3
Kidney Problems	**n=14,881**		
Yes	1,730	11.6	11.1-12.1
No	13,151	88.4	87.9-88.9
Coronary Artery Disease	**n=16,832**		
Yes	1,919	11.4	10.9-11.9
No	14,913	88.6	88.1-89.1

Table 4.2 Continued.

Categorical Characteristics	Frequency	Percentage	95% Confidence Interval
Myocardial Infarction	**n=16,945**		
Yes	1,445	8.5	8.1-9.0
No	15,500	91.5	91.1-91.9
Stroke	**n=17,087**		
Yes	857	5.0	4.7-5.3
No	16,230	95.0	94.7-95.3
Underweight	**n=17,445**		
Yes	83	0.5	0.4-0.6
No	17,362	99.5	99.4-99.6
Anemia	**n=17,018**		
Yes	1,619	9.5	9.1-10.0
No	15,399	90.5	90.1-90.9
Rheumatoid Arthritis	**n=15,836**		
Yes	932	5.9	5.5-6.3
No	14,904	94.1	93.8-94.5
Lung Cancer	**n=17,087**		
Yes	135	0.8	0.7-0.9
No	16,952	99.2	99.1-99.3
Continuous Characteristics	**Frequency**	**Median**	**Interquartile Range**
Age at Initial Exam (Years)	17,488	66	58-73
Age at Hire (Years)	17,453	26	22-34
[2]FEV_1 at initial	17,471	2.75	2.17-3.35
[3]Time between Exams (Years)	769	5	3-7
[2,3]FEV_1 change between Exams	769	-0.27	-1.06-0.43

[1]*Department of Energy*
[2]*Forced expiratory volume in one second*
[3]*Computed for participants with chronic obstructive pulmonary disease who returned for a rescreen exam.*

Approximately 43.6% of the participants reported a history of smoking. The median age at initial exam was 66 years old, and nearly 22% of the participants were 75 years old or older (**Table 4.2**).

Seventy three percent of the participants worked at weapons production facilities, 20.6% at science or laboratory facilities, and 6.4% at uranium processing facilities. Exposure to welding fumes was the most prevalent occupational exposure affecting 47.1% of the participants followed by cadmium (35.6%), silica (34.8%), and diesel exhaust (29.0%) exposures. The median age at hire was 26 years (interquartile range (IQR): 22-34 years), with 32.1% of participants employed for less than 5 years at a Department of Energy (DOE) facility.

Regarding clinical presentation, participants most frequently (43.6%) reported shortness of breath (43.6%), followed by frequent cough (33.7%), wheezing (26.6%), and other breathing problems (23.1%). Overweight or obesity was the most prevalent comorbid condition observed in 79.7% of the participants followed by hypertension (37.1%), non-pulmonary cancer (28.3%), diabetes (17.4%), asthma (13.2%), kidney problems (11.6%), coronary artery disease (11.4%), and the remaining conditions had a prevalence of <10%. The median FEV_1 at the initial exam was 2.8 (IQR: 2.2-3.4).

Only 22.3% of the participants returned for the first rescreening exam, and of those, only 19.7% (n=769) were classified as having COPD at their initial exam. The median time between exams for those with COPD was 5 years (IQR: 3-7 years). Approximately 59% of those with COPD showed a decline in the FEV_1 at their rescreen exam, and their median change in FEV_1 from the initial to rescreen exam was -0.27 (**Table 4.2**). All assessed comorbidities, except diabetes, had significant associations with COPD at a liberal alpha level of 0.2 and were included in the hierarchical cluster analysis (**Table 4.3**).

Table 4.3. Associations between COPD1 and several comorbidities among Department of Energy former workers who participated in the National Supplemental Screening Program, 2005-2019.

Characteristics	Odds Ratio	95% Confidence Interval	p-value
Lung Cancer			
Yes	3.94	2.82, 5.50	<0.0001
No	*Reference*		
Myocardial Infarction			
Yes	1.36	1.21, 1.54	<0.0001
No	*Reference*		
Coronary Artery Disease			
Yes	1.43	1.28, 1.60	<0.0001
No	*Reference*		
Hypertension			
Yes	1.07	0.99, 1.16	0.0717
No	*Reference*		
Stroke			
Yes	1.52	1.30, 1.78	<0.0001
No	*Reference*		
Diabetes			
Yes	0.96	0.87, 1.05	0.3673
No	*Reference*		
Underweight			
Yes	3.23	2.09, 4.98	<0.0001
No	*Reference*		
Overweight or Obese			
Yes	0.62	0.57, 0.67	<0.0001
No	*Reference*		
Kidney Problems			
Yes	1.21	1.08, 1.36	0.0011
No	*Reference*		
Rheumatoid Arthritis			
Yes	1.33	1.15, 1.54	0.0002
No	*Reference*		
Anemia			
Yes	1.08	0.96, 1.23	0.1978
No	*Reference*		
Non-Pulmonary Cancer			
Yes	1.35	1.24, 1.46	<0.0001
No	*Reference*		
Asthma			
Yes	1.92	1.74, 2.11	<0.0001
No	*Reference*		

[1]*Chronic obstructive pulmonary disease*

4.4.2 Comorbidity clusters

The overall optimal number of clusters was 4 with a range of 3 to 7 clusters. Cluster 1 was the largest with a median of 69.1% (IQR: 69.1%-77.6%) participants that had COPD across all datasets. Cluster 4 was the smallest and had a median of 2.1% (IQR:1.3%-4.7%) of the participants. Clusters 2 and 3 had medians of 21.4% (IQR: 12.1%-26.4%) and 4.9% (IQR: 2.3-7.3) of the participants, respectively.

