Prevalence and Sex-Specific Risk Factors for Asthma-COPD Overlap among Middle-Aged and Older Canadians

by

Edwina Veerasingam

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

in

Epidemiology

School of Public Health
University of Alberta

Abstract

Background: Asthma and chronic obstructive pulmonary disease (COPD) are major public health concerns and are among the most prevalent chronic respiratory diseases worldwide. However, a subset of patients presents with clinical features of both asthma and COPD, and recently, the term asthma-COPD overlap (ACO) was proposed to recognize this subset of patients. Studies show that individuals with ACO are more likely to experience a poorer quality of life, rapid disease progression, more frequent respiratory exacerbations, rapid decline in lung function, higher mortality, and greater healthcare utilization than patients with COPD or asthma alone. ACO disproportionately burdens females, and many epidemiological studies have reported a growing increase in ACO and COPD prevalence and mortality rates among females. Despite this, sex-specific differences and the role that sex and gender play in driving these disparities are not fully understood. This analysis aims to identify male and female-specific factors associated with ACO, COPD, and asthma. This study analyzed the baseline data from the Canadian Longitudinal Study on Aging (CLSA), a large population-based, prospective cohort study on middle-aged and older Canadian adults. The study cohort comprised of 30,097 adults between the ages of 45 and 85 years that participated in an in-home interview and a data collection site visit for physical assessment, blood, and urine sample collection.

Methods: Participants were categorized into four groups (control, asthma-COPD overlap (ACO), COPD only, and asthma only) based on self-reported response to the survey questions "has a doctor ever told you had asthma?" and "has a doctor told you that you have/had any of the following: emphysema, chronic bronchitis, chronic obstructive pulmonary disease (COPD), or chronic changes in lungs due to smoking?". ACO was defined as a positive response to both questions. Environmental data collected by the Canadian Urban Environmental Health Research

Consortium (CANUE) was linked to participant's reported postal code at the time of recruitment. The linked CANUE data includes annual average concentration exposure estimates for sulfur dioxide, nitrogen dioxide, ozone, and fine particulate matter. Multinomial logistic regression was used to identify significant male- and female-specific social, physical, and environmental predictors for ACO, COPD, and asthma in the multivariable analysis.

Results: The prevalence of ACO, COPD, and asthma was significantly greater in females than males (ACO: 2.17% vs. 1.41%; COPD: 3.22% vs. 2.87%; asthma: 13.31% vs. 10.11%). In the multivariable analysis, Aboriginal ethnicity, smoking, and lower education were significantly associated with obstructive lung disease for both males and females. In addition, marital status, province, age, and obesity were associated with asthma, COPD, or ACO among females but not males. While for males, unemployment was a significant factor for obstructive lung disease, which was not significant in females. Unemployed males had 2.60 times the likelihood of reporting ACO, and 2.23 times the likelihood of reporting COPD compared to employed males. Males with ACO and COPD had more severe lung obstruction than females. Subjects with ACO or COPD had more comorbidities, respiratory symptoms and were more likely to rate their health as "poor" than subjects with asthma or no respiratory symptom. Depression was the most commonly reported comorbidity for participants with ACO, irrespective of sex. Female subjects who were obese were 2.58 times more likely to develop ACO than females in the normal/underweight category. Participants with ACO were more likely to have hypothyroidism, and the proportion was higher among females. Hypothyroidism was not significantly related to COPD for males or females. Males with ACO were more likely to report having coughing and coughing with phlegm symptoms than females, and females with ACO were more likely than males to report shortness of breath and wheeze. No statistically significant associations were

observed between environmental exposure and respiratory outcomes for females. However, nitrogen dioxide was associated with an increased risk of asthma among males.

Conclusions: In the Canadian adult population, the prevalence of asthma, COPD, and ACO was greater among females than males. Risk factors for ACO varied between males and females. This study provides important and novel information to guide future research and development of public health programs to address the disproportionate burden of ACO and COPD mortality and morbidity among females in Canada.

Preface

This thesis is an original work by Edwina Veerasingam. The thesis has been written in a traditional format according to the guidelines of the Faculty of Graduate Studies and Research at the University of Alberta. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta and Memorial University Health Research Ethics Board.

Edwina Veerasingam was responsible for the data analyses, and preparation of the thesis. A. Senthilselvan provided guidance to the data analyses, interpretation of the results and preparation of the thesis.

Dedication

This thesis is dedicated to my family for their endless encouragement. I am eternally grateful to my parents, Sivagnanaverny Veerasingam and Veerasingam Murugesu, their unconditional support and love means the world to me.

I am also thankful to my three beautiful sisters, Thushara, Nereja, and Janarthane Veerasingam, and my one and only brother, Janarth Veerasingam. I am so grateful to each of them for making life interesting, fun, sometimes chaotic, but mostly comedic.

Lastly, I want to thank my incredible partner Ajandan Sivam. He has been a pillar of strength and support for me all these years. I am very thankful for his endless encouragement, inspiration, love, and the immeasurable joy he brings me.

Acknowledgements

I would like to express my immense gratitude to Dr. Ambikaipakan Senthilselvan, my supervisor and mentor. His direction, insight, and unwavering support has had a transformative effect in my journey as an epidemiology student, and I have become a better researcher as a result. I consider myself extremely fortunate in having Dr. Senthilselvan as a supervisor, and for many years to come I will look back on my time under his mentorship as a pivotal moment in my academic career.

I would also like to thank my supervisorial committee members Dr. Jeremy Beach and Dr. Zhiwei Gao for sharing their expertise and providing critical insights and comments on my presentations and my writing. Their contributions have been instrumental to my thesis, and I greatly appreciate them.

I would like to thank the CIHR and members of the CLSA research team for allowing me to access and analyze the CLSA data. The thesis was based on the project "Sex-specific environmental and genetic determinants of COPD in middle-aged and older Canadian adults: An analysis of CLSA data" which was funded by a Catalyst Grant: Analysis of CLSA Data from the Canadian Institutes of Health Research (CIHR). Edwina Veerasingam was supported by a graduate fellowship from the Catalyst Grant: Analysis of CLSA Data.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACO	Asthma-chronic obstructive lung disease overlap
BC	British Columbia
CANUE	Canadian Urban Environmental Health Research Consortium
CAO	Chronic airflow obstruction
CI	Confidence interval
CIHR	Canadian Institutes of Health Research
CLSA	Canadian Longitudinal Study on Aging
COPD	Chronic obstructive lung disease
DCS	Data collection site
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Obstructive Lung Disease
ICS	Inhaled corticosteroids
LABA	Long-acting β2-agonist
LAMA	Long-acting muscarinic antagonist
LLN	Lower Limit of Normal
NO_2	Nitrogen dioxide
O_3	Ozone
ON	Ontario
PEF	Peak Expiratory flow

$PM_{2.5}$	Fine particulate matter (particles that are 2.5 microns or less in diameter)
QC	Quebec
RRR	Relative risk ratio
SABA	Short-acting beta 2-agonist
SES	Socioeconomic status
SO_2	Sulphur dioxide
WHO	World Health Organization

Chapter 1

Introduction

1.1 Statement of Problem

Chronic obstructive pulmonary disease (COPD) and asthma are significant contributors to the burden of non-communicable disease and are among the most prevalent chronic respiratory diseases globally. These obstructive airway diseases pose substantial public health problems as they present concerning morbidity and mortality estimates and create formidable challenges for healthcare systems. According to the Global Burden of Disease Risk Summaries, 212 million people were living with COPD in 2019, and 3.28 million died from the disease (Institute of Health Metrics and Evaluation, 2020b). COPD is estimated to be the third leading cause of death worldwide and is the only chronic disease with increasing mortality (Lung Association of Saskatchewan, 2017; Pauwels et al., 2001). Alternatively, asthma contributes to fewer deaths but is more prevalent than COPD and is considered the leading respiratory disease among children. In 2019, asthma affected an estimated 262 million people and caused 461 000 deaths (Institute of Health Metrics and Evaluation, 2020a). In Canada, asthma and COPD place a substantial burden on healthcare resources, patient's quality of life, and contributes to a large extent of disease and death. It was reported in the 2018 Canadian Chronic Disease Surveillance System Report that 3.8 million Canadians over the age of one were living with asthma, and 2 million Canadians aged 35 years and older were living with COPD in 2011-2012 (Dai et al, 2018). In addition to this, there exists a small subset of patients that present with clinical features of both asthma and COPD, and more recently, the term asthma-COPD overlap (ACO) was proposed to recognize this subset of patients. Studies have shown that individuals with ACO are more likely to experience poor

health-related quality of life, rapid disease progression, more frequent respiratory exacerbations, rapid decline in lung function, higher mortality, and greater healthcare utilization than patients with COPD or asthma alone (Alshabanat et al., 2015; de Marco et al., 2013; Gerhardsson De Verdier et al., 2015; Global Initiative for Asthma, 2020; Kim et al., 2015; Tommola et al., 2017). Equally concerning is the mounting epidemiological evidence demonstrating a growing increase in COPD prevalence among females. Although COPD has historically been considered a disease of men, there has been a shift in disease burden towards women over the last two decades (Aryal et al., 2014). Studies conducted in various countries, including the USA, Canada, and the Netherlands, found that COPD prevalence was decreasing in men while increasing among women (Aryal et al., 2014; Bischoff et al., 2009; Gershon et al., 2010). Another Canadian study found that COPD mortality decreased for both males and females, but males demonstrated a more pronounced decrease than females (Gershon et al., 2010). In 2000, the number of women dying from COPD surpassed the number of men for the first time in the United States (Han et al., 2007; Nicolini et al., 2018). Although, adult-onset asthma affects females more often than males, 190 million prevalent female cases versus 168 million male cases in 2015, the global age-standardized mortality was higher in males (6.7 per 100,000) than females (5.6 per 100,000) (Harris, 2019; Soriano et al., 2017). Sex-specific differences on the burden of asthma-COPD overlap are poorly understood as there is no clear consensus in the literature. Several studies have shown that women are more likely than men to have ACO (de Marco et al., 2013; Koleade et al., 2019; Senthilselvan & Beach, 2018; Wheaton et al., 2018), while others found no significant differences between males and females (Alshabanat et al., 2015).

Taken together, it is apparent that men and women do not evenly bear the burden of these diseases. The role that sex and gender play in driving these disparities is not entirely understood. Obstructive airway

diseases are multifactorial and are associated with various environmental, physical, and social risk factors such as smoking (Louie et al., 2013), race and ethnicity (Hardin et al., 2011b; Ambikaipakan Senthilselvan & Beach, 2018), socioeconomic status (Global Initiative for Chronic Obstructive Lung Disease, 2020), obesity (Alshabanat et al., 2015; Franssen et al., 2008), and exposure to air traffic pollution (de Marco et al., 2013) and biomass fuels (Salvi & Barnes, 2009). However, the literature on sex-specific differences for ACO and COPD is limited. A greater understanding of sex-specific differences is needed to better comprehend the increasing female predominance for COPD and ACO. There are significant economic burdens, substantial healthcare resource consumption, and poor quality of life attributed to these obstructive airway diseases. Therefore, adequate assessment of risk factors, early identification of cases, and earlier steps to management can help improve health outcomes, lung functioning and mitigate progression to severe disease and worsened exacerbations. This thesis analyzes health data from a large Canadian study population to identify sex-specific physical, social, and environmental risk factors for asthma, COPD, and ACO.

1.2 Study Objectives

1.2.1 General Objectives

This analysis aims to identify male and female-specific factors associated with ACO, COPD, and asthma using data from the Canadian Longitudinal Study on Aging (CLSA).

1.2.2 Specific Objectives

1) To ascertain the prevalence of COPD, asthma, and ACO among male and female Canadian middle-aged and older adults.

2) To assess variations in lung function estimates obtained using obstructive airway measures for males and females.

3) To determine sex-specific physical, social, and environmental risk factors for COPD and ACO in middle-aged and older Canadian adults.

1.3 Thesis Submitted for the Partial Fulfilment of Master of Science in Epidemiology

This thesis follows the traditional chapter-based format and provides a complete and systematic account of this research project. Chapter 2 provides a comprehensive review of the literature on asthma, COPD, and ACO epidemiology. This literature review also reviews the current evidence on sex-specific differences currently identified for various social, physical, and environmental factors such as ethnicity, socioeconomic status, physical and mental comorbidities, smoking, marital status, and environmental factors. Epidemiological estimates related to disease burden, symptoms, and definitions were derived from reports by Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the Global Initiative for Asthma (GINA) and peer-reviewed literature.

Chapter 3 describes the research methodology undertaken by the CLSA and the methods used in this thesis. Sections 3.1 and 3.2 detail the objectives and development of the CLSA study. It also includes CLSA sample size, sampling design, recruitment, and sampling weights (Section 3.3 – 3.5). Section 3.5 presents the declaration of ethics approval by the Research Ethics Boards across Canada and the ethics approval from the University of Alberta and Memorial University Health Research Ethics Boards. Details on data access storage and data components requested from the CLSA are described in Section 3.6. The following five sections (Section 3.7 – 3.11) detail how categories were defined based on responses to survey questions, the protocol for taking spirometry measures, and the development of the Chronic Airflow Obstruction algorithm.

Further variable definitions include comorbidities, obesity, smoking status, household income, education, marital status, ethnicity, and employment, all determined by survey responses. The process of collecting environmental data is included in Section 3.12, and Section 3.13 details the statistical analysis, including a description of the variables and how they were recoded for data analysis. This section also discusses using the modified GOLD criteria and the CLSA-provided sample analytical weights for analysis. The following section details the process for descriptive analysis and multinomial logistic regression model building. The chapter concludes with a description of how sex-specific risk factors and respiratory health outcomes were obtained and tested in the study.

Chapter 4 details the results of the analysis and significant findings. In Section 4.1, the prevalence of ACO, COPD, and asthma are presented along with prevalence estimates across sex and age. Section 4.2 describes the baseline characteristics of the study population, and Section 4.3 details baseline characteristics by sex. The following two sections present the distribution of characteristics, respiratory symptoms, and general self-reported health for female and male participants across the different respiratory health outcomes. In Sections 4.6 and 4.7, factors associated with the respiratory health outcomes are presented for females and males, respectively. Chapter 4 concludes with a final section describing associations studied between environmental factors and respiratory health outcome groups for both males and females.

Lastly, Chapter 5, the final chapter, presents a summary of the results, and compares key findings with other studies presented in the literature and concludes with a final section with a discussion on the strengths, limitations of the study, important conclusions from the study and implications for future research.

References:

1. Alshabanat, A., Zafari, Z., Albanyan, O., Dairi, M., & Fitzgerald, J. M. (2015). Asthma and COPD overlap syndrome (ACOS): A systematic review and meta analysis. *PLoS ONE*, *10*(9), 1–15. https://doi.org/10.1371/journal.pone.0136065

2. Aryal, S., Diaz-Guzman, E., & Mannino, D. M. (2014). Influence of sex on chronic obstructive pulmonary disease risk and treatment outcomes. *International Journal of COPD*, *9*, 1145–1154. https://doi.org/10.2147/COPD.S54476

3. Bischoff, E. W. M. A., Schermer, T. R. J., Bor, H., Brown, P., Van Weel, C., & Van Den 4. Bosch, W. J. H. M. (2009). Trends in COPD prevalence and exacerbation rates in Dutch primary care. *British Journal of General Practice*, *59*(569), 927–933. https://doi.org/10.3399/bjgp09X473079

4. de Marco, R., Pesce, G., Marcon, A., Accordini, S., Antonicelli, L., Bugiani, M., Casali, L., Ferrari, M., Nicolini, G., Panico, M. G., Pirina, P., Zanolin, M. E., Cerveri, I., & Verlato, G. (2013). The Coexistence of Asthma and Chronic Obstructive Pulmonary Disease (COPD): Prevalence and Risk Factors in Young, Middle-aged and Elderly People from the General Population. *PLoS ONE*, *8*(5), 1–7. https://doi.org/10.1371/journal.pone.0062985

5. Franssen, F. M. E., O'Donnell, D. E., Goossens, G. H., Blaak, E. E., & Schols, A. M. W. J. (2008). Obesity and the lung: Obesity and COPD. *Thorax*, *63*(12), 1110–1117. https://doi.org/10.1136/thx.2007.086827

6. Gerhardsson De Verdier, M., Andersson, M., Kern, D. M., Zhou, S., & Tunceli, O. (2015). Asthma and Chronic Obstructive Pulmonary Disease Overlap Syndrome: Doubled Costs Compared with Patients with Asthma Alone. *Value in Health*, *18*(6), 759–766. https://doi.org/10.1016/j.jval.2015.04.010

7. Gershon, A. S., Wang, C., Wilton, A. S., Raut, R., & To, T. (2010). Trends in chronic obstructive pulmonary disease prevalence, incidence, and mortality in Ontario, Canada, 1996 to 2007: A population-based study. *Archives of Internal Medicine*, *170*(6), 560–565. https://doi.org/10.1001/archinternmed.2010.17

8. Global Initiative for Asthma. (2020). Global strategy for asthma management and prevention: Socioeconomics. *Global Initiative for Asthma*, *36*(6), 685–704. https://doi.org/10.1016/S0335-7457(96)80056-6

9. Han, M. L. K., Postma, D., Mannino, D. M., Giardino, N. D., Buist, S., Curtis, J. L., & Martinez, F. J. (2007). Gender and chronic obstructive pulmonary disease: Why it matters. *American Journal of Respiratory and Critical Care Medicine*, *176*(12), 1179–1184. https://doi.org/10.1164/rccm.200704-553CC

10. Harris, R. E. (2019). *Epidemiology of Chronic Disease*. Jones & Bartlett Learning.

11. Institute of Health Metrics and Evaluation. (2020a). Asthma. *The Lancet*, *396*, 108–109.

12. Institute of Health Metrics and Evaluation. (2020b). Global burden of disease 2019-Chronic obstructive pulmonary disease. *The Lancet*, *396*, S106–S107. https://www.thelancet.com/pb-assets/Lancet/gbd/summaries/diseases/copd.pdf

13. Kim, M. A., Noh, C. S., Chang, Y. J., Hong, Y. K., Lee, J. S., Lee, S. W., Lee, S. D., & Oh, Y. M. (2015). Asthma and COPD overlap syndrome is associated with increased risk of hospitalization. *International Journal of Tuberculosis and Lung Disease*, *19*(7), 864–869. https://doi.org/10.5588/ijtld.14.0327

14. Koleade, A., Farrell, J., Mugford, G., & Gao, Z. (2019). Female-specific risk factors associated with risk of ACO (asthma COPD overlap) in aboriginal people. *Journal of Asthma*, *57*(9), 1–8. https://doi.org/10.1080/02770903.2019.1621890

15. Lung Association of Saskatchewan. (2017). *COPD Fact Sheet*. Retrieved from https://sk.lung.ca/about-us/news-room/backgrounders-and-information-sheets/copd-fact-sheet

16. Nicolini, A., Barbagelata, E., Tagliabue, E., Colombo, D., Monacelli, F., & Braido, F. (2018). Gender differences in chronic obstructive pulmonary diseases: A narrative review. *Panminerva Medica*, *60*(4), 192–199. https://doi.org/10.23736/S0031-0808.18.03463-8

17. Pauwels, R., Buist, S., Calverley, P., Jenkins, C., & Hurd, S. (2001). Global strategy for the diagnosis, management and prevention of Chronic Obstructive Pulmonary Disease. NHBLI/WHO global initiative for Chronic Obstructive Lung Disease (GOLD) workshop summary. *Revista Portuguesa de Pneumologia*, *7*(4–5), 398–400. https://doi.org/10.1016/s0873-2159(15)30846-1

18. Salvi, S. S., & Barnes, P. J. (2009). Chronic obstructive pulmonary disease in non-smokers. *The Lancet*, *374*(9691), 733–743. https://doi.org/10.1016/S0140-6736(09)61303-9

19. Senthilselvan, A., & Beach, J. (2018). Characteristics of asthma and COPD overlap syndrome (ACOS) in the Canadian population. *Journal of Asthma*, *56*(11), 1129–1137. https://doi.org/10.1080/02770903.2018.1531997

20. Sin, D. D. (2017). Asthma-COPD overlap syndrome: What we know and what we don't. *Tuberculosis and Respiratory Diseases*, *80*(1), 11–20. https://doi.org/10.4046/trd.2017.80.1.11

21. Soriano, J. B., Abajobir, A. A., Abate, K. H., Abera, S. F., Agrawal, A., Ahmed, M. B., Aichour, A. N., Aichour, I., Eddine Aichour, M. T., Alam, K., Alam, N., Alkaabi, J. M., Al-Maskari, F., Alvis-Guzman, N., Amberbir, A., Amoako, Y. A., Ansha, M. G., Antó, J. M., Asayesh, H., Vos, T. (2017). Global, regional, and national deaths, prevalence,

disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet Respiratory Medicine*, *5*(9), 691–706. https://doi.org/10.1016/S2213-2600(17)30293-X

22. Tommola, M., Ilmarinen, P., Tuomisto, L. E., Lehtimäki, L., Haanpää, J., Niemelä, O., & Kankaanranta, H. (2017). Differences between asthma - COPD overlap syndrome and adult-onset asthma. *European Respiratory Journal*, *49*(5), 1–10.