The results of the Kruskal Wallis test showed that the prevalence of nearly all comorbid conditions, except asthma and underweight, varied across clusters (**Table 4.4**). Although there was evidence that lung cancer prevalence varied across clusters based on the Kruskal Wallis test ($p=0.0396$), there was no evidence of variation across clusters after Bonferroni correction was applied to the Dunn's test since all corrected p-values were > 0.05 (**Table 4.4**). As for the conditions which did vary across clusters, the prevalence of myocardial infarction was significantly ($p<0.05$) lower in cluster 1 (median: 5.3%) than in all other clusters (**Table 4.4**), while the prevalence in cluster 2 (median: 18.8%) was significantly ($p=0.0148$) lower than that in cluster 4 (median: 56.0%). Similarly, coronary artery disease prevalence was significantly ($p<0.05$) lower in cluster 1 (median: 6.3%) than all other clusters (**Table 4.4**). Cluster 2 (median: 29.1%) also had a significantly ($p=0.0240$) lower prevalence of coronary artery disease than cluster 4 (median: 77.8%). The results of the comparisons of the prevalence estimates of the rest of the comorbid conditions across clusters are shown in **Table 4.4**. Generally, cluster 1 had low prevalence of most comorbidity conditions. Cluster 2 had higher prevalence proportions of cardiovascular conditions when compared to cluster 1 while also having lower prevalences of most conditions than clusters 3 and 4. Both clusters 3 and 4 had high prevalence proportions of nearly all conditions.

Table 4.4. Summary of comorbidities within clusters of National Supplemental Screening Program participants with chronic obstructive pulmonary disease (n=3,647) across all imputed datasets (n=20), 2005-2019.

Comorbidity	Cluster 1 Median (IQR[1])	Cluster 2 Median (IQR[1])	Cluster 3 Median (IQR[1])	Cluster 4 Median (IQR[1])	Kruskal Wallis Test Statistic (p-value)	Clusters 1 & 2 Dunn's Test Statistic[2] (p-value)	Clusters 1 & 3 Dunn's Test Statistic[2] (p-value)	Clusters 1 & 4 Dunn's Test Statistic[2] (p-value)	Clusters 2 & 3 Dunn's Test Statistic[2] (p-value)	Clusters 2 & 4 Dunn's Test Statistic[2] (p-value)	Clusters 3 & 4 Dunn's Test Statistic[2] (p-value)
Lung Cancer	1.8 (1.4, 2.1)	2.3 (1.5, 4.1)	3.1 (1.8, 4.7)	1.3 (0.7, 2.2)	8.3 (0.0396)	1.45 (0.8721)	1.91 (0.3405)	-0.59 (1.000)	0.45 (1.000)	-2.04 (0.2473)	-2.49 (0.0765)
Myocardial Infarction	5.3 (3.4, 7.5)	18.8 (9.8, 32.7)	42.1 (12.5, 68.9)	56.0 (34.8, 80.3)	38.1 (<0.0001)	2.92 (0.0211)	4.31 (<0.0001)	5.95 (<0.0001)	1.39 (0.9907)	3.03 (0.0148)	1.64 (0.6063)
Coronary Artery Disease	6.3 (3.2, 11.0)	29.1 (10.8, 49.2)	53.2 (16.8, 84.3)	77.8 (36.1, 89.6)	37.4 (<0.0001)	2.91 (0.0215)	4.50 (<0.0001)	5.79 (<0.0001)	1.59 (0.6773)	2.88 (0.0240)	1.29 (1.000)
Hypertension	31.0 (20.2, 35.3)	66.8 (41.9, 76.0)	55.9 (34.6, 81.2)	80.1 (65.4, 93.6)	35.3 (<0.0001)	3.82 (0.0008)	3.64 (0.0016)	5.82 (<0.0001)	-0.17 (1.000)	2.00 (0.2705)	2.18 (0.1767)
Stroke	4.9 (3.5, 5.9)	9.7 (5.4, 12.2)	18.3 (7.2, 40.3)	31.1 (12.8, 70.7)	27.6 (<0.0001)	2.25 (0.1458)	3.98 (0.0004)	4.87 (<0.0001)	1.73 (0.5036)	2.62 (0.0528)	0.89 (1.000)
Kidney Problems	10.3 (8.2, 12.6)	9.7 (5.3, 21.5)	36.3 (19.8, 54.2)	49.4 (39.0, 72.0)	42.1 (<0.0001)	0.67 (1.000)	4.06 (0.0003)	5.50 (<0.0001)	3.40 (0.0041)	4.84 (<0.0001)	1.44 (0.8950)
Rheumatoid Arthritis	5.4 (4.0, 7.3)	10.0 (3.5, 13.0)	25.5 (9.3, 33.4)	37.0 (15.5, 53.7)	41.3 (<0.0001)	1.76 (0.4681)	4.54 (<0.0001)	5.78 (<0.0001)	2.78 (0.0327)	4.02 (0.0004)	1.24 (1.000)

Table 4.4. Continued.