23. Wheaton, A., Pleasants, R. A., Croft, J. B., Ohar, J. A., Heidari, K., Mannino, D. M., Liu, Y., & Strage, C. (2018). Gender and Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome. *Physiology & Behavior*, *176*(1), 139–148. https://doi.org/10.1016/j.physbeh.2017.03.040

Chapter 2

Literature Review

2.1 Methods

This chapter consists of a review of the scientific literature on asthma-COPD overlap (ACO). The first part of this chapter includes sections describing the epidemiology of ACO, COPD, and asthma, its burden of disease globally and nationally, the biological mechanisms involved, symptoms, diagnosis, and the management of these obstructive airway diseases.

Papers were selected from MEDLINE, an academic literature database. Searches were limited to peer-reviewed papers written in English. The abstracts of articles identified from these searches were examined, and studies found to be relevant were included in this review. Data pertaining to the epidemiology and burden estimates were ascertained from research articles and government reports. Information regarding the management and diagnosis of asthma, COPD, and ACO were identified through reports authored by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the Global Initiative for Asthma (GINA). A narrative review was carried out on the social, physical, environmental risk factors for ACO, COPD, and asthma. Sex-specific differences related to these factors were also included. Potential risk factors were identified by searches in MEDLINE, using the search criteria defined above. The reference lists of papers retrieved were used to identify additional studies relevant to this narrative review.

2.2. Background

Asthma and COPD are major public health concerns and are two of the most common chronic respiratory diseases worldwide (Hosseini et al., 2019). Asthma is characterized by chronic airway inflammation, whereas COPD is characterized by persistent respiratory symptoms in

addition to chronic inflammation of the airways (Global Initiative for Chronic Obstructive Lung Disease, 2020; Global Initiative for Asthma, 2020). However, there exists a subset of patients that present with clinical features of both asthma and COPD. The term asthma-COPD overlap (ACO) was coined to recognize this subset of patients. Studies have shown that individuals with ACO are more likely to experience worse health-related quality of life, rapid disease progression, more frequent respiratory exacerbations, rapid decline in lung function, higher mortality, and greater utilization of healthcare resources than patients with COPD or asthma alone (de Marco et al., 2013; Global Initiative for Asthma, 2020; Tommola et al., 2017).

ACO was initially referred to as asthma-COPD overlap syndrome until it was later revised in 2017 to asthma-COPD overlap (ACO) by Global Initiative for Asthma (GINA) and Global Initiative of Obstructive Lung Disease (GOLD). It was deemed no longer accurate to describe ACO as a "syndrome," but instead a collection of various clinical phenotypes with several different underlying mechanisms. In 2017, the GINA and GOLD report described ACO as a condition "characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD", however this was regarded as a description for clinical use rather than an official definition. Milne et al. states that unlike an official definition, an open description for ACO introduces new challenges for epidemiological and clinical studies (Milne et al., 2020). In more recent discussions surrounding ACO terminology, the 2020 GOLD report on COPD stated that organization would no longer refer to ACO but instead emphasize that asthma and COPD are different disorders that may share some common traits, clinical features such as eosinophilia, or degree of airflow reversibility (Global Initiative for Chronic Obstructive Lung Disease, 2020).

2.3 Definition of COPD

Chronic obstructive pulmonary disease is characterized by GOLD as a common preventable and treatable disease caused by persistent respiratory symptoms and airflow limitation that is due to airway or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors such as abnormal lung development (Global Initiative for Chronic Obstructive Lung Disease, 2020). COPD involves the presence of emphysema or chronic bronchitis, which may exist simultaneously or separately in an individual. Emphysema occurs with the destruction of the air spaces (alveoli) distal to the terminal bronchiole. Over time, the inner walls of these gas-exchanging surfaces of the lung weaken and rupture to create larger air spaces instead of many small ones. Chronic bronchitis is defined as the presence of a persistent cough with sputum production for at least three months in at least two consecutive years. (Global Initiative for Chronic Obstructive Lung Disease, 2020). Patients with emphysema and no bronchitis are characteristically barrel-chested, dyspneic with prolonged expiration due to air trapping in the lungs and are referred to as pink puffers due to adequate oxygenation. Chronic bronchitis involves chronic infection and inflammation of the lungs. Patients are characteristically obese, have excess carbon dioxide in the blood, and are referred to as blue bloaters due to a bluish tinge of the skin and lips (Harris, 2019). The main risk factor for COPD is tobacco smoking, but other environmental exposures such as biomass fuel exposure and air pollution may contribute to its development (Harris, 2019). Besides exposures, host factors that may increase COPD risk include genetic abnormalities, abnormal lung development, accelerated aging, and sex-specific differences (Global Initiative for Chronic Obstructive Lung Disease, 2020).

2.3.1 Burden and epidemiology of COPD

COPD is a significant public health issue that presents concerning global prevalence, morbidity, and mortality estimates and creates formidable challenges for healthcare systems worldwide, particularly in low-and-middle-income countries (LMICs) where roughly 90% of all deaths from COPD occur (Lõpez-Campos et al., 2016) (World Health Organization, 2010). COPD is often associated with a late onset, occurring mainly in middle-age and older adults, slow progressive symptoms, poor response to inhaled therapy, and is often associated with long-term smoking behaviour (Barnes, P., 2015). According to the Global Burden of Disease Study, in 2019, an estimated 212 million people were living with COPD worldwide, and 3.3 million deaths due to COPD occurred in the same year (Institute of Health Metrics and Evaluation, 2020b). Recent estimates position COPD as the third leading cause of death worldwide (World Health Organization, 2018). Although global estimates indicate that mortality due to COPD remains higher in males, mortality among females is increasing, reflecting trends in smoking rates among men and women (Dai et al., 2018)**.**

COPD is also a significant cause of chronic morbidity as many people suffer from this disease for years. People living with COPD experience impaired participation in daily life, school, work, and social activities (Dai et al., 2018). The economic burden of COPD is also rather considerable, and it has been found that COPD exacerbations account for $18 billion in direct costs annually in the United States (Lõpez-Campos et al., 2016). This is without considering lost productivity and lost wages for individuals with persistent symptoms or severe COPD. With the aging population and historically high smoking rates, we can expect COPD's societal, economic, and human burden to only increase (Global Initiative for Chronic Obstructive Lung Disease, 2020). In order to mitigate its impact and reverse its course, substantial public health initiatives

are needed to address COPD burden and modifiable risk factors, such as smoking and air pollution.

Between 2011-2012, approximately 2 million Canadians aged 35 years and older were living with COPD (Dai et al., 2018). The age-standardized prevalence of COPD among Canadians over the age of 35 increased from 7.1% in 2000-2001 to 9.5% in 2011-2012 (Dai et al., 2018)**.** The number of new COPD cases per year had declined from 2000-2001 through to 2011-2012, while the number of Canadians living with the disease had increased over the same period. All-cause mortality among those with COPD had also declined between 2000-2001 to 2011-2012, shadowing decreasing smoking rates (Dai et al., 2018). In 2011-2012, the prevalence of COPD increased steadily across the lifespan. COPD prevalence was similar among middle-aged males and females in Canada, until the 60-64 age group where the prevalence was consistently higher among males than females. In other words, among older Canadians, men were more likely to be affected by COPD (Dai et al., 2018). The incidence rates of COPD in Canada for 2011-2012 increased steadily for both males and females across the life span. Overall, the incidence rates ranged from 317.7 per 100,000 population in the 35-39 age group to 2309.6 per 100,000 in the 85 and older age group (Dai et al., 2018). Males had consistently higher COPD incidence rates than females of the same age group, with the gap between the two increasing with age (Dai et al., 2018).

2.4 Definition of Asthma

Asthma is a heterogeneous disease usually characterized by chronic airway inflammation. It is characterized by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and intensity, together with variable expiratory airflow

limitation (Global Initiative for Asthma, 2020). Asthma often has an early onset, and is found in children, adolescents, and adults (Barnes, P., 2015). Symptomatic airflow limitation is often triggered by exercise, allergens or irritant exposure, weather change, or viral respiratory infections. Airflow limitation may resolve on its own or in response to medication. Clinical phenotypes of asthma include allergic asthma, non-allergic asthma, adult-onset asthma, asthma with persistent airflow limitation, and asthma with obesity (Global Initiative for Asthma, 2020). Asthma is a chronic disease of the airways and often presents first during childhood or adolescence. It is categorized as atopic (allergic) and non-atopic (non-allergic). Atopic asthma occurs in response to known allergens such as pollen, mold, pets, and other allergic triggers. It is also called allergic asthma and is the most common form of asthma in the pediatric age (Comberiati et al., 2017). Triggers for non-atopic asthma include weather conditions, cold air, poor air quality, exercise, infections, and stress. Non-atopic asthma can be characterized by its onset later in life, a female predominance, and increased severity (Romanet-Manent et al., 2002).

2.4.1 Burden and epidemiology of asthma

Globally, asthma-related deaths decreased 26.7% from 541,000 in 1990 to 397,000 in 2015. In contrast, the number of prevalent asthma cases increased by 12.6%, from 318 million in 1990 to 358 million in 2015 (Harris, 2019). Overall, asthma affects more females than males (190 million and 168 million prevalent cases, respectively). However, the age-adjusted asthma-related mortality rate is higher in males (6.7 per 100,000) than females (5.6 per 100,000) (Soriano et al., 2017). The prevalence of asthma is greatest in countries with a high gross domestic product (GDP) and has been shown to follow an urban-rural gradient, with it being more common in urban areas (Harris, 2019; Holgate et al., 2015).

According to the 2018 Canadian Chronic Disease Surveillance System report, the age-standardized prevalence of asthma in Canada increased from 6.5% in 2000-2001, to 10.8% in 2011-2012 (Dai et al., 2018). The report further concluded that Canadians living with asthma had a slightly higher all-cause mortality rate than those without asthma (Dai et al., 2018). In 2011-2012, asthma prevalence increased steadily in childhood, peaking in the 15-19 age group. Asthma prevalence peaked earlier for males at 10-14 years of age (22.2%) compared to females, which was highest in the 15–19 age group (17.0%). Asthma prevalence was on a declining trend until the 30-34 age group and remained steady until the 60-64 age group after which there was an increase in prevalence for both males and females. Despite prevalence estimates being higher in females, males demonstrated a more pronounced increase in prevalence in the older age groups. In 2011-2012, a cross-over by gender in asthma prevalence was observed starting at the 25-29 age group, where the prevalence for males became lower than for females. This difference persisted throughout the middle and older age groups (Dai et al., 2018).

Asthma is the most common chronic disease in children. Childhood asthma is characterized by its male predominance before puberty, common remission (absence of asthma symptoms and medication use), and rare mortality (Trivedi & Denton, 2019; Vonk et al., 2004). Adult asthma affects an estimated 235 million people worldwide and is estimated to cause more than 350,000 deaths per year (WHO, 2020). Conversely, adult asthma is known for its female predominance and uncommon remission (Trivedi & Denton, 2019). Furthermore, childhood asthma severity is associated with duration of asthma symptoms, medication use, lung function, low socioeconomic status (SES), racial/ethnic minorities, and a neutrophilic phenotype. Alternatively, adult asthma severity is associated with increased immunoglobulin E antibodies (IgE), elevated fractional

exhaled nitric oxide (a marker for airway inflammation), obesity, smoking, low SES, and an eosinophilic phenotype (Trivedi & Denton, 2019).

2.5 Definition of asthma-COPD overlap (ACO)

Currently, there is no consensus on a standard definition for ACO. Instead, it is described clinically as a condition of persistent airflow limitation combined with features of both asthma and COPD. Similar to COPD, ACO is a disease mainly affecting middle-age and older adults. As stated by Milne et al. (2020), the lack of a universal definition highlights the issue of classifying ACO as a distinct disease entity since asthma and COPD can range in severity, and multiple presentations of the disease exist such that overlap can occur in various stages of the disease. This creates a wide range of phenotypical expressions and underlying mechanisms (Maselli & Hanania, 2018; Milne et al., 2020).

Epidemiological studies have attempted to define the disease, resulting in various definitions of ACO, such as a combination of multiple major and minor criteria like physician diagnosed or self-diagnosed asthma, peak expiratory flow variability, reversibility testing, airway hyperresponsiveness to methacholine or histamine, persistence of airflow obstruction over time as measured by spirometry, exposure to noxious particles/gases, smoking history, serum or sputum eosinophilia (Alshabanat et al., 2015; Maselli & Hanania, 2018).

2.5.1 Burden and epidemiology of asthma-COPD overlap (ACO)

The prevalence of ACO varies in epidemiological studies depending on the criteria used to define asthma and COPD. The reported prevalence rates for ACO have ranged between 15% and 55%, with variation by gender and age (Global Initiative for Asthma, 2019). In a population-based study from the U.S, the prevalence of ACO was estimated to be 3.2% (Kumbhare et al.,

2016) which was similar to the prevalence findings of 3.4% in a Swedish study (Ekerljung et al., 2018). This was higher than findings that reported 1.8% in Central and South America, 1.2% in Denmark, and 1.6% in Canada (Senthilselvan & Beach, 2018). A 2019 systematic review published on the global prevalence of ACO in the general population reported that the pooled prevalence of ACO was 2.0% globally (Hosseini et al., 2019).

The ongoing challenge in ascertaining epidemiological estimates is the varying criteria used for defining asthma-COPD overlap, and this is reflected in the variation of ACO prevalence in epidemiological studies. Milne et al. (2020) review of the literature concluded that various definitions of ACO are often used in epidemiological studies. The authors found that most studies define the ACO population using spirometry criteria, a history of asthma with fixed airflow obstruction, or a history of smoking and COPD with a significant bronchodilator response, most commonly defined as 200 mL and 12% increase in FEV_1. Other definitions included inflammatory markers typically associated with asthma, such as eosinophilia, and increased IgE levels in the presence of clinical COPD (Milne et al., 2020). Additionally, the definition for ACO used in studies sometimes varies according to the population being studied. This is highlighted in a 2019 study by Barczyk et al., which applied five different published definitions of ACO on a mixed population of patients with asthma and patients with COPD. The authors found poor agreement between the various definitions. Among the patient population group, 33% of patients met the diagnostic criteria of at least 1 ACO definition, and only 0.12% of patients met all five included definitions (Barczyk et al., 2019). However, despite this challenge, even conservative national estimates for ACO represent a significant population burden (H. Lee et al., 2020).

The prevalence of ACO is greater among patients with COPD than patients with asthma (Sin, 2017). Alshabanat et al. (2015) systematic review and meta-analysis on ACO determined that the pooled prevalence of ACO among patients with COPD was 27%. The review also concluded there was little consensus between studies on male and female differences in prevalence; some studies reported a female predominance, while others found no significant differences between males and females studied (Alshabanat et al., 2015). Many studies have found that individuals with ACO are more likely to experience worse health-related quality of life, rapid disease progression, more frequent respiratory exacerbations, rapid decline in lung function, higher mortality, and greater utilization of healthcare resources than compared to patients with COPD or asthma alone (Alshabanat et al., 2015; de Marco et al., 2013; Gerhardsson De Verdier et al., 2015; Global Initiative for Asthma, 2020; M. A. Kim et al., 2015; Tommola et al., 2017).

2.6 COPD symptoms

COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway or alveolar abnormalities or a history of exposure to risk factors for the disease. Respiratory symptoms associated with COPD include shortness of breath upon exertion, cough, sputum production, and lower respiratory tract infections occurring more frequently or lasting longer than expected (Barnes et al., 2015). As described in the GOLD 2020 report on COPD, chronic and progressive dyspnea is the most characteristic symptom of COPD and an estimated 30% of patients present with cough with sputum production. Furthermore, the manifestation and occurrence of respiratory symptoms can occur before the development of airflow limitation. It is also possible for significant airflow limitation to happen without the presence of chronic

dyspnea, cough and sputum production; or for respiratory symptoms to occur without the presence of airflow limitation (Global Initiative for Chronic Obstructive Lung Disease, 2020). Dyspnea, the medical term for shortness of breath, is the most important and distinguishing symptom of COPD. It is described as a sense of increased effort to breathe, chest heaviness, air hunger, or gasping. Chronic cough is typically one of the first signs of COPD to appear and can be productive (wet cough that produces phlegm) or unproductive (dry cough that does not produce phlegm). It is common for patients with COPD to bring up small quantities of sputum while coughing. Regular sputum production for three or more months in two consecutive years is the classical definition of chronic bronchitis (Global Initiative for Chronic Obstructive Lung Disease, 2020). However, this is suggested to be an incomplete definition that does not reflect the entire range of sputum production among patients with COPD (Global Initiative for Chronic Obstructive Lung Disease, 2020). Wheezing and chest tightness are also symptoms associated with COPD. Wheezing is described as a whistling or squeaking sound produced while breathing. An absence of wheezing or chest tightness does not exclude a diagnosis of COPD (Global Initiative for Chronic Obstructive Lung Disease, 2020).

Individuals with apparent COPD typically present symptoms in adulthood, although it has been shown that earlier presentations for the disease (<45 years) can be found among patients with an alpha-1-antitrypsin deficiency (Chambliss et al., 2018; Vestbo et al., 2013). COPD exacerbations are defined as periods of acute worsening of respiratory symptoms. They often result in additional therapy, and severe exacerbations can also be associated with acute respiratory failure. In addition, patients with COPD are progressively limited in their ability to undertake normal daily activities due to shortness of breath with exertion and peripheral muscle weakness. Peripheral muscle weakness is a known contributor in reducing exercise capacity for patients

with COPD (Rausch-Osthoff et al., 2014). This has cascading effect leading to activity avoidance, reduced quality of life, and early development of comorbidities such as cardiovascular disease (Thomas et al., 2013).

2.7 Asthma symptoms

Asthma is characterized by a history of respiratory symptoms including wheeze, dyspnea, chest tightness, and cough that vary over time and intensity, together with variable expiratory airflow limitation and airway hyper-responsiveness to a range of stimuli (Holgate et al., 2015). Symptoms are often triggered by exercise, laughter, allergens, and cold air. Asthma-related respiratory symptoms typically present during childhood. A history of allergic rhinitis or eczema, or a family history of asthma or allergy, increases the probability that the respiratory symptoms are due to asthma. It is important to note that these characteristics are non-specific and are not enough to confirm asthma. Moreover, they are not present in all asthma phenotypes (Global Initiative for Asthma, 2020).

2.8 ACO symptoms

In general, patients with ACO experience worse health outcomes, experience symptoms more frequently, and show a higher risk of exacerbations and hospitalizations than patients with COPD-only or asthma-only (Henriksen et al., 2018a; Louie et al., 2013; Sin, 2017; Wheaton et al., 2018). Patients with ACO also have an increased risk of rapid FEV_1 decline and COPD mortality (Sin, 2017). Symptoms for ACO include wheezing or chronic cough with or without sputum, which are considered an early symptom for ACO, and dyspnea or exercise intolerance, which are more late symptoms of ACO (Louie et al., 2013).