Comorbidity	Cluster 1 Median (IQR[1])	Cluster 2 Median (IQR[1])	Cluster 3 Median (IQR[1])	Cluster 4 Median (IQR[1])	Kruskal Wallis Test Statistic (p-value)	Clusters 1 & 2 Dunn's Test Statistic[2] (p-value)	Clusters 1 & 3 Dunn's Test Statistic[2] (p-value)	Clusters 1 & 4 Dunn's Test Statistic[2] (p-value)	Clusters 2 & 3 Dunn's Test Statistic[2] (p-value)	Clusters 2 & 4 Dunn's Test Statistic[2] (p-value)	Clusters 3 & 4 Dunn's Test Statistic[2] (p-value)
Anemia	0.09 (0.08, 0.10)	0.07 (0.03, 0.15)	0.25 (0.19, 0.38)	0.33 (0.22, 0.53)	35.7 (<0.0001)	-0.12 (1.000)	3.56 (0.0022)	4.64 (<0.0001)	3.68 0.0014	4.75 (<0.0001)	1.08 (1.000)
Non-Pulmonary Cancer	28.6 (24.4, 30.9)	48.7 (34.3, 56.3)	55.8 (44.2, 64.7)	60.5 (48.7, 76.9)	24.3 (<0.0001)	2.99 (0.0169)	4.21 (0.0002)	4.31 (<0.0001)	1.22 (1.000)	1.33 (1.000)	0.10 (1.000)
Overweight or Obese	68.5 (65.0, 73.8)	85.0 (67.3, 94.3)	79.7 (62.4, 89.1)	81.3 (75.7, 89.9)	10.2 (0.0172)	2.76 (0.0351)	1.91 (0.3379)	2.77 (0.0341)	-0.85 (1.000)	0.01 (0.9919)	0.86 (0.3913)
Underweight	1.1 (0.8, 1.4)	0.4 (0.1, 1.9)	0.4 (0.0, 1.7)	0.7 (0.0, 2.5)	2.2 (0.5320)						
Asthma	19.5 (17.1, 20.5)	16.3 (7.0, 24.0)	17.7 (11.5, 46.3)	25.3 (13.2, 57.9)	4.6 (0.205)						

[1]*Interquartile range*
[2]*Dunn's test was only performed on comorbidities which varied across clusters based on the Kruskal Wallis test ($p < 0.05$). The p-values are Bonferroni corrected p-values.*

4.4.3 Predictors of FEV_1 change

Several variables had significant ($p<0.2$) associations with FEV_1 change, including: age at initial exam, age at hire, FEV_1 at initial exam, sex, smoking status, frequent cough, shortness of breath, wheezing, other breathing problems, Department of Energy (DOE) job category, and welding fumes (**Table 4.5**). The comorbidity clusters did not have a significant ($p<0.436$) association with the FEV_1 change (**Table 4.5**). However, several of the comorbid conditions which comprise the clusters were significantly ($p<0.2$) associated with FEV_1 change. These included myocardial infarction, coronary artery disease, hypertension, stroke, kidney problems, lung cancer, non-pulmonary cancer, rheumatoid arthritis, anemia, and asthma (**Table 4.5**).

Overall, the root mean square errors (RMSE) of the regression random forest models were fairly low across the training (median: 0.85, IQR: 0.83-0.86) and testing (median: 0.84, IQR: 0.81-0.87) datasets. Yet, the amount of variance explained by the model was also low. Only 49.3% (IQR: 48.4%-52.1%) of the variance in the training data and 47.0% in the testing data (IQR: 44.1%-52.4%) were explained by the regression random forest model. At its maximum, the variance explained by the model was 53.8% for the training data and 56.6% for the testing data. However, even with the relatively poor model performance, the variable importance scores still provide interesting insight into which variables are most influential for predicting the FEV_1 change from initial to rescreen. The FEV_1 at initial exam (variable importance median: 449.1), age at initial exam (variable importance median: 75.0), age at hire (variable importance median: 68.1), and sex (variable importance median: 47.7) had the highest median variable importance scores (**Table 4.6**). The rest of the assessed variables had importance scores less than 20 *(***Table 4.6**).

Table 4.5. Associations of [1]FEV1 change and [1]FEV1 decline with several potential predictor variables among the National Supplemental Screening Program participants with chronic obstructive pulmonary at initial exam.