Henriksen et al. (2018) examined the prevalence and symptom profile of ACO in a large Norwegian population-based study. Researchers determined that wheezing attacks were the most frequently reported symptom in all three groups studied (ACO, COPD-only, and asthma-only), and 87.3% of 955 participants with the self-reported diagnosis of ACO reported wheezing attacks in the previous year. Combined cough, wheeze, and allergy were reported most frequently by participants with ACO. The study also consisted of a spirometry subgroup where 10% of the study sample underwent further examination with additional spirometry for diagnosis. Researchers determined that in this subgroup, the most apparent difference between ACO and asthma-only or COPD-only groups was with regard to dyspnea at rest. Dyspnea at rest was reported in 38.3% of participants in the ACO group, compared to 17.1% and 16.8% for COPD-only and asthma-only groups, respectively (p-value <0.01). Overall, the study found that participants with ACO generally had the highest frequency of respiratory symptoms, wheezing attacks, and dyspnea. The likelihood of reporting high physical activity levels was lowest in the ACO group (Henriksen et al., 2018). The increased risk for wheezing, dyspnea, frequent exacerbations, and increased hospitalizations among people with ACO compared to patients with COPD or asthma can be substantiated in other population studies (de Marco et al., 2013; Menezes et al., 2014; Miravitlles et al., 2013; Sin, 2017) and two systematic reviews of the literature on ACO (Alshabanat et al., 2015; Nielsen et al., 2015).

2.9 COPD diagnosis

COPD diagnosis involves an assessment of symptoms, risk factors, and spirometry measures (Global Initiative for Chronic Obstructive Lung Disease, 2020). GOLD recommends that COPD be considered for any patient who presents with dyspnea (shortness of breath), chronic cough or

sputum production, and a history of exposure to risk factors for the disease (tobacco smoke, biomass fuel smoke, occupational exposure to gas, dust, vapors, fumes or other chemical exposure, family history, childhood factors such as low birth weight, childhood respiratory infections). Spirometry is required to make the diagnosis. The presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation in patients with respiratory symptoms and significant exposure to noxious stimuli (Global Initiative for Chronic Obstructive Lung Disease, 2020).

2.10 Asthma diagnosis

Diagnosing asthma involves identifying a pattern of respiratory symptoms such as wheezing, dyspnea, chest tightness or cough, and variable expiratory airflow limitation (Global Initiative for Chronic Obstructive Lung Disease, 2020). These symptoms are not specific to asthma, and further assessment is required to substantiate a clinical diagnosis. This includes a detailed history of timing, duration, intensity, and triggers for these symptoms. If symptoms are worse during the nights or early mornings, occur irregularly over time with varying intensity, and are often triggered by exercise, laughter, cold air, or exposures to allergens, then a diagnosis of asthma is more probable. In addition, confirmed excessive variability in lung function is also necessary for the diagnosis. This involves the use of spirometry to measure one's forced expiratory volume in one second (FEV_1) as an indicator of reduced lung functioning. Additional lung function tests can be employed to support a diagnosis, such as a bronchodilator reversibility test, testing for peak expiratory flow (PEF), bronchial challenge test, and exercise challenge test. Assessing reversibility of symptoms aids the diagnostic process as signs of reversibility increases the likelihood of the presence of asthma. Reversibility or responsiveness refers to a rapid

improvement in FEV_1 or PEF, minutes after inhalation of a rapid-acting bronchodilator, or a sustained improvement over days or weeks after use of inhaled corticosteroids (Global Initiative for Asthma, 2020).

An asthma diagnosis is carried out slightly differently for children under five years because they cannot perform reproducible expiratory maneuvers at that age. Therefore, lung function testing is not generally used in the diagnosis of asthma for children under 5. Instead, GINA recommends alternatives such as a treatment trial for 2-3 months using a short-acting beta-2-agonist (SABA), low dose ICS or testing for allergic sensitization, and symptom and social behaviour assessment for asthma diagnosis in young children (Global Initiative for Asthma, 2020).

2.11 ACO diagnosis

Despite efforts to define ACO, there is currently no consensus on the definite diagnostic criteria. Diagnosing ACO is complex due to the similarities between the clinical features of COPD and asthma and the expression of a wide array of phenotypes. Tommola et al. (2017) describe three distinct pathways by which ACO may be considered. A patient with COPD develops asthma-like symptoms, and typical characteristics of asthma such as high reversibility of the airways, or a patient with asthma who is also a smoker goes on to develop COPD-like features such as non-reversible airway obstruction. The authors further identify a third pathway where patients with asthma develop non-reversible airway obstruction without a smoking history. However, the authors note that exposure to either tobacco smoking or biomass fuels is a requirement for the diagnosis of COPD, and is therefore a necessary factor for the diagnosis of asthma-COPD overlap (Tommola et al., 2017).

In 2015, a global expert panel reviewed multiple trials and generated a working definition for ACO involving major and minor criteria for its diagnosis (Sin, 2017), which has also been endorsed by the Spanish Society of Pneumology and Thoracic Surgery (SEPAR). There are three major criteria for ACO: I. persistent airflow limitation ($FEV_1/FVC \leq 0.70$ despite bronchodilator therapy) in patients age 40 years or older II. Significant smoking history of ≥10 pack-years or equivalent exposure to air pollution III. Documented history of atopy/asthma or bronchodilator response ≥ 400 mL in FEV_1. Minor criteria include I. Documented history of asthma or allergic conditions II. Bronchodilator response of $FEV_1 \geq 200$ mL and 12% from baseline on two or more visits III. Peripheral eosinophilia ≥ 300 cells/μL. To make a diagnosis of ACO, all three major criteria plus at least one minor criterion must be present (Hines & Peebles, 2017; Sin et al., 2016).

In 2017, GOLD and GINA published a joint report on ACO detailing a stepwise approach to diagnosis based on defining characteristics and differentiating between asthma, COPD, and ACO in the adult population. The first step involves establishing chronic airway disease by assessing patient clinical history, physical examination, radiology, and screening questionnaires. The second step consists of ascertaining whether asthma or COPD is the dominant phenotype by looking for and assembling characteristics of asthma or COPD. The third step involves carrying out spirometry (or PEF) to measure chronic airflow limitation. Step four is to implement initial therapy. The suggested therapy regimen varies depending on whether the syndromic assessment in previous steps favors asthma or COPD. The final step recommends referral to specialists for further diagnostic evaluation if necessary (Global Initiative for Asthma, 2017).

2.12 Management of COPD, asthma, and ACO

For patients diagnosed with asthma, pharmacological management involves inhaled corticosteroids (ICS), with additional treatment such as long-acting beta2-agonist (LABA) or long-acting muscarinic antagonist (LAMA), incorporated if necessary (Global Initiative for Asthma, 2020). For patients diagnosed with COPD, pharmacotherapy is initiated with bronchodilators (LABA or LAMA) or combination therapy with ICS, but not ICS alone (as monotherapy). For patients with ACO, GINA and GOLD recommend initiating treatment following the dominant phenotype. For patients with more asthma symptoms, physicians should begin treatment for asthma using low or moderate ICS. Depending on the severity, a long-acting beta 2-antagonist (LABA) can be incorporated. It is emphasized that patients are not treated with a LABA without ICS (LABA monotherapy) due to the risk of increased asthma exacerbations and asthma-related death. For patients with ACO who present with more COPD symptoms, therapy with a first-line bronchodilator is preferred. For patients with an equal number of asthma and COPD features, or if differential diagnosis is difficult, the recommendation is to start treating asthma with an ICS (Hines & Peebles, 2017). ACO treatment should also involve strategies for smoking cessation, pulmonary rehabilitation, influenza and pneumococcal vaccination, incorporation of physical activity, and treatment of comorbidities. As with COPD and asthma, the objective for ACO is to control symptoms, improve health status and quality of life, and prevent exacerbations (Col & Freiler, 2015; Global Initiative for Chronic Obstructive Lung Disease, 2020; Global Initiative for Asthma, 2020).

2.13 Male and female differences with COPD, asthma, and ACO

Sex refers to the biological differences between males and females, while gender refers to the socially constructed roles, behaviours, expressions and identities of girls, women, boys, men and gender diverse people (CIHR, 2020). Sex and gender-specific differences in respiratory conditions, such as asthma and COPD, have consistently been recognized in historical and contemporary literature. Such differences have been supported by epidemiological evidence on incidence, risk factors, severity, and burden of lung diseases, and clinical research on male and female lung anatomy, airway behaviour, and differences in clinical manifestations of the disease. Globally, the prevalence of COPD has increased during the past century with tobacco smoking being the most important risk factor especially in high income countries. Between 1990 to 2017, the relative increase in overall global prevalence was 5.9% (Soriano et al., 2020). High-income countries represented the greatest relative difference in prevalence estimates between 1990 to 2017 which was 4.4% in 1990 to 5.9% in 2017. One Canadian study reported a 64.8% increase in COPD cases between 1997 and 2007 in Ontario, Canada. The age- and sex- standardized prevalence increased from 7.8% in 1996 to 9.5% in 2007 (Gershon et al., 2010). The authors also reported that women were disproportionately burdened by COPD. Women had more than twice the increase in age-standardized COPD prevalence than men, and only demonstrated modest decreases in incidence and mortality comparatively (Gershon et al., 2010). Although COPD has historically been considered a disease of men, the burden of COPD has been shifting from males to females, and this has been reflected in the increased prevalence, morbidity, and mortality of COPD in women over the last two decades (Aryal et al., 2014). Prevalence data studied from 1998 to 2009 showed that COPD prevalence in the USA increased in women while it decreased

in men, and similar trends were found in the Netherlands (Aryal et al., 2014; Bischoff et al., 2009).

Historically, there has been a gap between males and females in the proportion of deaths attributed to COPD, with, in previous years, a higher percentage of deaths among males than females. However, by 2011, this gap between the sexes was no longer evident in Canada, due to the steady increase in mortality rates between 1950 and 2011 for women, while for men, the rate remained constant during the 1990s and then significantly decreased between 1998 and 2011 (Bryan & Navaneelan, 2015). This trend is echoed in the United States as well, where the COPD age-adjusted mortality rates for males increased during 1970-2000 and then declined during 2000-2015, whereas for women, the mortality rates increased during 1970-2000 and then plateaued (Harris, 2019), and in 2000, the number of women dying from COPD surpassed the number of men for the first time in the United States (Han et al., 2007; Nicolini et al., 2018).

According to an analysis from the Global Burden of Disease Study, in 2015, asthma was the most prevalent chronic respiratory disease worldwide, with twice the number of COPD cases. The reported prevalence of asthma was 12.6% higher in 2015 than in 1990 (358 million versus 318 million. Asthma has been reported to afflict females more often than males, 190 million prevalent cases versus 168 million cases. However, the global age-standardized mortality was higher in males (6.7 per 100,000) than females (5.6 per 100,000) (Harris, 2019; Soriano et al., 2017). At a population level, the burden of asthma shifts between the sexes and is closely tied to age. For males, asthma is a condition that presents predominantly during childhood and pre-puberty. For females, asthma most often develops during puberty or early adulthood and can follow them throughout their lives. Pregnancy and menopause can trigger exacerbations, and

compared to males, asthma for females is more severe and has a higher chance of mortality (Cadeddu et al., 2016; Fuseini & Newcomb, 2017).

According to the 2018 Report from the Canadian Chronic Disease Surveillance System on Asthma and COPD in Canada, between 2000 and 2012, the relative increase in the age-standardized prevalence for asthma among Canadians aged one year and older was 67% (Dai et al., 2018). Despite a decreased incidence, the prevalence of asthma increased from 2.1 million Canadians in 2000-2001 (6.5%) to 3.8 million Canadians (10.8%) in 2011-2012, and this increase was evident for both males and females. The age-standardized prevalence of asthma was greater among females than males throughout the study period (Dai et al., 2018). These findings are echoed by another Canadian study comparing asthma burden in Alberta and Ontario from 1995 to 2015. This study found that the age-standardized incidence of asthma has been on a descending trend for over two decades, and this is consistent for both males and females. Age-adjusted lifetime prevalence, however, has tripled in both sexes, from 3.9% in 1995 to 12.3% in 2015 for females and from 3.5% to 11.6% in males. All-cause mortality among people with asthma decreased overall and for both sexes; however, it was still greater when compared to people without asthma (Bosonea et al., 2020). Sex-specific differences in the burden of asthma-COPD overlap are unclear as there is no consensus in the literature. Some studies have shown that women are more likely than men to have ACO (de Marco et al., 2013; Koleade et al., 2019; Senthilselvan & Beach, 2018; Wheaton et al., 2018), while others found no significant differences between males and females (Alshabanat et al., 2015).

As the epidemiological evidence indicates, the burden of these diseases is not evenly borne across the sexes. Although the role that sex and gender play in driving these disparities are expressed in the literature, they are not entirely understood. Such differences have been ascribed

to male and female variations in lung and airway anatomy and physiology, the effect of sex hormones across the lifespan, and differences in phenotypic and clinical expressions of lung disease. Additionally, the various social, physical, mental genetic, and environmental risk factors affirm the multifaceted nature of COPD, asthma, and ACO and comprise male and female differences.

2.14 Sex-specific risk factors

In several studies, sex-specific differences have been demonstrated, with many identifying a female predominance for ACO. This, combined with the growing prevalence among females, warrants further investigation into the effects of various social, physical, and mental factors driving these sex-specific differences.

2.14.1 Smoking

Cigarette smoking is a significant risk factor for COPD. Between 15% and 50% of smokers develop COPD (Louie et al., 2013). The recent rise in smoking trends among women has contributed to the increasing number of women with COPD globally. Smoking has a greater impact on the lung function of females than males. Compared to males, females are more susceptible to tobacco, report having more severe disease despite lower overall tobacco consumption, and show earlier development of COPD (Lomauro & Aliverti, 2018). Studies also report that female smokers are at an increased risk for hospitalization for COPD, have a more rapid decline in lung function and more significant reductions in FEV_1 at comparable levels of smoking intensity as males (Prescott et al., 1997; Silverman et al., 2000; Xu et al., 1994). Conversely, females report an increased tendency to benefit from smoking cessation programs. The Lung Health Study, a multicenter clinical trial on smoking intervention to smokers with mild

and moderate COPD, demonstrated that females in their first year of sustained quitting had a 2.5 times greater improvement in percent predicted FEV_1 than males. In short, pulmonary function was improved more by smoking cessation programs in women than in men (Gut-Gobert et al., 2019; Han et al., 2007; Nicolini et al., 2018).

Furthermore, there is a significant proportion of individuals with COPD that have never smoked. Approximately 24-45% of patients with COPD are non-smokers (Salvi & Barnes, 2009), and the prevalence of non-smoking-related COPD is greater among females than males (Gut-Gobert et al., 2019). This onset of COPD could be explained by increased second-hand smoke, indoor and outdoor smoke exposure, genetics, occupational exposure, or other risk factors. Approximately 3 billion people are exposed to smoke from biomass fuel, and it is considered a leading risk factor for non-smoking-related COPD globally (Salvi & Barnes, 2009). In developing countries, women are at an increased risk of biomass smoke exposure from cooking in poorly ventilated homes (Gut-Gobert et al., 2019). Exposures to tobacco smoke, including cigarette smoking and second-hand smoke exposure, are important triggers of asthma. Smoking or exposure to second-hand smoke increases asthma morbidity and disease severity, and prolonged exposure contributes to a greater decline in lung function among asthmatics (Sears, 2015; Stapleton et al., 2011; Thomson et al., 2004). Subjects with asthma who smoke are also more likely to have more inadequate asthma control, have more severe respiratory symptoms, greater need for rescue medication, and worse indices of health status when compared to never-smokers (Thomson et al., 2004). Smoking during pregnancy negatively affects fetal lung development. Maternal smoking during pregnancy has been associated with an increased risk of asthma, wheezing, airway hyperresponsiveness, impaired lung function, and bronchitis among children. In utero, exposure

to cigarette smoke was associated with a reduced maximal expiratory flow. (Banderali et al., 2015; Spindel & McEvoy, 2016).

Some studies, but not all, have found a difference in risk of asthma associated with smoking between males and females. The Li et al. (2014) study comparing effects of in utero tobacco exposure for boys and girls, found that for boys, in utero exposure to smoking resulted in more considerable reductions in forced vital capacity, maximum expiratory flow, and FEV_1/FVC ratio, compared to boys with non-smoking mothers. However, for girls, in utero, cigarette exposure was only linked to a reduced FEV_1/FVC ratio when compared to girls who were not exposed. These findings suggest that the unfavorable effects of smoking exposure in utero might be greater in boys. (Postma, 2007). These findings were echoed in a United States longitudinal study on 9000 children between 7 and 14 years of age. Study findings determined that maternal smoking was associated with higher asthma rates in boys than in girls of all ages studied (Postma, 2007). Li et al., and Townsend et al., concluded that while in early childhood and utero, females display less susceptibility to maternal smoke, this changes in later life when females show greater susceptibility to smoke exposure. Smoking increased the risk of chronic airflow obstruction (CAO) among individuals with asthma. Among subjects without asthma, current smokers had 4.5 times higher risk of airflow obstruction compared with never-smokers (Sears, 2015).

Similarly, smoking is a risk factor for asthma-COPD overlap, and many older adults with a history of smoking and asthma develop clinical features of both asthma and COPD (Izbicki et al., 2019).

A systematic review and meta-analysis on the published literature on ACO found that subjects with ACO had a history of less smoking than patients with COPD (Alshabanat et al., 2015).

Some studies found that compared with participants with asthma only, those with ACO were more likely to have a smoking history (Haghighi et al., 2020; H. Lee et al., 2020; Senthilselvan & Beach, 2018). Children with asthma have an increased risk of developing chronic obstructive pulmonary disease (COPD) in adulthood (Trivedi & Denton, 2019). Hayden et al. (2018) found that smokers who had a history of asthma in childhood had a greater risk for developing low lung function and COPD as adults when compared to smokers who did not have asthma in childhood (Hayden et al., 2018).

2.14.2 Socioeconomic status, education, income

Socioeconomic status (SES) is often measured by education and income and serves as an indicator for social class and a predictor for various physical and mental health outcomes. SES is not only an important determinant of health and nutritional status but also determines accessibility and affordability of health care services. SES has long been recognized as a risk factor for respiratory disease, and a marked socioeconomic gradient in COPD prevalence has been demonstrated in epidemiological studies (Prescott, E., 1999; Kanervisto et al., 2011). Despite this, there is limited research on ACO and SES and even less research on observable differences for males and females concerning education and income level. Data from the U.S. NHANES cross-sectional survey indicated that the age-standardized prevalence of ACO was greater among people with low socioeconomic status (Qian Zhang, Huie Jing, 2017)

The risk of ACO has been associated with low education attainment, whereby the prevalence of ACO decreases as the education level increases. This protective effect that higher education has against the risk of ACO has been reported in multiple studies (de Marco et al., 2013; Kim et al., 2019; Senthilselvan & Beach, 2018). A study by Wheaton et al. explored male and female

differences in education and obstructive lung disease. They concluded that males and females with less than a high school education were more likely to report having asthma, COPD, or ACO, compared to participants with at least some college education. This finding was both statistically significant and consistent across sex (Wheaton et al., 2018). This observation for ACO is echoed in To et al., a prospective female-only study investigating participants with prevalent asthma for risk factors associated with COPD incidence. Researchers concluded that lower educational attainment was significantly associated with COPD incidence. In other words, compared to females with a university education, the cumulative incidence of ACO was higher for females with less than high school education. A higher risk of ACO was also observed for females with a high school/trade school/vocational school and college/business school when compared to females with a university education (To et al., 2018). A limited number of studies have explored income level, and sex-specific differences in ACO. The demographic characteristics in some research study populations have shown a higher proportion of ACO participants belonging to the lowest income category (Haghighi et al., 2020; Kim et al., 2019; Kumbhare et al., 2016).

Extrapolating from epidemiological studies on COPD, poverty is consistently associated with airflow obstruction, and lower SES is associated with an increased risk of developing COPD (Global Initiative for Chronic Obstructive Lung Disease, 2020). There are conflicting findings for SES and asthma, on the other hand. The theory of westernization and the hygiene hypothesis suggests that socioeconomic development or westernization predisposes individuals to the development of asthma, possibly through pathways detailed in the hygiene hypothesis, whereby exposure to infections early in childhood has led to the lower prevalence of asthma in rural areas (Soriano et al., 2017). Newer perspectives on the influence of the microbiome and gene-

environment interactions have challenged the hygiene hypothesis (Bloomfield et al., 2016). Surya Kant's (2013) paper on the socioeconomic dynamics of asthma indicated that asthma prevalence was higher among poor communities than affluent ones in developed nations, but higher among affluent than poor populations in developing countries. This possibly reflects lifestyle differences in exposure to environmental irritants, allergens, or access to health care and diagnosis determined by socioeconomic status (Kant, 2013). Research findings vary in their conclusions on low SES and asthma, with some reporting it increases the risk for asthma, while others concluding it lowers the risk or there exists no association at all (Kant, 2013). The ambiguity and lack of consensus on SES and asthma limit current understanding of this issue. Additional research is needed to understand the role of SES and income level with asthma and subsequently ACO.

2.14.3 Race

Racial and ethnic differences contextualized by social inequities, occupational and environmental exposure, and genetic susceptibility adds to the complex nature social factors play in driving asthma, COPD, and ACO prevalence. There is limited literature detailing the role of race and ethnicity on ACO risk and its interaction with other social dynamics, such as income, education, and sex. The Genetic Epidemiology of COPD (COPDGene) Study is a U.S. multicenter, longitudinal study designed to investigate the underlying genetic factors of COPD, improve classification of COPD phenotypes, and explore associations with susceptibility genes. It has enrolled more than 10,000 smokers with and without COPD across the various GOLD stages and includes both non-Hispanic white and African American subjects. Patients with asthma were not targeted for inclusion, but nor were they excluded, and ACO sub-group analysis

was undertaken for participants with both COPD and asthma. Hardin et al. found that COPDGene study subjects with coexisting asthma and COPD were more frequently African Americans and women. In subjects with COPD, African American race was associated with a two-fold increase in the risk of reporting an asthma diagnosis, supporting the theory that different races may possess a different level of COPD susceptibility and clinical presentation than other populations. It was also observed that among COPD participants with exacerbations, black respondents reported worse quality of life scores than white participants with COPD exacerbations (Hardin et al., 2014; Hardin et al., 2011a). Taken together, Hardin et al. (2014) demonstrate that both women and African American subjects are overrepresented in the ACO population. The overrepresentation of African Americans with ACO was observed in other studies (Qian Zhang, Huie Jing, 2017; Stringer et al., 2019). In contrast, Senthilselvan & Beach analysis of the Canadian Health Measures Survey found no significant association between Caucasian ethnicity and risk of obstructive lung disease (Senthilselvan & Beach, 2018). A recent study by Koleade et al. showed that among Indigenous Peoples in Canada, females were almost two times more likely to have ACO than males (Koleade et al., 2019). The literature on ACO in this specific population group is scarce. A systematic review and meta-analysis on asthma and COPD prevalence comparing Aboriginal and non-Aboriginal participants from New Zealand, Australia, and Canada, found that overall, Aboriginal subjects were more likely to report having asthma than non-Aboriginals, and this was greater among Canadian Aboriginals compared to Canadian non-Aboriginals The Aboriginal population in Canada had 1.80 times the odds of reporting asthma than non-Aboriginal Canadians (Ospina et al., 2012). The sex-specific difference in asthma prevalence was not reported in this study (Ospina et al., 2012). The review identified one study for COPD and noted that COPD rates were similar in Native Americans and

non-Native Americans (Ospina et al., 2012). Racial disparities in asthma prevalence were also reported by Hardin et al., whereby the findings concluded that African Americans reported a higher incidence of asthma than white participants (Hardin et al., 2014). This is supported by Wheaton et al., however, the disparity observed was only found in males. There were no differences reported in asthma, COPD, or ACO between black and white female respondents (Wheaton et al., 2018). Caucasians with COPD showed less loss of lung function per pack-year smoked than African Americans. Moreover, mortality data appear to show a growing increase in deaths due to COPD among women and African Americans. This supports findings in other studies suggestive of increased susceptibility to tobacco smoke in these groups and most vulnerability for African American women (Dransfield et al., 2006).

2.14.4 Marital status

Few studies have examined the impact marital status has on respiratory health outcomes, and even less have studied its influence on ACO. Senthilselvan & Beach reported that subjects with ACO or COPD are more likely to be single or widowed, and less likely to be married when compared to subjects without obstructive lung disease (Senthilselvan & Beach, 2018). Koleade et al. observed that in their study on female-specific risk factors for ACO, Aboriginal females in Canada were two times more likely to be associated with ACO if they reported being widowed, separated, or divorced in comparison to those being married. Marital status was not associated with ACO for Aboriginal males (Koleade et al., 2019). There is evidence that marriage behaves as a protective factor for COPD. Females in the U.S. who remarried after a divorce or bereavement showed a statistically significant decrease in their risk for developing COPD (Noda et al., 2009). This may be a consequence of or mediated by negative psychosocial factors from

grief or separation, a change in socioeconomic status brought on by an increase in household income, reduced stress or shared burden of housework, and improved health behaviours (Noda et al., 2009).

2.14.5 Physical and mental factors

Several studies have reported a high number of comorbidities among patients with ACO than patients with COPD (Alshabanat et al., 2015; Kumbhare et al., 2016) or asthma alone (Senthilselvan & Beach, 2018; Tommola et al., 2017). Obesity has been consistently identified as a risk factor for ACO, COPD, and asthma (Franssen et al., 2008; Fuller-Thomson et al., 2018; Kumbhare et al., 2016; Lambert et al., 2017; Peters et al., 2018; Senthilselvan & Beach, 2018; Sood, 2011). Specifically, research has shown that patients with ACO are more likely to be obese (Kim et al., 2019; Menezes et al., 2014; Senthilselvan & Beach, 2018; Zhou & Zhao, 2021). Senthilselvan & Beach reported that the likelihood of being obese for subjects in the ACO group was more than twice that for subjects without obstructive lung disease. People with ACO are also at a greater risk for diabetes (Kim et al., 2019), osteoporosis (van Boven et al., 2016) cancer (Kim et al., 2019; Senthilselvan & Beach, 2018) anxiety (Kang et al., 2019; van Boven et al., 2016), and depression (Kang et al., 2019; M. Kim et al., 2019; Senthilselvan & Beach, 2018). People with ACO also have worse cardiovascular health (Kim et al., 2019; Senthilselvan & Beach, 2018; Shantakumar et al., 2018), lower quality of life (Col & Freiler, 2015; Hardin et al., 2011a; Kang et al., 2016; Kauppi et al., 2011) worse self-rated health (Chung et al., 2014; J. Kang et al., 2016; Senthilselvan & Beach, 2018), greater respiratory symptoms and poorer lung functioning than those with asthma or COPD alone (Chung et al., 2015; Col & Freiler, 2015; Hardin et al., 2011b; Senthilselvan & Beach, 2018). Sex-specific differences in the types of

comorbidities associated with ACO are also apparent in the literature. Wheaton et al. found that males and females who were obese were more likely to have ACO, compared to those who were normal weight or overweight. This association was similar between males and females (Wheaton et al., 2018). Both men and women with ACO reported higher rates of coronary heart disease compared to participants with no obstructive airway disease (Wheaton et al., 2018). Females with ACO reported more depression and were more likely to report their health as fair or poor when compared to males with ACO (Wheaton et al., 2019). Previous research on COPD also observed a greater prevalence of depression, anxiety, and worse symptom-related quality of life for females with COPD than males (Han et al., 2007).

2.14.6 Environment

Environmental factors such as outdoor air pollution and biomass smoke including harmful particles can lead to chronic respiratory diseases. The WHO estimates that approximately 2.4 billion people use biomass fuel as their primary energy source for cooking and heating. Biomass fuels are responsible for 1.6 million deaths annually (Willett et al., 1999). It has been found that in rural populations, females exposed to high levels of biomass smoke are at greater risk for COPD than males (Salvi & Barnes, 2009). Women are also more likely to spend more time indoors for cooking and consequently are at greater risk of exposure to biomass fuels than men (Nicolini et al., 2018). Females may also have a greater susceptibility to the harmful effects of air pollution (Cadeddu et al., 2016). A study on the results of PM_{10} exposure found that adverse effects were more severe in women and never-smokers (Lee et al., 2020). Previous research has seen a significant association between exposure to traffic air pollution and COPD prevalence (de Marco et al., 2013; Salvi & Barnes, 2009), but not for ACO prevalence (de Marco et al., 2013;

To et al., 2018). To et al. reported that in a female-only population study, exposure to fine particulate matter, a significant air pollutant, was not associated with ACO however, rural residence was associated with ACO (To et al., 2018).

2.15 Summary

This literature review was undertaken to explore the nature of existing research on ACO, social, physical and environmental risk factors for ACO, and sex-related disparities in the burden and risk for disease. This review included studies that examined the association between ACO, asthma or COPD and various factors, as well as articles that explored male and female differences. Despite the limited number of studies examining sex-specific differences, male and female disparities were observed for various factors such as race, education level, smoking and comorbid conditions. However, the findings from this review still underscore the scarce literature on this topic, especially in a Canadian context. The results from this thesis will provide additional information to the current literature on sex-specific risk factors for COPD, asthma, and ACO among middle-aged and older Canadian adults.

References:

1. Alshabanat, A., Zafari, Z., Albanyan, O., Dairi, M., & Fitzgerald, J. M. (2015). Asthma and COPD overlap syndrome (ACOS): A systematic review and meta analysis. *PLoS ONE*, *10*(9), 1–15. https://doi.org/10.1371/journal.pone.0136065

2. Aryal, S., Diaz-Guzman, E., & Mannino, D. M. (2014). Influence of sex on chronic obstructive pulmonary disease risk and treatment outcomes. *International Journal of COPD*, *9*, 1145–1154. https://doi.org/10.2147/COPD.S54476

3. Banderali, G., Martelli, A., Landi, M., Moretti, F., Betti, F., Radaelli, G., Lassandro, C., & Verduci, E. (2015). Short and long term health effects of parental tobacco smoking during pregnancy and lactation: A descriptive review. *Journal of Translational Medicine*, *13*(1), 1–7. https://doi.org/10.1186/s12967-015-0690-y

4. Barczyk, A., Maskey-Warzęchowska, M., Górska, K., Barczyk, M., Kuziemski, K., Śliwiński, P., Batura-Gabryel, H., Mróz, R., Kania, A., Obojski, A., Tażbirek, M., Celejewska-Wójcik, N., Guziejko, K., Brajer-Luftmann, B., Korzybski, D., Damps-Kostańska, I., & Krenke, R. (2019). Asthma-COPD Overlap - A Discordance Between Patient Populations Defined by Different Diagnostic Criteria. *Journal of Allergy and Clinical Immunology: In Practice*, *7*(7), 2326-2336. https://doi.org/10.1016/j.jaip.2019.04.022

5. Barnes, P. J., Burney, P. G. J., Silverman, E. K., Celli, B. R., Vestbo, J., Wedzicha, J. A., & Wouters, E. F. M. (2015). Chronic obstructive pulmonary disease. *Nature Reviews Disease Primers*, *1*(12), 1–22. https://doi.org/10.1038/nrdp.2015.76

6. Bischoff, E. W. M. A., Schermer, T. R. J., Bor, H., Brown, P., Van Weel, C., & Van Den Bosch, W. J. H. M. (2009). Trends in COPD prevalence and exacerbation rates in Dutch primary care. *British Journal of General Practice*, *59*(569), 927–933.

https://doi.org/10.3399/bjgp09X473079

7. Bloomfield, S. F., Rook, G. A. W., Scott, E. A., Shanahan, F., Stanwell-Smith, R., & Turner, P. (2016). Time to abandon the hygiene hypothesis: New perspectives on allergic disease, the human microbiome, infectious disease prevention and the role of targeted hygiene. *Perspectives in Public Health*, *136*(4), 213–224. https://doi.org/10.1177/1757913916650225

8. Bosonea, A. M., Sharpe, H., Wang, T., Bakal, J. A., Befus, A. D., Svenson, L. W., & Vliagoftis, H. (2020). Developments in asthma incidence and prevalence in Alberta between 1995 and 2015. *Allergy, Asthma and Clinical Immunology*, *16*(1), 1–11. https://doi.org/10.1186/s13223-020-00485-3

9. Bryan, S., & Navaneelan, T. (2015). Deaths from Chronic Obstructive Pulmonary Disease in Canada , 1950 to 2011. *Health at a Glance*, *82*, 1–8.

10. Buist, A. S., McBurnie, M. A., Vollmer, W. M., Gillespie, S., Burney, P., Mannino, D. M., Menezes, A. M., Sullivan, S. D., Lee, T. A., Weiss, K. B., Jensen, R. L., Marks, G. B., Gulsvik, A., & Nizankowska-Mogilnicka, E. (2007). International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study. *Lancet*, *370*(9589), 741–750. https://doi.org/10.1016/S0140-6736(07)61377-4

11. Cadeddu, C., Capizzi, S., Colombo, D., Nica, M., & De Belvis, A. G. (2016). Literature review of gender differences in respiratory conditions: a focus on asthma and Chronic Obstructive Pulmonary Disease (COPD). *Igiene e Sanita Pubblica*, *72*(5), 481–504.

12. Canadian Institutes of Health Research. (2020). What is gender? What is sex? Retrieved online July 3, 2020. https://cihr-irsc.gc.ca/e/48642.html

13. Chambliss, J. M., Sur, S., & Tripple, J. W. (2018). Asthma versus chronic obstructive

pulmonary disease, the Dutch versus British hypothesis, and role of interleukin-5. *Current Opinion in Allergy and Clinical Immunology*, *18*(1), 26–31. https://doi.org/10.1097/ACI.0000000000000409

14. Chung, J. W., Kong, K. A., Lee, J. H., Lee, S. J., Ryu, Y. J., & Chang, J. H. (2014). Characteristics and self-rated health of overlap syndrome. *International Journal of COPD*, *9*, 795–804. https://doi.org/10.2147/COPD.S61093
15. Chung, W. S., Lin, C. L., & Kao, C. H. (2015). Comparison of acute respiratory events between: Asthma-COPD overlap syndrome and COPD patients. *Medicine (United States)*, *94*(17), e755. https://doi.org/10.1097/MD.0000000000000755
16. Col, L., & Freiler, J. F. (2015). The Asthma-COPD Overlap Syndrome. *Federal Practitioner*, *32*(Suppl. 10), 19–23.
17. Comberiati, P., Di Cicco, M. E., D'Elios, S., & Peroni, D. G. (2017). How much asthma is atopic in children? *Frontiers in Pediatrics*, *5*(5), 5–8. https://doi.org/10.3389/fped.2017.00122
18. Dai, S., Bancej, C., Loukine, L., Waters, C., & Baclic, O. (2018). Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Canada, 2018. *Report from the Canadian chronic disease surveillance system*, *31(1)*.
19. de Marco, R., Pesce, G., Marcon, A., Accordini, S., Antonicelli, L., Bugiani, M., Casali, L., Ferrari, M., Nicolini, G., Panico, M. G., Pirina, P., Zanolin, M. E., Cerveri, I., & Verlato, G. (2013). The Coexistence of Asthma and Chronic Obstructive Pulmonary Disease (COPD): Prevalence and Risk Factors in Young, Middle-aged and Elderly People from the General Population. *PLoS ONE*, *8*(5), 1–7. https://doi.org/10.1371/journal.pone.0062985
20. Dransfield, M. T., Davis, J. J., Gerald, L. B., & Bailey, W. C. (2006). Racial and gender

differences in susceptibility to tobacco smoke among patients with chronic obstructive pulmonary disease. *Respiratory Medicine*, *100*(6), 1110–1116. https://doi.org/10.1016/j.rmed.2005.09.019

21. Ekerljung, L., Mincheva, R., Hagstad, S., Bjerg, A., Telg, G., Stratelis, G., & Lötvall, J. (2018). Prevalence, clinical characteristics and morbidity of the Asthma-COPD overlap in a general population sample. *Journal of Asthma*, *55*(5), 461–469. https://doi.org/10.1080/02770903.2017.1339799
22. Eva Prescott, J. V. (1999). Socioeconomic status and chronic obstructive pulmonary disease. *TAF Preventive Medicine Bulletin*, *12*(1), 87–96. https://doi.org/10.5455/pmb.1-1331198324
23. Franssen, F. M. E., O'Donnell, D. E., Goossens, G. H., Blaak, E. E., & Schols, A. M. W. J. (2008). Obesity and the lung: Obesity and COPD. *Thorax*, *63*(12), 1110–1117. https://doi.org/10.1136/thx.2007.086827
24. Fuller-Thomson, E., Howden, K. E. N., Fuller-Thomson, L. R., & Agbeyaka, S. (2018). A Strong Graded Relationship between Level of Obesity and COPD: Findings from a National Population-Based Study of Lifelong Nonsmokers. *Journal of Obesity*, *2018*. https://doi.org/10.1155/2018/6149263
25. Fuseini, H., & Newcomb, D. C. (2017). Mechanisms driving gender differences in asthma. *Physiology & Behavior*, *17*(13), 100–106. https://doi.org/10.1007/s11882-017-0686-1.Mechanisms
26. Gerhardsson De Verdier, M., Andersson, M., Kern, D. M., Zhou, S., & Tunceli, O. (2015). Asthma and Chronic Obstructive Pulmonary Disease Overlap Syndrome: Doubled Costs Compared with Patients with Asthma Alone. *Value in Health*, *18*(6), 759–766.

https://doi.org/10.1016/j.jval.2015.04.010

27. Gershon, A. S., Wang, C., Wilton, A. S., Raut, R., & To, T. (2010). Trends in chronic obstructive pulmonary disease prevalence, incidence, and mortality in Ontario, Canada, 1996 to 2007: A population-based study. *Archives of Internal Medicine*, *170*(6), 560–565. https://doi.org/10.1001/archinternmed.2010.17

28. Global Initiative for Asthma. (2020). Global strategy for asthma management and prevention: Socioeconomics. *Global Initiative for Asthma*, *36*(6), 685–704. https://doi.org/10.1016/S0335-7457(96)80056-6

29. Global Initiative for Asthma. (2019). *Global Strategy for Asthma Management and Prevention.* Retrieved from www.ginasthma.org.

30. Global Initiative for Asthma. (2017). *Diagnosis and initial treatment of asthma, COPD, and asthma - COPD overlap : A joint project of GINA and GOLD updated April 2017*. Retrieved from https://ginasthma.org/wp-content/uploads/2019/11/GINA-GOLD-2017-overlap-pocket-guide-wms-2017-ACO.pdf

31. Global Initiative for Chronic Obstructive Lung Disease (2020). GOLD 2020 Report. *Global Initiative for Chronic Obstructive Lung Disease*.

32. Guerra, S., Sherrill, D. L., Bobadilla, A., Martinez, F. D., & Barbee, R. A. (2002). The Relation of Body Mass Index to Asthma, Chronic Bronchitis, and Emphysema. *Chest, 122*(4), 1256-1263.

33. Gut-Gobert, C., Cavaillès, A., Dixmier, A., Guillot, S., Jouneau, S., Leroyer, C., Marchand-Adam, S., Marquette, D., Meurice, J. C., Desvigne, N., Morel, H., Person-Tacnet, C., & Raherison, C. (2019). Women and COPD: Do we need more evidence? *European Respiratory Review*, *28*(151). https://doi.org/10.1183/16000617.0055-2018

34. Haghighi, A., Cone, J. E., Li, J., & de la Hoz, R. E. (2020). Asthma-COPD overlap in World Trade Center Health Registry enrollees, 2015–2016. *Journal of Asthma*, 2015–2016. https://doi.org/10.1080/02770903.2020.1817935

35. Han, M. L. K., Postma, D., Mannino, D. M., Giardino, N. D., Buist, S., Curtis, J. L., & Martinez, F. J. (2007). Gender and chronic obstructive pulmonary disease: Why it matters. *American Journal of Respiratory and Critical Care Medicine*, *176*(12), 1179–1184. https://doi.org/10.1164/rccm.200704-553CC

36. Hardin, M., Cho, M., McDonald, M.-L., Beaty, T., Ramsdell, J., Bhatt, S. P., van Beek, E. J. R., Make, B. J., Crapo, J. D., Silverman, E. K., & Hersh, C. P. (2014). The clinical and genetic features of the COPD asthma overlap syndrome. *European Respiratory Journal*, *44*(2), 341–350. https://doi.org/10.1183/09031936.00216013.