Characteristics	[1]FEV_1 Change			[1]FEV_1 Decline		
	Point Estimate	95% Confidence Interval	P-value	Odds Ratio	95% Confidence Interval	P-value
Age at Initial Exam	-0.03	-0.04, -0.02	<0.0001	1.05	1.09, 1.07	<0.0001
Age at Hire	-0.01	-0.02, -0.0004	0.0411	1.01	0.9978, 1.03	0.0938
[1]FEV_1 at Initial Exam	0.94	0.88, 1.01	<0.0001	0.14	0.11, 0.19	<0.0001
Sex			<0.0001			<0.0001
Male	0.70	0.51, 0.89	<0.0001	0.41	0.30, 0.58	<0.0001
Female	*Reference*					
Smoking Status			0.1620			0.1753
Yes	-0.12,	-0.30, 0.50	0.1620	1.23	0.91, 1.65	0.1753
No	*Reference*					
Frequent Cough			<0.0001			0.0005
Yes	-0.45	-0.62, -0.28	<0.0001	1.72	1.27, 2.34	0.0005
No	*Reference*					
Shortness of Breath			<0.0001			<0.0001
Yes	-0.52	-0.68, -0.36	<0.0001	1.99	1.48, 2.66	<0.0001
No	*Reference*					
Wheezing			<0.0001			<0.0001
Yes	-0.45	-0.63, -0.28	<0.0001	1.91	1.40, 2.60	<0.0001
No	*Reference*					
Other Breathing Problems			<0.0001			<0.0001
Yes	-0.61	-0.78, -0.43	<0.0001	2.26	1.63, 3.13	<0.0001
No	*Reference*					
[2]DOE Job Category			0.1942			0.2781
Uranium Processing Facilities	-0.36	-0.75, 0.03	0.0733	1.72	0.85, 3.51	0.1319
Weapons Production	-0.11	-0.33, 0.10	0.3074	1.03	0.71, 1.49	0.8792
Science and Laboratory Facilities	*Reference*					
Welding Fumes Exposure			0.0907			0.0312
Yes	0.14	-0.02, 0.31	0.0907	0.73	0.55, 0.97	0.0312
No	*Reference*					
Cluster Assignment			0.4357			0.7412
Cluster 2	-0.14	-0.63, 0.35	0.5677	1.23	0.60,	0.5633
Cluster 3	-0.38	-1.05, 0.30	0.2786	1.79	0.48,	0.3791
Cluster 4	-0.70	-1.66, 0.26	0.1577	4.87	0.00, 80331	0.9851
Cluster 1	*Reference*					
Myocardial Infarction			0.0025			0.0112
Yes	-0.42	-0.69, -0.15	0.0025	1.92	1.16, 3.17	0.0112
No	*Reference*					
Coronary Artery Disease			0.0051			0.0278
Yes	-0.34	-0.58, -0.10	0.0051	1.63	1.05, 2.51	0.0278
No	*Reference*					

Table 4.5 Continued.

Characteristics	Point Estimate	[1]FEV_1 Change 95% Confidence Interval	P-value	Odds Ratio	[1]FEV_1 Decline 95% Confidence Interval	P-value
Hypertension			0.1138			0.0116
Yes	-0.143	-0.32, 0.35	0.1138	1.49	1.09, 2.02	0.0116
No	*References*					
Stroke			0.0258			0.5535
Yes	-0.37	-0.70, -0.05	0.0258	1.18	0.68, 2.06	0.5535
No	*Reference*					
Kidney Problems			0.0158			0.0548
Yes	-0.31	-0.56, -0.06	0.0158	1.57	0.99, 2.50	0.0548
No	*Reference*					
Lung Cancer			0.0663			0.0584
Yes	-0.52	-1.04, -0.004	0.0663	2.80	0.96, 8.14	0.0584
No	*Reference*					
Non-Pulmonary Cancer			0.0666			0.0364
Yes	-0.17	-0.35, 0.01	0.0666	1.40	1.02, 1.92	0.0364
No	*Reference*					
Rheumatoid Arthritis			0.1468			0.1345
Yes	-0.24	-0.57, 0.09	0.1468	1.57	0.87, 2.86	0.1345
No	*Reference*					
Anemia						0.0142
Yes	-0.46	-0.74, -0.19	0.0009	1.87	1.13, 3.08	0.0142
No	*Reference*					
Asthma			<0.0001			0.0049
Yes	-0.43	-0.63, -0.23	<0.0001	1.68	1.17, 2.42	0.0049
No	*Reference*					
Time Between Exam	0.01	-0.02, 0.44	0.5281	0.98	0.93, 1.04	0.5686
Race			0.6056			0.4745
Non-Black	-0.09	-0.43, 0.25	0.6056	1.24	0.69, 2.22	0.4745
Black	*Reference*					
Duration of Employment			0.3840			0.1760
5-9 years	-0.09	-0.35, 0.16	0.4698	1.32	0.85, 1.68	0.2130
10-14 years	0.16	-0.14, 0.46	0.2989	0.76	0.46, 2.06	0.2781
15-19 years	0.03	-0.28, 0.31	0.9197	1.33	0.79, 1.25	0.2835
20-24 years	0.24	-0.12, 0.60	0.1942	0.81	0.44, 1.48	0.4876
25-29 years	-0.23	-0.57, 0.12	0.2054	1.59	0.86, 2.97	0.1417
≥ 30 years	0.01	-0.24, 0.26	0.9433	1.31	0.85, 2.02	0.2265
<5 years	*Reference*					
Cadmium Exposure			0.3749			0.3665
Yes	0.08	-0.09, 0.25	0.3749	0.87	0.65, 1.17	0.3665
No	*Reference*					
Silica Exposure			0.2828			0.0422
Yes	0.10	-0.07 0.27	0.2828	0.73	0.54, 0.99	0.0422
No	*Reference*					
Diesel Exhaust Exposure			0.5130			0.2289
Yes	0.06	-0.12, 0.25,	0.5130	0.82	0.60, 1.13	0.2289
No	*Reference*					