37. Hardin, M., Silverman, E. K., Barr, R. G., Hansel, N. N., Schroeder, J. D., Make, B. J., Crapo, J. D., & Hersh, C. P. (2011). The clinical features of the overlap between COPD and asthma for the COPDGene Investigators. *Respiratory Research*, *12*(127), 1–8. https://respiratory-research.biomedcentral.com/track/pdf/10.1186/1465-9921-12-127?site=respiratory-research.biomedcentral.com

38. Hardin, M., Silverman, E. K., Barr, R. G., Hansel, N. N., Schroeder, J. D., Make, B. J., Crapo, J. D., Hersh, C. P., Curtis, J., Kazerooni, E., Hanania, N., Alapat, P., Bandi, V., Guntupalli, K., Guy, E., Mallampalli, A., Trinh, C., Atik, M., DeMeo, D., Allen, A. (2011). The clinical features of the overlap between COPD and asthma. *Respiratory Research*, *12*(1), 127. https://doi.org/10.1186/1465-9921-12-127

39. Harris, R. E. (2019). *Epidemiology of Chronic Disease*. Jones & Bartlett Learning.

40. Hayden, L. P., Cho, M. H., Raby, B. A., Beaty, T. H., Silverman, E. K., & Hersh, C. P.

(2018). Childhood asthma is associated with COPD and known asthma variants in COPDGene: A genome-wide association study. *Respiratory Research*, *19*(1), 1–11. https://doi.org/10.1186/s12931-018-0890-0

41. Henriksen, A. H., Langhammer, A., Steinshamn, S., Mai, X. M., & Brumpton, B. M. (2018a). The Prevalence and Symptom Profile of Asthma–COPD Overlap: The HUNT Study. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, *15*(1), 27–35. https://doi.org/10.1080/15412555.2017.1408580

42. Henriksen, A. H., Langhammer, A., Steinshamn, S., Mai, X. M., & Brumpton, B. M. (2018b). The Prevalence and Symptom Profile of Asthma–COPD Overlap: The HUNT Study. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, *15*(1), 27–35. https://doi.org/10.1080/15412555.2017.1408580

43. Hines, K. L., & Peebles, R. S. (2017). Management of the Asthma-COPD Overlap Syndrome (ACOS): A Review of the Evidence. *Current Allergy and Asthma Reports*, *17*(3), 4–9. https://doi.org/10.1007/s11882-017-0683-4

44. Holgate, S. T., Wenzel, S., Postma, D. S., Weiss, S. T., Renz, H., & Sly, P. D. (2015). Asthma. *Nature Reviews Disease Primers*, *1*(9), 1–22. https://doi.org/10.1038/nrdp.2015.25

45. Hosseini, M., Almasi-Hashiani, A., Sepidarkish, M., & Maroufizadeh, S. (2019). Global prevalence of asthma-COPD overlap (ACO) in the general population: A systematic review and meta-analysis. *Respiratory Research*, *20*(1), 4–13. https://doi.org/10.1186/s12931-019-1198-4

46. Izbicki, G., Teo, V., Liang, J., Russell, G. M., Holland, A. E., Zwar, N. A., Bonevski, B., Mahal, A., Eustace, P., Paul, E., Phillips, K., Wilson, S., George, J., & Abramson, M. J.

(2019). Clinical characteristics of patients with asthma COPD overlap (ACO) in Australian primary care. *International Journal of COPD*, *14*, 2745–2752. https://doi.org/10.2147/COPD.S220346

47. Kanervisto, M., Vasankari, T., Laitinen, T., Heliövaara, M., Jousilahti, P., & Saarelainen, S. (2011). Low socioeconomic status is associated with chronic obstructive airway diseases. *Respiratory Medicine*, *105*(8), 1140–1146. https://doi.org/10.1016/j.rmed.2011.03.008

48. Kang, H. R., Hong, S. H., Ha, S. Y., Kim, T. B., & Lee, E. K. (2019). Differences in the risk of mood disorders in patients with asthma-COPD overlap and in patients with COPD alone: A nationwide population-based retrospective cohort study in Korea. *Respiratory Research*, *20*(1), 1–13. https://doi.org/10.1186/s12931-019-1039-5

49. Kang, J., Yao, W., Cai, B., Chen, P., Ling, X., & Shang, H. (2016). Current situation of asthma-COPD overlap syndrome (ACOS) in chinese patients older than 40 years with airflow limitation: Rationale and design for a multicenter, cross-sectional trial (study protocol). *Journal of Thoracic Disease*, *8*(12), 3744–3751. https://doi.org/10.21037/jtd.2016.12.108

50. Kant, S. (2013). Socio-economic dynamics of asthma. *Indian Journal of Medical Research*, *138*(10), 446–448.

51. Kauppi, P., Kupiainen, H., Lindqvist, A., Tammilehto, L., Kilpeläinen, M., Kinnula, V. L., Haahtela, T., & Laitinen, T. (2011). Overlap syndrome of asthma and COPD predicts low quality of life. *Journal of Asthma*, *48*(3), 279–285. https://doi.org/10.3109/02770903.2011.555576

52. Kim, M. A., Noh, C. S., Chang, Y. J., Hong, Y. K., Lee, J. S., Lee, S. W., Lee, S. D., & Oh, Y. M. (2015). Asthma and COPD overlap syndrome is associated with increased risk of

hospitalization. *International Journal of Tuberculosis and Lung Disease*, *19*(7), 864–869. https://doi.org/10.5588/ijtld.14.0327

53. Kim, M., Tillis, W., Patel, P., Davis, R. M., & Asche, C. V. (2019). Association between asthma/chronic obstructive pulmonary disease overlap syndrome and healthcare utilization among the US adult population. *Current Medical Research and Opinion*, *35*(7), 1191–1196. https://doi.org/10.1080/03007995.2019.1565531

54. Koleade, A., Farrell, J., Mugford, G., & Gao, Z. (2019). Female-specific risk factors associated with risk of ACO (asthma COPD overlap) in aboriginal people. *Journal of Asthma*, *57*(9), 1–8. https://doi.org/10.1080/02770903.2019.1621890

55. Kumbhare, S., Pleasants, R., Ohar, J. A., & Strange, C. (2016). Characteristics and prevalence of asthma/chronic obstructive pulmonary disease overlap in the United States. *Annals of the American Thoracic Society*, *13*(6), 803–810. https://doi.org/10.1513/AnnalsATS.201508-554OC

56. Lambert, A. A., Putcha, N., Drummond, M. B., Boriek, A. M., Hanania, N. A., Kim, V., Kinney, G. L., McDonald, M. L. N., Brigham, E. P., Wise, R. A., McCormack, M. C., & Hansel, N. N. (2017). Obesity Is Associated With Increased Morbidity in Moderate to Severe COPD. *Chest*, *151*(1), 68–77. https://doi.org/10.1016/j.chest.2016.08.1432

57. Lee, H., Kim, S. H., Kim, B. K., Lee, Y., Lee, H. Y., Ban, G. Y., Kim, M. H., Kim, J. H., Kwon, J. W., Park, S. Y., Jung, J. W., Park, S. Y., Park, C. S., Rhee, C. K., Lee, T., Lee, J. H., Kim, S. R., Park, J. S., Park, H. W., Yoon, H. J. (2020). Characteristics of Specialist-Diagnosed Asthma-COPD Overlap in Severe Asthma: Observations from the Korean Severe Asthma Registry (KoSAR). *Allergy: European Journal of Allergy and Clinical Immunology*, *March 2020*, 223–232. https://doi.org/10.1111/all.14483

58. Lee, Y. M., Lee, J. H., Kim, H. C., & Ha, E. (2020). Effects of PM10 on mortality in pure COPD and asthma-COPD overlap: difference in exposure duration, gender, and smoking status. *Scientific Reports*, *10*(1), 1–10. https://doi.org/10.1038/s41598-020-59246-2

59. Lomauro, A., & Aliverti, A. (2018). Sex differences in respiratory function. *Breathe*, *14*(2), 131–140. https://doi.org/10.1183/20734735.000318

60. Lõpez-Campos, J. L., Tan, W., & Soriano, J. B. (2016). Global burden of COPD. *Respirology*, *21*(1), 14–23. https://doi.org/10.1111/resp.12660

61. Louie, S., Zeki, A. A., Schivo, M., Chan, A. L., Yoneda, K. Y., Morrissey, B. M., & Albertson, T. E. (2013). The asthma–chronic obstructive pulmonary disease overlap syndrome: pharmacotherapeutic considerations. *Expert Review of Clinical Pharmacology, 6*(2), 197–219. https://doi.org/10.1586/ecp.13.2

62. Maselli, D. J., & Hanania, N. A. (2018). Asthma COPD overlap: Impact of associated comorbidities. *Pulmonary Pharmacology and Therapeutics*, *52*(June), 27–31. https://doi.org/10.1016/j.pupt.2018.08.006

63. Menezes, A. M. B., De Oca, M. M., Pérez-Padilla, R., Nadeau, G., Wehrmeister, F. C., Lopez-Varela, M. V., Muiño, A., Jardim, J. R. B., Valdivia, G., & Tálamo, C. (2014). Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype : COPD-Asthma. *Chest*, *145*(2), 297–304. https://doi.org/10.1378/chest.13-0622

64. Milne, S., Mannino, D., & Sin, D. D. (2020). Asthma-COPD Overlap and Chronic Airflow Obstruction: Definitions, Management, and Unanswered Questions. *Journal of Allergy and Clinical Immunology: In Practice*, *8*(2), 483–495. https://doi.org/10.1016/j.jaip.2019.10.044

65. Miravitlles, M., Soriano, J. B., Ancochea, J., Muñoz, L., Duran-Tauleria, E., Sánchez, G.,

Sobradillo, V., & García-Río, F. (2013). Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. *Respiratory Medicine*, *107*(7), 1053–1060. https://doi.org/10.1016/j.rmed.2013.03.007

66. Nicolini, A., Barbagelata, E., Tagliabue, E., Colombo, D., Monacelli, F., & Braido, F. (2018). Gender differences in chronic obstructive pulmonary diseases: A narrative review. *Panminerva Medica*, *60*(4), 192–199. https://doi.org/10.23736/S0031-0808.18.03463-8

67. Nielsen, M., Bårnes, C. B., & Ulrik, C. S. (2015). Clinical characteristics of the asthma–COPD overlap syndrome – A systematic review. *International Journal of COPD*, *10*(1), 1443–1454. https://doi.org/10.2147/COPD.S85363

68. Noda, T., Ojima, T., Hayasaka, S., Hagihara, A., Takayanagi, R., & Nobutomo, K. (2009). The health impact of remarriage behavior on chronic obstructive pulmonary disease: Findings from the US longitudinal survey. *BMC Public Health*, *9*, 1–6. https://doi.org/10.1186/1471-2458-9-412

69. Ospina, M. B., Voaklander, D. C., Stickland, M. K., King, M., Senthilselvan, A., & Rowe, B. H. (2012). Prevalence of asthma and chronic obstructive pulmonary disease in Aboriginal and non-Aboriginal populations: A systematic review and meta-analysis of epidemiological studies. *Canadian Respiratory Journal*, *19*(6), 355–360.

70. Peters, U., Dixon, A., & Forno, E. (2018). Obesity and Asthma. *Physiology & Behavior*, *176*(5), 139–148. https://doi.org/10.1016/j.jaci.2018.02.004

71. Postma, D. S. (2007). Gender Differences in Asthma Development and Progression. *Gender Medicine*, *4*(Suppl. 2), 133–146. https://doi.org/10.1016/S1550-8579(07)80054-4

72. Prescott, E., Bjerg, A. M., Andersen, P. K., Lange, P., & Vestbo, J. (1997). Gender difference in smoking effects on lung function and risk of hospitalization for COPD: Results front a

Danish longitudinal population study. *European Respiratory Journal*, *10*(4), 822–827. https://doi.org/10.1183/09031936.97.10040822

73. Qian Zhang, Huie Jing, & H. C. S. (2017). Prevalence and Features of Asthma-COPD Overlap in the U.S. 2007-2012. *Physiology & Behavior*, *176*(5), 139–148. https://doi.org/10.1016/j.physbeh.2017.03.040

74. Rausch-Osthoff, A. K., Kohler, M., Sievi, N. A., Clarenbach, C. F., & Van Gestel, A. J. R. (2014). Association between peripheral muscle strength, exercise performance, and physical activity in daily life in patients with Chronic Obstructive Pulmonary Disease. *Multidisciplinary Respiratory Medicine*, *9*(1), 1–7. https://doi.org/10.1186/2049-6958-9-37

75. Romanet-Manent, S., Charpin, D., Magnan, A., Lanteaume, A., & Vervloet, D. (2002). Allergic vs nonallergic asthma: What makes the difference? *Allergy: European Journal of Allergy and Clinical Immunology*, *57*(7), 607–613. https://doi.org/10.1034/j.1398-9995.2002.23504.x

76. Salvi, S. S., & Barnes, P. J. (2009). Chronic obstructive pulmonary disease in non-smokers. *The Lancet*, *374*(9691), 733–743. https://doi.org/10.1016/S0140-6736(09)61303-9

77. Sears, M. R. (2015). Smoking, asthma, chronic airflow obstruction and COPD. *European Respiratory Journal*, *45*(3), 586–588. https://doi.org/10.1183/09031936.00231414

78. Senthilselvan, A., & Beach, J. (2018). Characteristics of asthma and COPD overlap syndrome (ACOS) in the Canadian population. *Journal of Asthma*, *56*(11), 1129–1137. https://doi.org/10.1080/02770903.2018.1531997

79. Shantakumar, S., Pwu, R. F., D'Silva, L., Wurst, K., Kuo, Y. W., Yang, Y. Y., Juan, Y. C., & Chan, K. A. (2018). Burden of asthma and COPD overlap (ACO) in Taiwan: A nationwide population-based study. *BMC Pulmonary Medicine*, *18*(1), 1–12.

https://doi.org/10.1186/s12890-017-0571-7

80. Silverman, E. K., Weiss, S. T., Drazen, J. M., Chapman, H. A., Carey, V., Campbell, E. J., Denish, P., Silverman, R. A., Celedon, J. C., Reilly, J. J., Ginns, L. C., & Speizer, F. E. (2000). Gender-related differences in severe, early-onset chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, *162*(6), 2152–2158. https://doi.org/10.1164/ajrccm.162.6.2003112

81. Sin, D. D. (2017). Asthma-COPD overlap syndrome: What we know and what we don't. *Tuberculosis and Respiratory Diseases*, *80*(1), 11–20. https://doi.org/10.4046/trd.2017.80.1.11

82. Sin, D. D., Miravitlles, M., Mannino, D. M., Soriano, J. B., Price, D., Celli, B. R., Leung, J. M., Nakano, Y., Park, H. Y., Wark, P. A., & Wechsler, M. E. (2016). What is asthma COPD overlap syndrome? Towards a consensus definition from a round table discussion. *European Respiratory Journal*, *48*(3), 664–673. https://doi.org/10.1183/13993003.00436-2016

83. Sood, A. (2011). Sex differences: Implications for the obesity-asthma association. *Exercise and Sport Sciences Reviews*, *39*(1), 48–56. https://doi.org/10.1097/JES.0b013e318201f0c4

84. Soriano, J. B., Abajobir, A. A., Abate, K. H., Abera, S. F., Agrawal, A., Ahmed, M. B., Aichour, A. N., Aichour, I., Eddine Aichour, M. T., Alam, K., Alam, N., Alkaabi, J. M., Al-Maskari, F., Alvis-Guzman, N., Amberbir, A., Amoako, Y. A., Ansha, M. G., Antó, J. M., Asayesh, H., Vos, T. (2017). Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet Respiratory Medicine*, *5*(9), 691–706.

https://doi.org/10.1016/S2213-2600(17)30293-X

85. Soriano, J. B., Kendrick, P. J., Paulson, K. R., Gupta, V., Abrams, E. M., Adedoyin, R. A., Adhikari, T. B., Advani, S. M., Agrawal, A., Ahmadian, E., Alahdab, F., Aljunid, S. M., Altirkawi, K. A., Alvis-Guzman, N., Anber, N. H., Andrei, C. L., Anjomshoa, M., Ansari, F., Antó, J. M., Vos, T. (2020). Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Respiratory Medicine*, *8*(6), 585–596. https://doi.org/10.1016/S2213-2600(20)30105-3

86. Spindel, E. R., & McEvoy, C. T. (2016). The role of nicotine in the effects of maternal smoking during pregnancy on lung development and childhood respiratory disease: Implications for dangers of e-cigarettes. *American Journal of Respiratory and Critical Care Medicine*, *193*(5), 486–494. https://doi.org/10.1164/rccm.201510-2013PP

87. Stapleton, M., Howard-Thompson, A., George, C., Hoover, R. M., & Self, T. H. (2011). Smoking and asthma. *Journal of the American Board of Family Medicine*, *24*(3), 313–322. https://doi.org/10.3122/jabfm.2011.03.100180

88. Stringer, W. W., Porszasz, J., Bhatt, S. P., McCormack, M. C., Make, B. J., & Casaburi, R. (2019). Physiologic insights from the COPD genetic epidemiology study. *Chronic Obstructive Pulmonary Diseases*, *6*(3), 256–266. https://doi.org/10.15326/jcopdf.6.3.2019.0128

89. Thomas, M., Decramer, M., & O'Donnell, D. E. (2013). No room to breathe: The importance of lung hyperinflation in COPD. *Primary Care Respiratory Journal*, *22*(1), 101–111. https://doi.org/10.4104/pcrj.2013.00025

90. Thomson, N. C., Chaudhuri, R., & Livingston, E. (2004). Asthma and cigarette smoking.

European Respiratory Journal, *24*(5), 822–833. https://doi.org/10.1183/09031936.04.00039004

91. To, T., Zhu, J., Gray, N., Feldman, L. Y., Villeneuve, P. J., Licskai, C., Gershon, A., & Miller, A. B. (2018). Asthma and chronic obstructive pulmonary disease overlap in women incidence and risk factors. *Annals of the American Thoracic Society*, *15*(11), 1304–1310. https://doi.org/10.1513/AnnalsATS.201802-078OC

92. Tommola, M., Ilmarinen, P., Tuomisto, L. E., Lehtimäki, L., Haanpää, J., Niemelä, O., & Kankaanranta, H. (2017). Differences between asthma - COPD overlap syndrome and adult-onset asthma. *European Respiratory Journal*, *49*(5), 1–10. https://doi.org/10.1183/13993003.02383-2016

93. Trivedi, M., & Denton, E. (2019). Asthma in children and adults—what are the differences and what can they tell us about asthma? *Frontiers in Pediatrics*, *7*(6), 1–15. https://doi.org/10.3389/fped.2019.00256

94. van Boven, J. F. M., Román-Rodríguez, M., Palmer, J. F., Toledo-Pons, N., Cosío, B. G., & Soriano, J. B. (2016). Comorbidome, pattern, and impact of asthma-COPD overlap syndrome in real life. *Chest*, *149*(4), 1011–1020. https://doi.org/10.1016/j.chest.2015.12.002

95. Vestbo, J., Hurd, S. S., Agustí, A. G., Jones, P. W., Vogelmeier, C., Anzueto, A., Barnes, P. J., Fabbri, L. M., Martinez, F. J., Nishimura, M., Stockley, R. A., Sin, D. D., & Rodriguez-Roisin, R. (2013). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease GOLD executive summary. *American Journal of Respiratory and Critical Care Medicine*, *187*(4), 347–365. https://doi.org/10.1164/rccm.201204-0596PP

96. Vonk, J. M., Postma, D. S., Boezen, H. M., Grol, M. H., Schouten, J. P., Koëter, G. H., & Gerritsen, J. (2004). Childhood factors associated with asthma remission after 30 year follow up. *Thorax*, *59*(11), 925–929. https://doi.org/10.1136/thx.2003.016246

97. Wang, L., Wang, K., Gao, X., Paul, T. K., Cai, J., & Wang, Y. (2015). Sex difference in the association between obesity and asthma in U.S. adults: Findings from a national study. *Respiratory Medicine*, *109*(8), 955–962. https://doi.org/10.1016/j.rmed.2015.06.001

98. Wheaton, A. G., Liu, Y., Croft, J. B., VanFrank, B., Croxton, T. L., Punturieri, A., Postow, L., & Greenlund, K. J. (2019). Chronic Obstructive Pulmonary Disease and Smoking Status — United States, 2017. *Morbidity and Mortality Weekly Report*, *68*(24), 533–538. https://doi.org/10.15585/mmwr.mm6824a1

99. Wheaton, A., Pleasants, R. A., Croft, J. B., Ohar, J. A., Heidari, K., Mannino, D. M., Liu, Y., & Strage, C. (2018). Gender and Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome. *Physiology & Behavior*, *176*(1), 139–148. https://doi.org/10.1016/j.physbeh.2017.03.040

100. Willett, L. J., Hashim, S. A. F., Tompson, R. V., & Loyalka, S. K. (1999). Effect of surface heterogeneities on condensation on an aerosol particle. *Journal of Aerosol Science*, *30*(5), 569–585. https://doi.org/10.1016/S0021-8502(98)00741-1

101. World Health Organization. (2020). *Asthma*. Retrieved from https://www.who.int/news-room/fact-sheets/detail/asthma

102. World Health Organization. (2010). Global status report on noncommunicable diseases. *World Health Organization*, *53*(9), 1689–1699. https://doi.org/10.1017/CBO9781107415324.004

103. World Health Organization. (2018). *WHO - The top 10 causes of death*. Retrieved from

http://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death

104. Xu, X., Weiss, S. T., Rijcken, B., & Schouten, J. P. (1994). Smoking, changes in smoking habits, and rate of decline in FEV1: New insight into gender differences. *European Respiratory Journal*, *7*(6), 1056–1061. https://doi.org/10.1183/09031936.94.07061056

105. Zhou, X. L., & Zhao, L. Y. (2021). Comparison of clinical features and outcomes for asthma-COPD overlap syndrome vs. COPD patients: A systematic review and meta-analysis. *European Review for Medical and Pharmacological Sciences*, *25*(3), 1495–1510. https://doi.org/10.26355/eurrev_202102_24857

Chapter 3

Methods

3.1 Canadian Longitudinal Study on Aging (CLSA)

The Canadian Longitudinal Study on Aging (CLSA) is an ongoing population-based, prospective cohort study that follows more than 50,000 participants between the ages of 45 and 85 at the time of recruitment, for 20 years or until death (Raina, P et al., 2016). The study is designed to explore the development of disease and disability as people age, specifically Canadian adults, middle-aged and older (Raina, P et al., 2016). It has recruited participants from all 10 Canadian provinces and collects biological samples and physical assessments to support a wide variety of aging-related research questions (Raina, P et al., 2019). To that end, the CLSA study provides a unique opportunity to examine the similarities and differences between males and females on important genetic, environmental, and social risk factors associated with COPD, asthma, and ACO, respectively.

The research presented in this thesis is a cross-sectional analysis of the data of 30,097 participants collected at baseline, specifically a subset of individuals recruited as part of the CLSA Comprehensive cohort.

3.2 Development of the CLSA

The CLSA was funded by the Government of Canada through the Canadian Institutes of Health Research and the Canadian Foundation for Innovation (Raina, P et al., 2018). The target sample size of the CLSA was 50,000 participants, for which recruitment began in 2010 and baseline data collection was completed in 2015. CLSA investigators conducted baseline data collection for 51,388 men and women aged 45 to 85 years living across Canada (CLSA, 2016). As part of the

CLSA overarching prospective cohort study design, participants will undergo repeated data collection waves every three years and be followed for at least 20 years or until death (or reasonable termination from the study).

3.3 CLSA Sample Size, sampling design, and weights

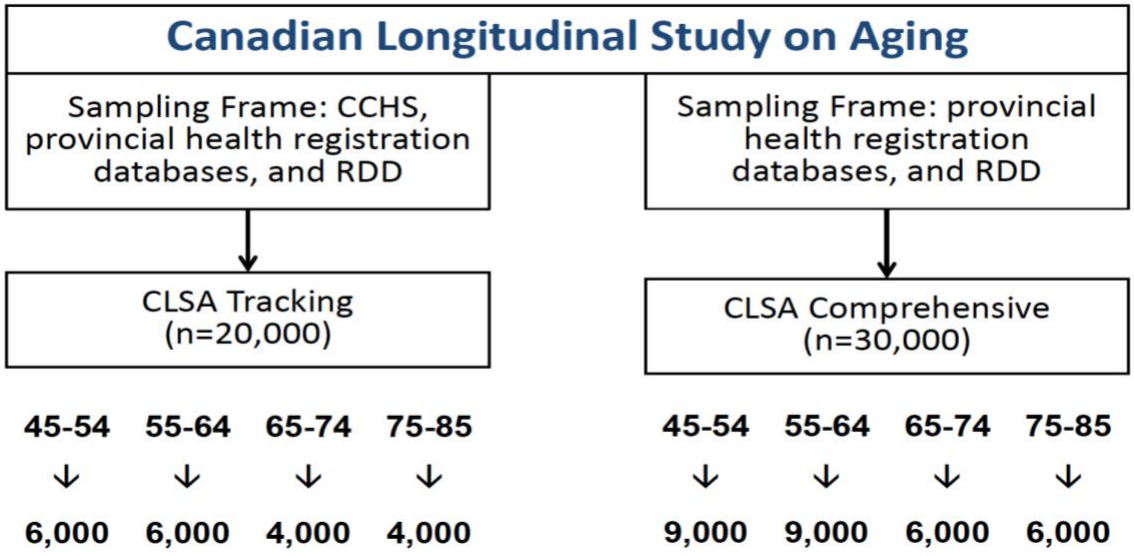


Figure 3.1: CLSA Sampling scheme adapted from Raina, P., 2014; Canadian Community Health Survey (CCHS); Random Digit Dialing (RDD).

There are two complementary cohorts that encompass the CLSA study. Each component employs a different mode of data collection and uses a different sampling design. Participants were selected into one of the two cohorts and classified as either the "Tracking cohort" or the "Comprehensive cohort". In the Tracking cohort, 21,241 participants were randomly selected from 10 Canadian provinces and provided questionnaire data through telephone interviews. The Comprehensive cohort includes 30,097 randomly selected participants living in areas extending 25-50 km away from one of the 11 established Data Collection Sites (DCSs) located in 7 provinces. Participants in the Comprehensive cohort provided data through an in-home interview

and a DCS visit, where they took part in an in-depth physical assessment and provided blood and urine samples (CLSA, 2021). The Biorepository and Bioanalysis Centre in Hamilton, Ontario is the central location for storing and analyzing the biological specimens collected at each of the Data Collection Sites (DCS). The biorepository consists of 31 cryo-freezers that hold approximately five million biological samples for the study. CLSA participants were asked to provide their provincial health insurance number (HIN) for linkage with administrative data but this was not mandatory for recruitment. About 96% of Comprehensive participants provided their HINs, and 99% consented to provide biological samples (Raina, P et al., 2018). The target sample for the CLSA Comprehensive was 30,000 persons. Nine of the DCS were to recruit 3,000 participants each, while two DCS in British Columbia aimed to recruit 1,500 participants. The sampling of the Tracking cohort was intended to provide results that are generalizable to the Canadian population, while the Comprehensive cohort, though national in scope, is not nationally representative (Raina, P et al., 2018).

3.4 Recruitment of study participants in the CLSA comprehensive cohort

Figure 3.2: Participant recruitment chart adapted from Raina, P., 2014

Participants in the Comprehensive cohort were recruited using provincial health registry mail-outs and telephone-sampling random digit dialing. Researchers for the Quebec Longitudinal Study on Nutrition and Aging (NuAge) asked NuAge participants if they would provide consent to share their information with the CLSA. CLSA researchers approached NuAge participants that fell in the 75-85 age group who provided their consent and contact information. Baseline data were collected between May 2012 and May 2015 for Comprehensive participants.

Excluded from the CLSA study are residents of the Canadian territories, some remote regions, persons on Federal First Nations reserves and other provincial First Nations settlements, full-time members of the Canadian Armed Forces, institutionalized persons (including long-term care), individuals with cognitive impairment, and those unable to respond in English or French.

3.5 Sampling weights

Sampling weights were created such that the total CLSA sample (Tracking cohort plus the Compressive cohort) is generalizable to the Canadian population. Sampling weights also correct for differences in the sample that might lead to bias and discrepancies between the sample and reference population. Analytic and inflation weights were calculated as part of the sampling weights and were provided to the researchers by the CLSA project team. Inflation weights provide an estimate of how many people in each province (and in Canada) are represented by each CLSA participant. Analytic weights are proportional to the inflation weights and were rescaled so that mean of the weights within the DCS part of each province will be equal to 1 (CLSA, 2017). For this present thesis, CLSA analytic weights were used for the Comprehensive cohort in the statistical analysis.

3.6 Dataset: data access and storage

For access to the CLSA data, a completed CLSA Data and Biospecimen Request Application (Application no: 19CA006) was submitted to and approved by the CLSA team. The comprehensive cohort dataset from CLSA was obtained through a catalyst grant from the Canadian Institutes of Health Research (Catalyst Grant: Analysis of CLSA Data.).

The proposed thesis research is concentrated on the analysis of data from 30,097 participants in the Comprehensive cohort. Baseline data on social and demographic measures, physical assessments including height and weight, spirometry measures, health status including self-reported chronic conditions, respiratory symptoms, and disease algorithms, and environmental data linked to the Canadian Urban Environmental Health Research Consortium for data on

exposures to sulfur dioxide, nitrogen dioxide, ozone, and fine particulate matter were requested. Dataset is stored in a secured server at the School of Public Health, University of Alberta.

3. 7 Respiratory health outcomes

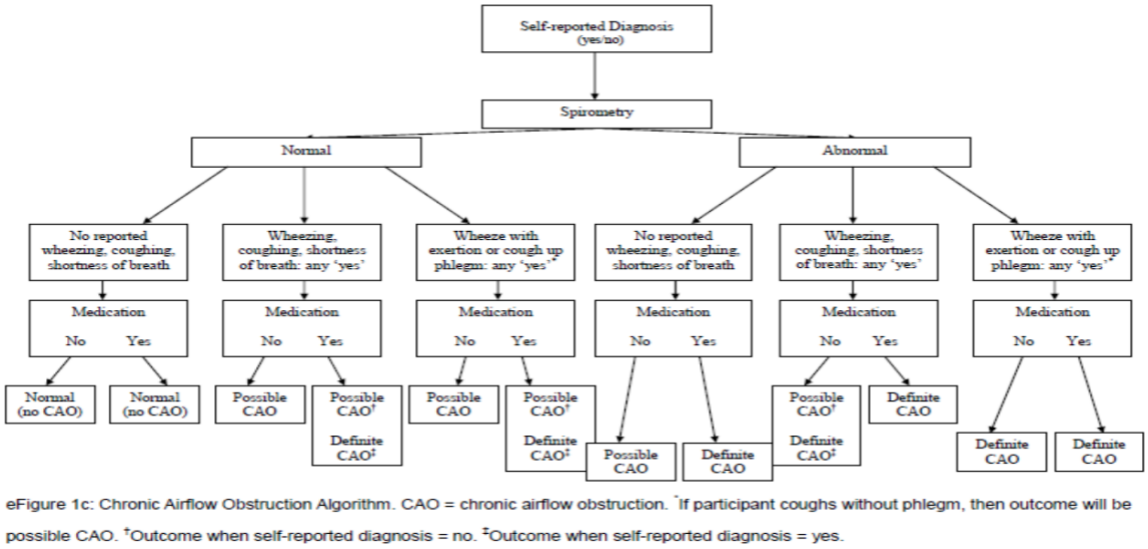
Subjects were categorized into four mutually exclusive groups (control, asthma-COPD overlap (ACO), COPD only, and asthma only) based on responses provided to the survey questions "Has a doctor ever told you had asthma?" and "has a doctor told you that you have/had any of the following: emphysema, chronic bronchitis, chronic obstructive pulmonary disease (COPD), or chronic changes in lungs due to smoking?" (CLSA, 2014). Subjects who reported healthcare professionals had diagnosed them with emphysema, chronic bronchitis, COPD, or chronic changes in lungs due to smoking were assigned to a broader COPD group. Respondents reporting a physician diagnosis for asthma but not for COPD were assigned to the asthma-only group. Subjects who reported healthcare professionals had diagnosed them with asthma and COPD were assigned to the asthma-COPD syndrome group (ACO). Finally, participants who recounted no physician diagnosis of either asthma or COPD were assigned to the control group. For the statistical analysis, a categorical variable with four categories was defined to represent the four mutually exclusive groups: COPD-only, asthma-only, ACO, control group.

3. 8 Respiratory symptoms and general health

To determine the presence of chronic cough, chronic cough with phlegm, shortness of breath, and wheeze, responses to the following questions from the CLSA baseline questionnaire were used, **"**Have you had wheezing or whistling in your chest at any time within the last 12 months?", **"**Do you become short of breath walking on flat surfaces?"**, "**Have you usually coughed on most days within the last 12 months?" **"**Do you bring up phlegm on most days

during the year?", **"**Are you currently taking or using any medications for respiratory problems?" (CLSA, 2014). Responses were recoded into dichotomous yes or no variables for chronic cough, chronic cough with phlegm, shortness of breath, and wheeze, respectively. Participant's self-rated general health was determined from the question, "In general, would you say your health is excellent, very good, good, fair, or poor?".

3.9 Chronic airflow obstruction (CAO) algorithm



eFigure 1c: Chronic Airflow Obstruction Algorithm. CAO = chronic airflow obstruction. *If participant coughs without phlegm, then outcome will be possible CAO. †Outcome when self-reported diagnosis = no. ‡Outcome when self-reported diagnosis = yes.

Figure 3. 3: Chronic airflow obstruction (CAO) algorithm adapted from Raina, P., 2014

To address the potential for low accuracy that self-reported diagnoses may have for identifying chronic diseases, CLSA investigators developed and validated a disease ascertainment algorithm for chronic airflow obstruction (CAO). The algorithm, as depicted in Figure 1, includes self-reported responses on the presence of symptoms for COPD or asthma, medication use for respiratory symptoms and abnormal/normal consideration of the FEV_1/FVC ratio derived from

the spirometry lung function test, and comparison against sex-specific reference values for the lower limit of normal (LLN) (Hankinson, J.L., 1999).

A categorical variable for CAO was defined to represent individuals with "No CAO" (normal) or "Possible/Definite CAO". Participants who answered "no" to COPD or asthma symptoms and have normal-range FEV_1/FVC ratios are considered non-diseased, regardless of medication use. Participants who report symptoms and have normal range FEV_1/FVC ratios are classified as "possible CAO", regardless of medication use. An abnormal FEV_1/FVC ratio, irrespective of symptoms but with no report of medication use, also results in a classification of "possible CAO". An abnormal FEV_1/FVC ratio with a positive report of medication use is classified as "definite CAO". In the case of participants who self-report "yes" to the symptoms of COPD or asthma, more algorithm pathways lead to "definite CAO" to reflect the importance of a positive self-report. The algorithm was validated on a population of definite cases and controls to derive the sensitivity and specificity of the CAO algorithm. Optimal sensitivity and specificity estimates arise when "possible CAO" is classified as test negative or "no CAO", and medication use is included in the algorithm (100% sensitivity, 80% specificity) (Oremus, M et al., 2013).

3. 10 Spirometry measurements

The spirometry measurement was conducted using the TruFlow Easy-On Spirometer (NDD Medical Technologies, Andover, Massachusetts, USA). Only those with major contraindications did not perform the test (CLSA, 2014). Maximal inspiratory and expiratory maneuvers were performed to obtain FEV_1 and forced vital capacity (FVC). Only participants who performed at least three acceptable efforts, with their best two FVC and FEV_1 within 150 ml, were included. The best FEV_1 and FVC were used for analysis. Median percent-predicted lung function values

and lower limit of normal (LLN) values were obtained using reference equations established for the Canadian population (Coates et al., 2016). For the analysis, the best FEV_1 and FVC measures were used, and observations with extreme values were considered outliers and were omitted. Spirometry data on 21,307 (71%) participants of the 30 097 in the comprehensive cohort were analyzed.

3.11 Variable definitions

Responses to the CLSA baseline questionnaire were used to determine variables for age, sex, ethnicity, marital status, education, household income, province, smoking status, obesity, comorbidities, and self-rated general health.

3.11.1 Comorbidities

A binary variable was defined to indicate the presence of comorbidity based on the participant's self-report of a health professional diagnosis of heart disease, diabetes, cancer, arthritis, osteoporosis, depression, underactive thyroid disease, stroke, or kidney disease. Data were elucidated from responses to the questions "Has a doctor ever told you that you had cancer?", "Has a doctor ever told you that you have heart disease (including congestive heart failure, or CHF)?", "Has a doctor ever told you that you have diabetes, borderline diabetes or that your blood sugar is high?", "Has a doctor ever told you that you have a mood disorder such as depression (including manic depression), bipolar disorder, mania, or dysthymia?", "Has a doctor ever told you that you have osteoporosis, sometimes called low bone mineral density, or thin, brittle or weak bones?", "Has a doctor ever told you that you have rheumatoid arthritis?", "Has a doctor ever told you that you have an UNDER-active thyroid gland", "Has a doctor ever told you

that you have experienced a Stroke or CVA? (Cerebrovascular accident)?", "Has a doctor ever told you that you have kidney disease or kidney failure?" (CLSA, 2014).

3.11.2 Obesity categories

Based on height and weight calculated at the DCS by trained professionals (CLSA, 2016), each participant's corresponding body mass index (BMI) was calculated, and obesity categories were defined as underweight (BMI: < 18.5 kg/m^2) normal (BMI:18.5-24.9 kg/$m^{2)}$, overweight (BMI: 25.0 – 29.9 kg/m^2) and obese (BMI ≥ 30.0 kg/m^2). Due to the small number of participants in the underweight category (0.72% of the study sample), the data were grouped with the underweight and normal weight categories combined.

3.11.3 Smoking status

The variable for smoking status was derived with participant responses to the question: "What is your smoking status?", responses included "Yes I currently smoke" (classified as a current smoker), "No I don't smoke and never have" (classified as never smoker) or "Don't smoke now but have in the past" (classified as a former smoker) (CLSA, 2014).

3.11.4 Household income

Total household income was generated by each participant's answers to the question "What is your best estimate of the total household income received by all household members, from all sources, before taxes and deductions, in the past 12 months?" Responses were then categorized into "less than $20,000", "$20,000 or more, but less than $50,000", "$50,000 or more, but less than $100,000", and "$100,000 or more" (CLSA, 2018).

3.11.5 Education

The CLSA in-home questionnaire collected information regarding the highest level of education obtained by participants. Answers were then categorized and defined as “less than secondary school”, “secondary school education”, “post-secondary education” (CLSA, 2018).

3.11.6 Marital status

Respondents answered the question, “What is your current marital/partner status?”. A variable was generated for marital status, and participant answers were categorized as “single”, “married”, and “widowed/divorced/separated” (CLSA, 2018).

3.11.7 Ethnicity

As part of the CLSA in-home questionnaire, participants were asked, “People living in Canada come from many different cultural and racial backgrounds are you…?” Respondents selected from the following list of options: White, Chinese, South Asian, Filipino, Latin American, Southeast Asian, Arab, West Asian, Japanese, Korean, North American Indian, Inuit, Metis, Other, Don’t know/No answer, Refused (CLSA, 2018).

3.11.8 Employment

Participants were asked for their response to the question, “Are you currently working at a job or business? This includes part-time jobs, seasonal work, contract work, self-employment, or any other paid work regardless of the number of hours worked”. Responses were categorized into a dichotomous categorical variable for employment (yes/no) (CLSA, 2018).