Table 4.5. Continued.

Characteristics	[1]FEV_1 Change			[1]FEV_1 Decline		
	Point Estimate	95% Confidence Interval	P-value	Odds Ratio	95% Confidence Interval	P-value
Underweight			0.3901			0.8415
Yes	-0.36	-1.19, 0.46	0.3901	1.16	0.27, 4.89	0.8415
No	*Reference*					
Overweight or Obese			0.9099			0.1520
Yes	-0.01	-0.20, 0.18	0.9099	1.26	0.92, 1.74	0.1520
No	*Reference*					

[1]*Forced expiratory volume in one second*
[2]*Department of Energy*

Table 4.6. Importance scores for predictors of change in [1]FEV1 and [1]FEV1 decline for National Supplemental Screening Program participants with chronic obstructive pulmonary at initial exam (n=769) across all imputed datasets (n=20)

	Predicting [1]FEV_1 Change[3]		Predicting [1]FEV_1 Decline[4]	
Characteristic	**Median**	**IQR**	**Median**	**IQR**
[1]FEV_1 at Initial Exam	449.1	444.3, 457.5	124.1	121.1, 125.7
Age at Initial Exam	75.0	72.1, 76.9	33.3	31.9, 34.5
Age at Hire	58.1	57.0, 59.9	28.5	27.6, 29.6
Sex				
Male	47.71	45.7, 53.1	12.7	11.2, 14.6
Female	*Reference*			
Other Breathing Problems				
Yes	16.5	14.9, 18.8	4.6	4.0, 5.0
No	*Reference*			
Frequent Cough				
Yes	12.3	11.2, 13.9	4.2	4.0, 4.4
No	*Reference*			
Asthma				
Yes	11.6	9.6, 12.7	3.4	3.1, 3.7
No	*Reference*			
Shortness of Breath				
Yes	11.5	10.8, 12.9	4.7	4.4, 5.1
No	*Reference*			
Wheezing				
Yes	10.0	9.0, 11.2	4.0	3.8, 4.4
No	*Reference*			
Welding Fumes				
Yes	10.0	9.5, 10.5	5.4	4.6, 5.5
No	*Reference*			
Smoking Status				
Yes	9.0	8.6, 9.7	5.0	4.8, 5.3
No	*Reference*			
Non-Pulmonary Cancer				
Yes	8.8	8.2, 9.5	3.7	3.5, 3.8
No	*Reference*			
Hypertension				
Yes	8.0	7.6, 8.3	3.9	3.8, 4.3
No	*Reference*			
Anemia				
Yes	7.6	6.7, 7.9	2.8	2.6, 3.0
No	*Reference*			
Kidney Problems				
Yes	7.5	6.6, 9.2	N/A	N/A
No	*Reference*			

Table 4.6. Continued.

Characteristic	Predicting [1]FEV_1 Change[3] Median	IQR	Predicting [1]FEV_1 Decline[4] Median	IQR
Rheumatoid Arthritis				
Yes	6.4	5.9, 7.5	1.9	1.7, 2.2
No	*Reference*			
Coronary Artery Disease				
Yes	5.1	4.7, 5.5	2.6	2.4, 2.8
No	*Reference*			
Stroke				
Yes	5.0	4.4, 5.8	N/A	N/A
No	*Reference*			
Myocardial Infarction				
Yes	4.6	4.3, 4.7	2.7	2.6, 3.1
No	*Reference*			
[2]DOE Job Category				
Uranium Processing Facilities	3.3	3.0, 3.7	N/A	N/A
Weapons Production	7.9	7.4, 8.4	N/A	N/A
Science and Laboratory Facilities	*Reference*			
Lung Cancer				
Yes	1.9	1.6, 2.2	0.9	0.8, 1.0
No	*Reference*			
Silica Exposure				
Yes	N/A	N/A	5.1	5.0, 5.4
No	*Reference*			
Overweight and Obese				
Yes	N/A	N/A	4.3	4.1, 4.4
No	*Reference*			
Duration of Employment				
5-9 years	N/A	N/A	3.4	3.2, 3.5
10-14 years	N/A	N/A	3.5	3.2, 3.6
15-19 years	N/A	N/A	4.3	4.0, 4.6
20-24 years	N/A	N/A	1.7	1.6, 1.8
25-29 years	N/A	N/A	2.4	2.1, 2.6
≥ 30 years	N/A	N/A	2.8	2.7, 3.0
<5 years	*Reference*			

[1]*Forced expiratory volume in one second*
[2]*Department of Energy*
[3]*Variable importance scores are based on regression random forest models.*
[4]*Variable importance scores are based on classification random forest models.*

4.4.4 Predictors of FEV_1 decline

The following variables had significant ($p<0.2$) associations with FEV_1 decline: age at initial exam, age at hire, FEV_1 at initial exam, sex, smoking status, frequent cough, shortness of breath, wheezing, other breathing problems, welding fume exposure, silica exposure, and duration of employment (**Table 4.5**). Similar to the results of the FEV_1 change models, there was no significant ($p<0.741$) association between FEV_1 decline and comorbidity clusters. However, when assessed individually, several comorbid conditions had significant associations with FEV_1 decline, including: myocardial infarction, coronary artery disease, hypertension, kidney problems, lung cancer, non-pulmonary cancer, anemia, asthma, and overweight or obese, (**Table 4.5**).

Unlike the regression random forest models, however, the classification random forest model performed fairly well in predicting FEV_1 decline. The median classification accuracy across all imputed datasets was 76.8% (IQR: 75.4%-77.8%) in the training data and 76.5% (IQR: 75.0%-78.8%) in the testing data. The model also produced similar levels of performance based on sensitivity and specificity assessment with medians of 78.8% (IQR: 77.8 %-79.6%) and 73.5% (IQR: 72.7%-74.8%), respectively, for the training data. In the testing data, the median sensitivity was 82.8% (IQR: 79.4%-85.6%) while the median specificity was 68.7% (IQR: 64.6%-71.7%). Variables which had the highest importance score for predicting FEV_1 decline were: FEV_1 at initial exam (median variable importance score: 124.1), age at initial exam (median variable importance score: 33.3), age at hire (median variable importance score: 28.5), and sex (median variable importance score: 12.7) (**Table 4.6**). The scores for the remaining variables were all less than 6.0.

4.5 Discussion

This study was designed to identify and describe clusters of COPD comorbidities within an occupational cohort of former US DOE workers. The study also investigated predictors of lung function changes or decline. Study findings may be useful in enhancing health programs screening for comorbidities and for medical management of COPD.

4.5.1 Comorbidity Cluster Identification

This study identified four unique clusters of COPD-related comorbidity conditions, which is consistent with the 4-6 comorbidity clusters identified in previous studies [201,202,214–216]. In the current study, cluster 1 had lower prevalence proportions of myocardial infarction, coronary artery disease, hypertension, non-pulmonary cancer, and overweight or obesity than all other clusters. This suggests that cluster 1 may represent a cluster of otherwise healthy individuals with COPD, which is consistent with findings from other studies [201,202,214,216]. In previous studies, a lower general prevalence of all comorbid conditions was significantly associated with less severe COPD outcomes [214,216]. Unfortunately, the severity of long-term COPD outcomes similar to those used in previous studies could not be assessed in this study. Thus, cluster 1 represents a less severe COPD cluster potentially requiring less complicated medical management.

Cluster 2 had a higher prevalence of cardiovascular conditions than cluster 1 while also having a lower prevalence of many non-cardiovascular conditions than clusters 3 and 4. Thus, cluster 2 is a high cardiovascular disease prevalence cluster, which is consistent with findings from many other studies [201,202,214–216]. In general, the pathophysiological processes for cardiac function and respiration are interrelated [217]. Thus, respiratory dysfunction such as that

produced by COPD could lead to cardiac abnormalities, which can ultimately result in worse prognosis when both COPD and cardiovascular disease occur [214,217].

Both clusters 3 and 4 had higher prevalence proportions of most conditions than clusters 1 and 2, which is suggestive of more complicated or severe COPD within these clusters [214,216]. Although not statistically different, the lung cancer prevalence in cluster 3 was double the prevalence in cluster 4, which suggests that cluster 3 may be comprised of individuals with high lung cancer prevalence. The co-occurrence of COPD and lung cancer has been reported by other studies which estimated that 40%-70% of those with lung cancer develop COPD while those with COPD are 2-7 times more likely to develop lung cancer [218,219]. Although the biological mechanism resulting in the co-occurrences of COPD and lung cancer is unknown, it is thought to be related to a combination of genomic factors, chronic inflammation, and shared risk factors [218,219].