3.12 Environmental data

Participant data in the CLSA is linked to environmental data collected by the Canadian Urban Environmental Health Research Consortium (CANUE). CANUE is a CIHR-funded initiative to gather and develop measures related to a range of environmental factors to study how they affect a wide variety of health outcomes. CANUE and CLSA collaborate and link data on air quality, neighbourhood factors, weather and climate, and greenness indicators to the CLSA data on health and aging. Data is linked to participant reported postal code at the time of recruitment (CLSA, 2018; CANUE, 2018). The linked CANUE data includes annual average concentration exposure estimates for sulfur dioxide, nitrogen dioxide, ozone, and fine particulate matter. Exposure levels are collected by the National Air Pollution Surveillance (NAPS) stations within 50 km of reported address (CLSA, 2017; Hystad, P et al., 2011; Robichaud, A., Ménard, R., 2014; van Donkelaar, A et al., 2015). The NAPS program provides long-term air quality data of a uniform standard across Canada. Average yearly exposure estimates and average estimates during warm and cold seasons were provided in the CLSA. However, due to a considerable degree of missing data on exposure estimates for the warm and cold seasons, only 1-year average data were used. The 1-year average exposure data on SO_2, NO_2, O_3, $PM_{2.5}$ are taken one year before the first interview date.

3.13 Statistical analysis

All statistical analysis, including data cleaning, recoding, descriptive analysis, and regression analysis, was performed using STATA (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.). The procedures for the analysis of complex survey data in STATA were used in statistical analysis.

3.13.1 Recoded variables

The variable for sex was categorized as a dichotomous variable (0: Female, 1: Male). Age groups were considered a categorical variable with four categories: 45-54 years, 55-64 years, 65-74 years, and over 75 years of age. The variable 'province' was recoded into five categories: Eastern Canada (Newfoundland and Labrador, Nova Scotia), Quebec, Ontario, Prairies (Manitoba, Alberta), and British Columbia. Ethnicity was recoded into three categories: White, Aboriginal, and non-white non-Aboriginal. Household income was categorized into four categories: ≤$19K, $20K - <$49K, $50K-<$99K, and ≥$100,000. The self-rated perceived general health variable was recoded into four response categories: Excellent/Very Good, Good, Fair, and Poor. Education was recoded into three categories: below secondary school (less than high school) graduation, secondary school (high school) education and certificate, university certificate and above. The variable for obesity was categorized into three levels: underweight and normal, overweight, and obese. Marital status was considered a categorical variable with three categories: single, married, and widowed, divorced, or separated.

3.13.2 Use of weights in statistical analysis

Sample analytical weights were provided by the CLSA investigators for the Comprehensive cohort participants. The analytical weights supplied are proportional to the inflation weights but rescaled to sum to the sample size within the DCS part of each province so that their mean value equalled 1 within that area. The variables [wghts_analytic_com] and [wghts_geostrat_com] in the CLSA dataset were used to set the data in STATA using code [svyset] before executing further statistical commands for the analysis of survey data.

3.13.3 Descriptive analysis

Descriptive analysis was carried out for 30,097 participants in the CLSA Comprehensive cohort. Demographic, socioeconomic, health status, and measures of airway obstruction were compared across the different respiratory outcomes (ACO, COPD-only, asthma-only, and control groups) for both males and females, respectively. For the analysis of overall association, chi-squared tests for categorical variables and multiple linear regression for continuous variables were carried out.

3.13.4 Model building-multinomial logistic regression

Since the outcome variable of interest (ACO, COPD-only, asthma-only, control) is a categorical variable with more than two outcomes on a nominal scale, multinomial logistic regressions (MLR) were used to investigate male and female-specific risk factors of the outcome. An MLR model was made for males and females independently. Model building occurred in steps, beginning with fitting a univariate model and testing for significance of p-value <0.20 in the overall likelihood ratio test. The subsequent model was fitted with all variables significant at the univariate level. Wald's tests were conducted, retaining only statistically significant variables at p-value <0.05 cut-off. With the reduced main effects model, interactions of interest were tested (age group with smoking status, obesity, and marital status). For females, only the interaction between age group and smoke was retained, while for males none of the studied interactions were deemed significant. Next, the irrelevant alternative assumption (IIA) was tested on the penultimate model (Long, J.S., Freese, J., 2014); the linearity assumption was not tested as there were no continuous independent variables in either model. For both male and female models, the IIA was not violated. Final multinomial logistic regression models were established for both males and females.

3.14 Association between sex-specific risk factors and respiratory health outcomes

The prevalence of ACO, COPD, and asthma stratified by males and females were obtained using weighted proportions. Chi-squared statistics were used to test overall significant differences in general characteristics between control, ACO, COPD-only, and asthma-only groups for males and females, respectively. Multinomial logistic regression analysis was used to test the differences in risk factors between ACO, COPD-only, and asthma-only groups for males and females.

3.15 Association between airway obstruction and respiratory health outcomes

Various measures of airway obstruction are included in the study and were compared against the different respiratory health outcomes. Measures of airway obstruction include mean percent predicted estimates for FEV_1, FVC, and FEV_1/FVC, modified-GOLD criteria, CAO, and the lower limit of normal (LLN) criteria 1 and 2 (see below). Percent predicted lung function values were obtained by comparing the spirometry measures of the study population against predicted FEV_1, FVC, and FEV_1/FVC estimates using a reference equation established for the Canadian population (Coates, AL. et al., 2015). LLN criteria compares spirometry measures against estimates in the lower 5^{th} percentile of a healthy, non-smoking population. LLN criteria 1 is defined as $FEV_1/FVC < LLN_{FEV1/FVC,}$ and LLN criteria 2 is defined as $FEV_1/FVC < LLN_{FEV1/FVC}$ & $FEV_1 < LLN_{FEV1}$ (Pellegrino, R. et al., 2005). Since post-bronchodilator spirometry measurements were not obtained in the Canadian Health Measures Survey (the survey data used in establishing reference equations for the Canadian population) nor in the CLSA data collection, a modification of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages for COPD, based on pre-bronchodilator spirometry, was used to classify subjects into the following

COPD severity categories: No airflow limitation ($FEV_1/FVC \geq 0.70$)**,** Gold Stage I/mild COPD ($FEV_1/FVC < 0.70$ and $FEV_1 \geq 80\%$ predicted)**,** Gold Stage II/moderate COPD ($FEV_1/FVC < 0.70$ and $50\% \leq FEV_1$ 80% predicted)**,** Gold Stage III or IV/severe and very severe COPD ($FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ predicted) (GOLD, 2017). Due to the small sample size, GOLD stage III (severe) and IV (very severe) were collapsed into one category. The modified GOLD criteria were categorized into four levels: no obstruction, GOLD stage I (mild), GOLD stage II (moderate), GOLD stage III, IV (severe and very severe).

3.16 Research Ethics Approval and Thesis Consent

The CLSA has received approval from all associated Research Ethics Boards (RED) across Canada for baseline, follow-up one, and subsequent amendments (Raina, P et al., 2018). Ethics approval for the presented thesis research was obtained from the University of Alberta and Memorial University Health Research Ethics Board.

References:

1. Canadian Urban Environmental Health Research Consortium. (2018). CIHR Operating Grant for CANUE Data: Webinar. Retrieved from https://canue.ca/cihr-operating-grant-for-canue-data-webinar/

2. Coates, AL., Wong, SL., Tremblay, C., & Hankinson, JL. (2015). Reference Equations for Spirometry in the Canadian Population. *Annals of the American Thoracic Society,* 13(6):833-841.

3. Global Initiative for Chronic Obstructive Lung Disease. (2017) Pocket Guide to COPD Diagnosis, Management, and Prevention. Online. Retrieved https://bit.ly/3sOwqiY

4. Hankinson JL, Odencrantz JR, & Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;*159*(1):179-187.

5. Hystad P, Setton E, Cervantes A, Poplawski K, Deschenes S, Brauer M, van Donkelaar A, Lamsal L, Martin R, Jerrett M, & Demers P. (2011). Creating national air pollution models for population exposure assessment in Canada. *Environmental Health Perspectives*, *119*(8), 1123-1129. https://doi.org/10.1289/ehp.1002976.

6. Long, J.S., & Freese, J. (2014). *Regression Models for Categorical Dependent Variables Using Stata*. College Station, TX: Stata Press.

7. Oremus, M., Postuma, R., Griffith, L., Balion, C., Wolfson, C., Kirkland, S., Patterson, C., Shannon, H., CLSA Algorithms Validation Group, & Raina, P. (2013). Validating Chronic Disease Ascertainment Algorithms for Use in the Canadian Longitudinal Study of Aging. *Canadian Journal on Aging, 32*(3), 232-239.

8. Pellegrino, R., Viegl, G., Brusasco, V., Crapo, R.O., Burgos, F., Casaburi, R., Coates, A., C. P. M. van der Grinten, P. Gustafsson, J. Hankinson, R. Jensen, D. C. Johnson, N.

MacIntyre, R. McKay, M. R. Miller, D. Navajas, O. F. Pedersen, & Wanger, J. (2005) Interpretive strategies for lung function tests. *European Respiratory Journal*, *26*(5), 948-968.

9. Raina, P. (2014). CLSA as a Platform for Studying Disease and Disability in an Aging Population. Online. Retrieved from https://bit.ly/2NsaTgO

10. Raina, P. (2014). CLSA Follow-up 1. Online. Retrieved from https://clsa-elcv.ca/doc/519

11. Raina, P., Wolfson, C., & Kirkland, S. (2016). CLSA Protocol. Retrieved from https://clsa-elcv.ca/doc/511.

12. Raina, P., Wolfson, C., Kirkland, S., & Griffith, L.E. (2018). The Canadian Longitudinal Study on Aging (CLSA) Report on Health and Aging in Canada: Findings from Baseline Data Collection 2010-2015. Online. Retrieved from https://clsa-elcv.ca/stay-informed/new-clsa/2018/canadian-longitudinal-study-aging-releases-first-report-health-and-aging

13. Raina, P., Wolfson, C., Kirkland, S., Griffith, L.E., Balion, C., Cossette, B., Dionne, I., Hofer, S., Hogan, D., Heuval, ER., Liu-Ambrose, T., Menec, V., Mugford, G., Patterson, C., Payette, H., Richards, B., Shannon, H., Sheets, D., Taler, V., Thompson, M., Tuokko, H., Wister, A., Wu, C., & Young, L. (2019). Cohort Profile: The Canadian Longitudinal Study on Aging. *International Journal of Epidemiology, 48*(6), 1752:1753j.

14. Robichaud, A., & Ménard R. (2014). Multi-year objective analyses of warm season ground-level ozone and PM2.5 over North America using real-time observations and the Canadian operational air quality models. *Atmospheric Chemistry and Physics, 14*(4),1769-1800; https://doi.org/10.5194/acp-14-1769-2014

15. The Canadian Longitudinal Study on Aging. (2014). Data Collection Site Questionnaires. Online. Retrieved from https://clsa-elcv.ca/doc/1122

16. The Canadian Longitudinal Study on Aging. (2014). Standard Operating Procedure Spirometry. Online. Retrieved from https://clsa-elcv.ca/doc/523

17. The Canadian Longitudinal Study on Aging. (2017). CLSA Technical Document: Sampling and Computation of Response Rates and Sample Weights for the Tracking Participants and Comprehensive Participants. Online. Retrieved from https://www.clsa-elcv.ca/doc/1041

18. The Canadian Longitudinal Study on Aging. (2017). Data Support Materials Air Pollution and Meteorological Exposure Measurements. Online. Retrieved from https://www.clsa-elcv.ca/doc/1905

19. The Canadian Longitudinal Study on Aging. (2016). Standard Operating Procedure Standing Height and Weight User Guide. Online. Retrieved from https://www.clsa-elcv.ca/doc/1112

20. The Canadian Longitudinal Study on Again. (2018). In-Home Questionnaire – Baseline Comprehensive. Online. Retrieved from https://clsa-elcv.ca/doc/1048

21. The Canadian Longitudinal Study on Aging. (2020). Physical Assessment in the CLSA Baseline and Follow-up 1 Data Collection. Online. Retrieved from https://www.clsa-elcv.ca/doc/3653

22. The Canadian Longitudinal Study on Aging. (2021). Data Collection. Online. Retrieved from https://www.clsa-elcv.ca/researchers/data-collection

23. van Donkelaar A, Martin RV, Brauer M, & Boys BL. (2015). Use of satellite observations for long-term exposure assessment of global concentrations of fine particulate matter. *Environmental Health Perspect*ive, *123*,135–143. https://doi.org/10.1289/ehp.1408646

Chapter 4

Results

4.1 Prevalence of respiratory outcomes

Table 4.1. presents overall prevalence and sex-specific prevalence estimates for three respiratory outcomes. The study found that the overall prevalence estimates for ACO, COPD, and asthma were 1.80%, 3.05%, and 11.74%, respectively. The difference in prevalence between males and females was statistically significant, with prevalence estimates being greater among females than males for all three respiratory conditions. The prevalence of ACO was 2.17% in females compared to 1.41% in males ($p<0.001$), and the prevalence of COPD was 3.22% for females compared to 2.87% for males ($p<0.001$). Among female participants, 13.31% had asthma compared to 10.11% of male participants ($p<0.001$). In addition, participants with COPD were more likely to be classified as having ACO than participants with asthma (37.10% of COPD respondents versus 13.27% of asthma respondents (Table 4.1). Comparatively, the proportion of females with COPD who reported a diagnosis of asthma was greater than the proportion of males with COPD, 40.29% and 32.95%, respectively ($p<0.05$). The difference in the proportion of asthma patients with ACO did not differ significantly between males and females. As shown in Figure 4.1, the prevalence of ACO and COPD increased with age, whereas the prevalence of asthma decreased with age. Figures 4.2 and 4.3 present the prevalence of the respiratory outcomes stratified by age and sex. The trend observed in Figure 4.1 remains the same for both males and females, where the prevalence for ACO and COPD increased with age while asthma prevalence decreased with age. As shown in Figures 4.2 and 4.3, the prevalence of ACO and asthma was higher for females than males across all age groups. The prevalence for COPD was

higher in females than males across every age group except for 55-64, where males had a marginally higher prevalence for COPD (3.07% for males vs. 3.00% for females).

Table 4.1 Prevalence of respiratory outcomes by sex

	Female (%)	Male (%)	Total (%)	p-value
Asthma-only	13.31	10.11	11.74	<0.001
COPD-only	3.22	2.87	3.05	<0.001
ACO	2.17	1.41	1.80	<0.001
ACO in Asthma Patients	14.01	12.24	13.27	0.141
ACO in COPD Patients	40.29	32.95	37.10	0.008

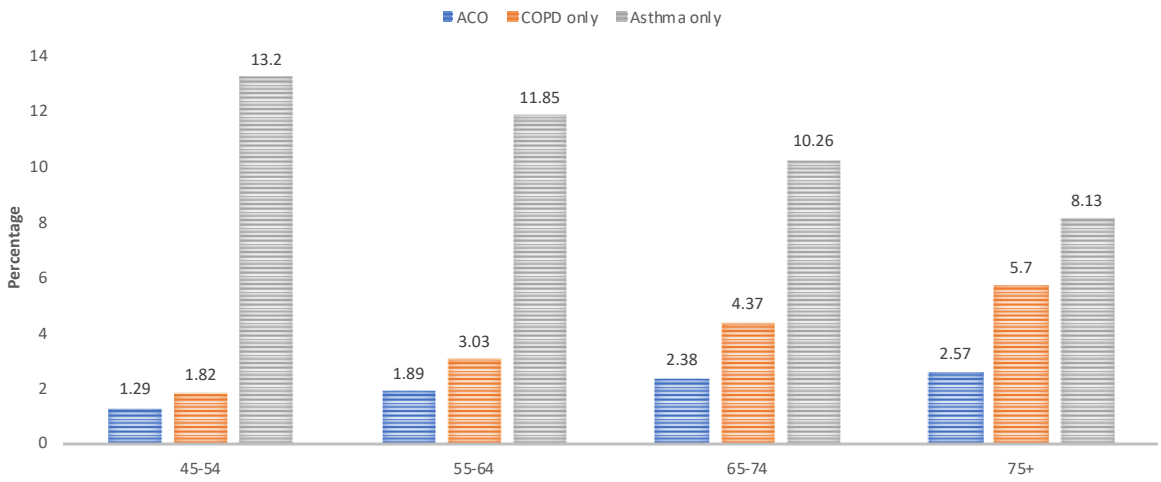


Figure 4.1 Prevalence of respiratory outcomes by age groups

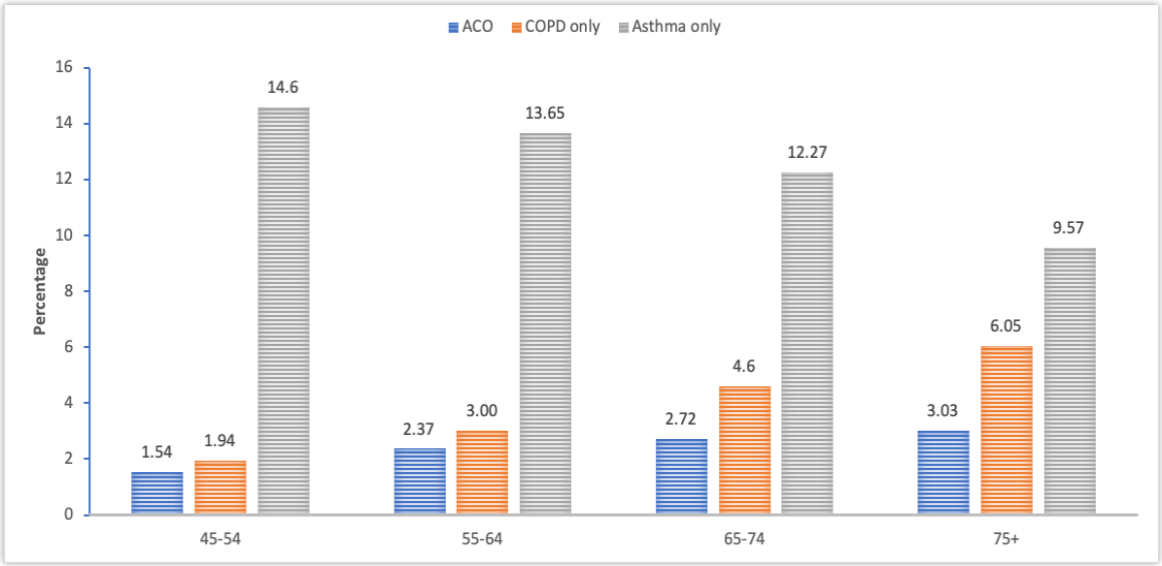


Figure 4.2 Prevalence of respiratory outcomes for females by age group

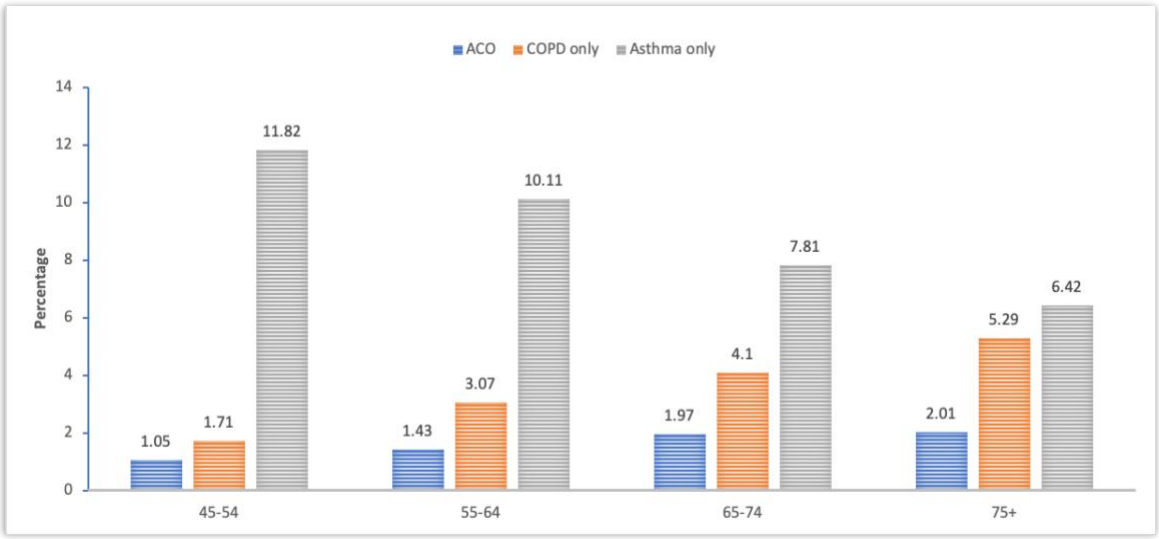


Figure 4.3 Prevalence of respiratory outcomes for males by age groups

4.2 Distribution of baseline characteristics

As shown in Table 4.2a, there was a similar proportion of males (49.16%) and females (50.84%) in the study. Of the 30,097 participants, 90.85% were Caucasian, followed by 4.94% non-Caucasian and non-Aboriginal group, and 4.21% Aboriginal. Respondents were mostly married (76.54%), and most of the sample had at least a university certificate or above. Among respondents, 44.78% reported a household income of ≥ $100,000/year. Nearly half of the participants were classified as never smokers, 40.65% as former smokers, and 9.40% were categorized as current smokers. Based on calculated body mass index classification, 40.02% of study participants were classified as overweight and 28.94% as obese (Table 4.2b). A majority (62.27%) of respondents described their health as "very good/excellent" while 7.33% rated it as "fair" and 1.42% considered their health to be "poor". Of the comorbidities examined, 52.06% reported having at least one of the following comorbidities: diabetes, heart disease, cancer, depression, osteoporosis, rheumatoid arthritis, underactive thyroid disease, kidney disease, and stroke. The most commonly reported comorbidity was depression (16.50%), followed by diabetes (15.71%).