4.5.2 Prediction of FEV_1 Change

The current study identified significant associations between FEV_1 change and multiple comorbid conditions including history of asthma, myocardial infarction, and kidney problems. However, the importance of these comorbid conditions in predicting FEV_1 change was limited. The biological mechanism driving the co-occurrence of multiple comorbidities and COPD is thought to be multifactorial arising from the interplay of genetic, environmental, and lifestyle factors such as smoking [220]. The reason for the limited predictive importance of the comorbid conditions is unclear but might be related to the population studied. This study included individuals with potentially higher exposure to noxious substances, which could also contribute to lung function changes, than the general population [24,95]. Another potential reason is the differences between machine learning and traditional statistical approaches [221]. A study by

Boueiz et al reported similar findings and attributed it to methodological differences between traditional statistical analyses and novel machine learning approaches [221].

Although comorbidities had limited abilities for predicting FEV_1 change, several other factors were identified as important predictors. For instance, age at initial exam was one of the strongest predictors of FEV_1 change in this study, a finding that is consistent with reports from other studies [83,222,223]. Across a healthy lifespan, lung function is expected to change, and even decline, with age, most likely resulting from the natural consequences of respiratory aging such as loss of respiratory muscle strength or pulmonary elasticity [83]. This notion is often true for COPD as the condition is characterized by accelerated lung function decline [22]. Age at hire was also of high importance for predicting FEV_1 change in the current study. However, it is difficult to compare the importance of age at hire to results from other studies as occupational factors are often not included in studies of the general population [83,221–223]. Suffice it to say that these findings may be suggestive of the importance occupational factors play in lung function changes especially given that exposure to welding fumes was a significant, albeit weak, predictor in this study.

4.5.3 Prediction of FEV_1 Decline

The significant association between FEV_1 decline and cardiovascular disease identified in this study is consistent with reports from other studies [224–229]. Lung function impairment can result in cardiovascular disease/events [229], among both individuals with and those without COPD [227,228]. As was the case for FEV_1 change, cardiovascular disease had limited predictive importance in predicting FEV_1 decline among those with COPD. By contrast, a study by Whittaker et al reported no significant association between cardiovascular disease and accelerated FEV_1 decline among individuals with COPD [225]. The low predictive importance of

cardiovascular diseases for predicting FEV_1 decline may be due to variations in lung trajectories [22]. Traditionally, accelerated FEV_1 decline after complete respiratory maturity is a characteristic of COPD [22], but a second lung trajectory is also recognized [22,84]. Instead of experiencing accelerated FEV_1 decline after reaching normal lung capacity, these individuals never fully reach peak respiratory maturity and experience a normal rate of respiratory decline that can also result in COPD [22,84].

Contrary to reports from other studies [83,230–232], smoking was not an important predictor of FEV_1 decline in this study. One possible explanation is the potential role of occupational factors in lung function decline. As previously mentioned, the current study used data from an occupational cohort, whose members may have been exposed to other substances that could affect lung function decline such as welding fumes and silica exposure [233–235]. The limited predictive ability of smoking in the current study and the fact that several occupational factors such as welding fumes, silica, and duration of employment were predictors of FEV_1 decline is suggestive of a possible occupational exposure contribution to lung function decline. Additionally, the pervasiveness of ever smokers within the cohort could also be impacting the predictive ability of the smoking variable. However, the identification of other occupational factors such as age at hire, which was significant predictors of both FEV_1 decline and FEV_1 change, further highlights the possible importance of occupational factors in lung function.

4.5.4 Strengths and Limitations

A strength of this study is the application of novel methods in a unique occupational cohort that allowed for the concurrent assessment of occupational factors, demographic characteristics, and medical history. Additionally, by focusing on the relatively short time period

for lung function prediction, this study aimed to identify individual characteristics that could be modified before long-term changes occurred.

A limitation of this study is that it relied on a number of self-reported measures which could be impacted by recall bias [134]. Additionally, self-reported asthma was investigated as risk factor for predicting lung function change and decline as a way to account for the irregular obstruction experienced by those with asthma since the data did not capture any other indications of asthmatic symptoms. The study may also be subject to volunteer bias, which is inherent to the screening program as participants must self-select to participate in the National Supplemental Screening Program (NSSP) [134]. The potential voluntary bias may also impact the generalizability of results [134,211]. Finally, the current study uses the GOLD criterion as the standard for defining COPD instead of the lower limit of normal standard which was not available in the NSSP data.

4.6 Conclusions

This study identified clusters of COPD related comorbidities and important predictors of lung function changes and decline within an occupational cohort. Study findings suggest that occupational cohorts not only have different COPD-related comorbidities than the general population but may also have different predictors of lung function changes than the general population. Thus, the findings from this study can be used to target modifiable predictors as well as guide enhanced monitoring efforts.

CHAPTER 5

5.1 Summary, Discussions, and Conclusions

This chapter reviews the objectives of the study, summarizes the salient findings, and provides conclusions and recommendations for future research. The study investigated and identified county-level geographic disparities and determinants of chronic obstructive pulmonary disease (COPD) within the state of Florida. Additionally, it investigated and identified individual-level predictors of COPD occurrence and severity as well as comorbidity clusters and predictors of lung function changes and decline among DOE former workers. The main purpose of this study was to provide useful information for tailoring public health and disease management initiatives to reduce disparities and burden of COPD.

Spatial clusters of high COPD prevalence were identified in Florida, indicating that burden of the disease was not uniform across the state. Counties with high percentages of smokers and asthma patients tended to have high COPD prevalence, implying that targeting these predictors for public health interventions would potentially reduce disease burden. For instance, implementing targeted smoking cessation programs within counties with high smoking prevalence may be helpful in reducing COPD prevalence [6]. Additional research is warranted to better understand the mechanism driving the observed positive association between percentage of asthma and county-level COPD prevalence. Specifically, future research should assess the role of asthma-COPD overlap syndrome in COPD as well as the role of shared risk factors in pathogenesis so that appropriate interventions can be implemented.

At the individual level, smoking, history of asthma, and age were all positively associated with COPD occurrence and severity among former DOE workers. These findings emphasize the continued role of traditional risk factors in occupational cohorts whose exposure experience may

be different from that of the general population. They also highlight the need for better understanding of novel risk factors such a history of asthma. The significant association between lower body mass index (BMI) and both COPD occurrence and severity highlights the importance of investigating the role of physiological conditions in COPD pathogenesis. Future studies should assess whether low BMI is part of the causal pathway for COPD or an artifact of reverse causation [182–184]. Occupational exposure to silica and diesel exhaust were positively associated with COPD occurrence and severity, respectively. These findings provide additional support for the role occupational exposures in COPD development and progression [13,188,189]. Future research should focus on incorporating quantitative measurements of these exposures into analyses so as to assess a possible dose-response relationship.

Welding fumes and silica exposure were important predictors of lung function change and lung function decline, respectively. The significance of these factors in predicting lung function emphasizes the importance of considering occupational exposures when assessing COPD progression. It is worth noting that baseline forced expiratory volume in one second (FEV_1) and age were two of the strongest predictors of both lung function change and decline, which highlights the role of lung trajectories in COPD progression. This may provide a possible avenue for intervention through initiatives that maintain or increase FEV_1 over a lifespan. Similar to the predictors of COPD prevalence, occurrence, and severity, history of asthma was an important, albeit weak, predictor of lung function changes along with several other conditions including cardiovascular conditions and kidney problems. Cardiovascular conditions were also important for predicting lung function decline. Based on these findings, it would be prudent to take comorbidities into consideration when assessing lung function in COPD patients. The observed associations between different comorbid conditions and lung function change and

decline may suggest shared genetic, environmental, and lifestyle risk factors of COPD and its comorbidities [220]. Future studies will need to investigate these to improve our understanding of the mechanisms involved and potentially provide information to better guide control and disease management efforts.

Finally, this study identified four comorbidity clusters among DOE former workers who had COPD. The overall lower prevalence of all comorbid conditions in cluster 1 is suggestive of an otherwise generally healthy cluster. The higher prevalence of cardiovascular conditions in cluster 2 compared to cluster 1 is suggestive of possible cardiovascular abnormalities arising from the respiratory dysfunction produced by COPD since there is evidence that respiratory and cardiovascular health are interrelated [214,217]. The high prevalence of lung cancer in cluster 3 is suggestive of a lung cancer specific cluster while the overall high prevalence of all comorbidities in cluster 4 might suggest a cluster made of potentially more seriously ill former DOE workers. Overall, the comorbidities clusters identified in this study emphasize the importance of considering the patterns of co-occurring conditions in COPD disease management. Future studies will need to investigate if cluster membership results in differences in the long-term prognosis of COPD.

This study used several self-reported measures of exposure which may be subject to recall bias [134]. Future studies will need to use quantifiable measures of occupational exposures and physician diagnosed comorbidities to mitigate the impact of recall bias. Additionally, the study of DOE former workers was based on a voluntary screening program which may be prone to self-selection bias which might impact the generalizability of the results [134]. The above weakness notwithstanding, this study had several strengths including application of rigorous statistical methods utilizing a combination of spatial statistics, machine learning, and tradition

statistical methodologies for assessing multiple aspects of COPD. Moreover, this study used a comprehensive approach to assess occupational, environmental, and socio-behavioral predictors of COPD prevalence, occurrence, severity, and lung function.

In conclusion, this study identified geographic disparities and predictors of COPD prevalence in Florida. These findings are useful for guiding policy and resource allocation to reduce disparities and burden of the condition. Additionally, the study identified individual-level predictors of COPD occurrence, severity, and lung function while also assessing comorbidity clusters among former DOE workers. This information is useful for guiding health screening and disease management programs.

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VITA

Sara Chesnee Howard was born on March 5, 1992, in Knoxville, Tennessee. She earned a Bachelor of Art degree (2014) in Biology with a minor in Chemistry from Tusculum College, and a Master of Public Health (2017) with a concentration in Epidemiology from East Tennessee State University. Since 2017, she has worked as an epidemiologist at Oak Ridge Associated Universities where she conducts epidemiological research, provides biostatistical support, and supports archival efforts of historical research databases, primarily for occupational health and radiation exposure studies.