Table 4.2a Distribution of baseline characteristics of the study participants

	N= 30097 (%)
Sex	
Female	50.84
Male	49.16
Age Group (years)	
45-54	41.96
55-64	29.75
65-74	17.47
75 and above	10.82
Ethnicity	
White	90.85
Non-white, Non-Aboriginal	4.94
Aboriginal	4.21
Education	
Below Secondary	4.51
Secondary and Certificate	44.60
University Certificate and Above	50.89
Marital Status	
Single	7.71
Married	76.54
Widowed, Divorced, Separated	15.74
Household Income	
≤ $19,999	4.21
$20,000 - $49,999	17.78
$50,000-$99,999	33.23
≥ $100,000	44.78
Employed	
Yes	90.11
No	9.89
Province	
Eastern	17.58
Quebec	20.14
Ontario	21.32
Prairies	20.17
British Columbia	20.78
Smoking Status	
Never smoker	49.95
Current smoker	9.40
Former smoker	40.65

Table 4.2b Distribution of obesity, comorbidities, and general self-rated health of the study participants

	N= 30097 (%)
Obesity	
Underweight or Normal weight	31.05
Overweight	40.02
Obese	28.94
Comorbidities	
Diabetes	15.71
Heart Disease	9.13
Depression	16.50
Osteoporosis	7.21
Rheumatoid Arthritis	2.97
Cancer	12.62
Underactive Thyroid Disease	12.00
Kidney Disease	2.45
Stroke	1.35
Any Comorbidity	52.06
General Self Rated Health	
Excellent/ Very Good	62.27
Good	28.98
Fair	7.33
Poor	1.42

4.3 Characteristics of the study participants by sex

The characteristics of male and female participants are shown in Table 4.3. The distribution of the following variables differed significantly between males and females at the 99.9% confidence level: age, ethnicity, marital status, household income, employed, province, smoking status, obesity, and self-rated health. All comorbidities, except kidney disease ($p = 0.39$) and stroke ($p<0.05$), were also significant at $p<0.001$. Based on the age distributions, there appear to be more females in the 65-74 and 75 years and above age groups and more males in the 45-54 years and 55-64 years age groups.

For both female and male respondents, the majority of participants were Caucasian. Males were more likely than females to report having at least a university certificate, while females were more likely than males to report having a secondary school education and below. More females reported being widowed, divorced, or separated than males (21.7% vs. 9.57%). In addition, 50.4% of males reported a household income of ≥ $100,000 a year, while only 39.0% of females reported a household income at this level. There were more females in the never smoker category than males, and more males reported being a current smoker or former smoker than females. Male participants were more likely to be classified as overweight or obese (30.0%) than female participants (27.9%). Compared to females, males were more likely to report a diagnosis of heart disease, diabetes, and stroke. In contrast, a greater proportion of females reported a diagnosis of depression, osteoporosis, cancer, and underactive thyroid disease compared to males ($p<0.001$). More females than males rated their health as “excellent” or very good, while males were more likely to rate their health as “good”, “fair”, or “poor”.

Table 4.3 Distribution of baseline characteristics by sex

	Female (%)	Male (%)	Total (%)	p-value*
Age Group (years)				<0.001
45-54	40.94	43.01	41.96	
55-64	28.68	30.86	29.75	
65-74	18.86	16.04	17.47	
75 years and above	11.52	10.09	10.82	
Ethnicity				<0.001
White	91.2	90.5	90.9	
Non-white, Non-Aboriginal	4.37	5.52	4.94	
Aboriginal	4.44	3.98	4.21	
Education				<0.001
Below Secondary	5.02	3.98	4.51	
Secondary and Certificate	47.42	41.68	44.60	
University Certificate and Above	47.56	54.34	50.89	
Marital Status				<0.001
Single	8.04	7.37	7.71	
Married	70.24	83.06	76.54	
Widowed, Divorced, Separated	21.71	9.57	15.74	
Household Income				<0.001
≤$19,999	5.36	3.05	4.21	
$20,000 - $49,999	21.47	14.09	17.78	
$50,000-$99,999	34.14	32.32	33.23	

≥$100,000	39.02	50.54	44.78	
Employed				<0.001
Yes	87.30	92.73	90.11	
No	12.70	7.27	9.89	
Province				<0.001
Eastern	19.04	16.08	17.58	
Quebec	20.29	20.00	20.14	
Ontario	21.09	21.56	21.32	
Prairies	18.70	21.69	20.17	
British Columbia	20.88	20.67	20.78	
Smoking Status				<0.001
Never smoker	52.00	47.83	49.95	
Current smoker	8.55	10.28	9.40	
Former smoker	39.44	41.89	40.65	
Obesity				<0.001
Underweight or Normal weight	37.77	24.10	31.05	
Overweight	34.34	45.89	40.02	
Obese	27.90	30.01	28.94	
Comorbidities				
Diabetes	14.26	17.21	15.71	<0.001
Heart Disease	6.67	11.17	9.13	<0.001
Depression	20.67	12.19	16.50	<0.001

Osteoporosis	12.33	1.90	7.21	<0.001
Rheumatoid Arthritis	3.73	2.18	2.97	<0.001
Cancer	13.52	11.69	12.62	<0.001
Underactive Thyroid Disease	18.45	5.36	12.00	<0.001
Kidney Disease	2.38	2.54	2.45	0.39
Stroke	1.17	1.53	1.35	0.006
Any Comorbidity	58.69	45.29	52.06	<0.001
General Self Rated Health				<0.001
Excellent/ Very Good	63.85	60.63	62.27	
Good	27.70	30.30	28.98	
Fair	7.04	7.63	7.33	
Poor	1.40	1.44	1.42	

* p-values were obtained from chi-square tests for comparison between males and females

4.4. Characteristics for female participants in the respiratory health outcome groups

Tables 4.4.1 and 4.4.2 present the distribution of characteristics for female participants in the various respiratory outcome groups. Compared to females in the control group, females with ACO were more likely to be in the 55–64, 65-74, and 75 years and above age groups. The age distribution was significantly different for females with ACO, COPD, and asthma than females in the control group. The distribution across ethnic groups differed significantly ($p < 0.001$) between females with ACO or asthma compared to control. Aboriginal females were less likely to report having no respiratory illness. Among females, the highest proportion with less than secondary school graduation was from the ACO group, followed by females with COPD. Females with ACO were more likely to be single (17.12% vs. 7.39%) and less likely to be married (51.40% vs. 71.67%) than females in the control group, with the difference being statistically significant ($p<0.001$). Fewer females with ACO reported a household income of ≥$100,000 compared to females in the control group, 18.6% and 40.1%, respectively ($p<0.001$). The distribution of smoking status was significantly different for females with ACO and COPD than females in the control group. Females with ACO and COPD were less likely to report being never smokers compared to the control group, 29.50%, 23.92%, and 53.46%, respectively. The largest proportion of females with ACO and COPD were former smokers, followed by never smokers. Distribution of obesity significantly differed for females with asthma, ACO and COPD compared to controls. Female participants who were classified as obese were more likely to report having ACO compared to control, COPD, or asthma. The proportion reporting comorbidities was the highest among females with ACO compared to the control groups (Table 4.4.2). Compared to controls, females with ACO and COPD had significantly more heart disease, diabetes, osteoporosis, rheumatoid arthritis, depression, kidney disease, and stroke. Females with

ACO were more likely to report underactive thyroid disease than females in the COPD group ($p<0.05$), asthma group ($p<0.001$), and control group ($p<0.001$). More females with COPD reported having cancer than compared to the controls ($p<0.001$) or females in the asthma group ($p<0.05$).

Table 4.4.1 Distribution of baseline characteristics for females among control, ACO, COPD only, and asthma only groups.

	Control group (%)	ACO group (%)	COPD only group (%)	Asthma only group (%)	p-value*
Age Group (years)					<0.001
45-54	41.35	29.04[c]	24.70 [c]	45.01 [c]	
55-64	28.53	31.29	26.76	29.38	
65-74	18.62	23.59	26.94	17.35	
75 years and above	11.50	16.07	21.61	8.26	
Ethnicity					<0.001
White	91.56	89.06 [c]	90.23	89.4 [c]	
Non-white, Non-Aboriginal	4.48	2.61	3.88	4.28	
Aboriginal	3.96	8.33	5.88	6.32	
Education					<0.001
Below Secondary	4.79	10.82 [c]	10.61 [c]	4.18 [b]	
Secondary and Certificate	47.32	56.25	56.61 5	43.73	
University Certificate and Above	47.89	32.93	32.73	52.09	
Marital Status					<0.001
Single	7.39	17.12 [c]	8.49 [c]	10.18 [c]	
Married	71.67	51.40	51.85	69.99	
Widowed, Divorced	20.93	31.48	39.66	19.83	

Household Income					<0.001
≤$19,999	4.67	16.13 [c]	14.60 [c]	5.19	
$20,000 - $49,999	20.92	34.75	32.30	19.68	
$50,000-$99,999	34.28	30.50	30.49	34.87	
≥$100,000	40.13	18.62	22.71	40.26	
Employed					<0.001
Yes	87.75	76.76 [b]	78.66 [a]	87.91	
No	12.25	23.24	21.34	12.09	
Province					<0.001
Eastern	19.08	14.38	21.91 [b]	18.33 [b]	
Quebec	20.69	28.52	15.93	17.13	
Ontario	20.63	20.75	24.40	23.62	
Prairies	19.03	16.52	16.82	17.48	
British Columbia	20.56	19.83	20.95	23.44	
Smoking Status					<0.001
Never smoker	53.46	29.50 [c]	23.92 [c]	53.96	
Current smoker	7.85	22.12	22.60	6.84	
Former smoker	38.69	48.37	53.48	39.20	
Obesity					<0.001
Underweight or	39.58	24.26 [c]	34.26 [c]	29.92 [c]	
Normal weight					
Overweight	34.69	28.65	30.28	34.54	

Obese	25.74	47.09	35.47	35.54

***** p-values from chi-squared for overall comparisons between control, ACO, COPD and asthma groups.
[a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$ from chi-squared statistics for comparison with controls after adjusting for multiple comparisons using Bonferroni's correction.

Table 4.4.2 Distribution of comorbidities for females among control, ACO, COPD only, and asthma only groups.

	Control group (%)	ACO group (%)	COPD only group (%)	Asthma only group (%)	p-value*
Comorbidities					
Heart Disease	6.00	16.39 [c g]	15.23 [c g]	6.89	<0.001
Diabetes	13.12	27.29 [c g]	22.54 [c f]	16.96 [c]	<0.001
Cancer	13.06	16.64	19.61 [c f]	14.34	<0.001
Osteoporosis	11.69	20.97 [c g]	24.18 [c g]	12.11	<0.001
Rheumatoid Arthritis	3.19	8.12 [c]	7.63 [c]	5.27 [c]	<0.001
Depression	18.80	37.66 [c f]	29.68 [c]	26.83 [c]	<0.001
Kidney Disease	2.12	4.44 [a]	4.08 [b]	3.02	<0.001
Stroke	1.02	4.63 [b f]	2.48 [b]	1.26	<0.001
Underactive Thyroid Disease	18.09	29.15 [c d g]	19.96	18.38	<0.001
Any Comorbidity	56.67	78.73 [c g]	76.67 [c g]	63.67 [c]	<0.001

*p-values obtained from logistic regression analysis after adjusting for age group and smoking.
[a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$ from chi-squared statistics for comparison with controls after adjusting for multiple comparisons using Bonferroni's correction.
[d]$p<0.05$, [e]<0.001 from chi-squared statistics for comparison with COPD after adjusting for multiple comparisons using Bonferroni's correction.
[f]$p<0.05$, [g]<0.001 from chi-squared statistics for comparison with asthma after adjusting for multiple comparisons using Bonferroni's correction.

4.5 Distribution of respiratory symptoms and general health for female participants in the respiratory health outcome groups.

Table 4.5.1 presents the distribution of symptoms perceived general health among the four outcome groups. After adjusting for age and smoking, there were significant differences between females with ACO, COPD, and asthma-only compared to control group for all symptoms. Among females, a greater proportion with ACO reported having symptoms than the other groups. The proportion of shortness of breath at rest, shortness of breath while walking, wheeze during exertion, and wheeze in the last 12 months was significantly greater in the ACO group compared to the COPD, asthma and control group. There was a statistically significant difference between the four outcome groups in the general self-rated health for females. The proportion of female subjects reporting poor health was the highest in the ACO group, after adjusting for age and smoking status.

The distributions of airway obstruction measures for females are presented in Table 4.5.2. Proportion of female respondents that were classified as having definite chronic airway obstruction (CAO) was greatest in the ACO group compared to all other respiratory groups (43.87% versus 0.82% in the control group). This finding was statistically significant ($p<0.001$). For females, the mean FEV_1, FVC and FEV_1/FVC predicted values were the lowest for participants reporting a diagnosis of ACO. The highest proportion of participants that meet LLN criteria 1 and 2 were from the ACO group, followed by the COPD group. Under the modified-GOLD criteria, participants with ACO were more likely to be classified as modified-GOLD stage III or IV, a classification reserved for severe and very severe airway obstruction, than compared to COPD, asthma, and control groups.

Table 4.5.1 Distribution of respiratory symptoms and general health for females among control, ACO, COPD only and asthma only groups.

	Control group (%)	ACO group (%)	COPD group (%)	Asthma group (%)	p-value*
Regular cough	10.48	39.94 [b e]	31.35 [b e]	19.95 [b]	<0.001
Regular cough with phlegm	3.56	23.24 [b e]	20.10 [b e]	8.90 [b]	<0.001
Shortness of breath at rest	1.80	23.88 [b d e]	8.50 [b]	10.41 [b]	<0.001
Shortness of breath walking on flat surfaces	5.15	41.14 [b d e]	23.43 [b e]	14.27 [b]	<0.001
Wheeze during exertion	4.38	43.67 [b d e]	22.60 [b]	19.35 [b]	<0.001
Wheeze in the last 12 months	10.95	69.86 [b d e]	44.69 [b]	44.88 [b]	<0.001
Perceived general health					<0.001
Very good/Excellent	66.95	32.03 [b e]	44.30 [b e]	55.82 [c]	
Good	26.33	37.98	34.74	32.45	
Fair	5.67	23.22	17.12	9.75	
Poor	1.05	6.77	3.84	1.98	

*p-values obtained after adjusting for age group and smoking using multinomial logistic and logistic regression analysis. The distribution of general health was compared between control and ACO, COPD only and asthma only groups.
[a]$p<0.05$, [b]$p<0.001$ for comparisons with controls after adjusting for multiple comparisons using Bonferroni's correction.
[c]$p<0.05$, [d]$p<0.001$ for comparisons with COPD after adjusting for multiple comparisons using Bonferroni's correction.
[e]$p<0.001$ for comparisons with asthma after adjusting for multiple comparisons using Bonferroni's correction.

Table 4.5.2 Distribution of airway obstruction using modified GOLD and non-GOLD criteria for females among control, ACO, COPD only and asthma only groups.

	Control group (%)	ACO group (%)	COPD group (%)	Asthma group (%)	p-value*
Mean (SE)					
FEV_1 Predicted (%)	97.28 (0.17)	82.87 [c] (1.38)	86.46 [c] (1.02)	91.80 [c] (0.44)	<0.001
FVC Predicted (%)	95.86 (0.15)	87.16 [c] (1.13)	89.58 [c] (0.86)	92.55 [c] (0.38)	<0.001
FEV_1/FVC Predicted (%)	101.2 (0.08)	94.55 [c] (0.78)	96.58 [c] (0.55)	98.67 [c] (0.24)	<0.001
	(%)	(%)	(%)	(%)	
Chronic Airway Obstruction (Definite)	0.42 [c]	43.87 [c]	22.40 [c]	22.23 [c]	<0.001
Non-GOLD staging criteria					
LLN Criteria 1	3.47	24.52[c]	17.22 [c]	9.18 [c]	<0.001
LLN Criteria 2	1.56	15.91 [c]	12.22 [c]	4.73 [c]	<0.001
Modified-GOLD criteria**					<0.001
No airflow limitation	92.89	68.07 [c]	71.28 [c]	85.57 [c]	
Stage I (mild)	3.42	4.42	8.73	5.45	
Stage II (moderate)	3.46	23.22	17.33	8.62	
Stage III, IV (severe and very severe)	0.23	4.29	2.66	0.35	

*p-values for overall comparison between ACO, COPD, asthma only groups and control subjects.
**Due to the small sample size, Stage III and IV were collapsed together in modified gold criteria.
[a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$ from chi-squared statistics for comparison with controls after adjusting for multiple comparisons using Bonferroni's correction.

4.6 Distribution of characteristics for male participants in the respiratory health outcome groups.

Tables 4.6.1 and 4.6.2 present the distribution of characteristics for male participants in the various respiratory outcome groups. Among males, the group with the largest proportion in the 45-54 years age group were in the asthma-only group (50.29%), and this pattern was similar to female participants. For males in the older age groups, 55-64, 65-74, and 75 years and above, COPD was more likely to be reported. The distribution of ethnic groups differed significantly between males with ACO and males in the control group ($p<0.001$). In the control group, 3.80% of males identified as Aboriginal, while in the ACO group this number increased to 12.73% of Aboriginal males. Similar to females, the highest proportion of males that had less than a secondary school graduation was among ACO, followed by COPD, and the differences were significantly different ($p<0.001$). There was a significant difference in the distribution of marital status between males in the control group and males in the ACO and COPD-only group ($p<0.001$). There was a higher proportion of single and widowed, divorced, or separated participants in the ACO or COPD group, compared to the control group ($p<0.001$). Married participants were more likely to be in the control or asthma-only group. Also consistent with findings for female participants, male participants with ACO or COPD were less likely than controls or asthma-only participants to report a household income of ≥ $100,000, with the difference being statistically significant. Among the participants who reported the lowest level of household income (≤ 19,999), the largest proportion were in the ACO group. Males with ACO or COPD were also less likely to report being employed in comparison to the control group ($p<0.001$). The distribution of smoking status differed significantly between ACO and COPD groups and the control group ($p<0.001$). Among controls, 48.9% were never smokers, but that

number is was considerably lower for males with ACO or COPD to 18.9% and 17.4% respectively. The largest proportion of males with ACO and COPD were former smokers, followed by current smokers. Compared to males in the control or asthma group, males with ACO and COPD were less likely to report being never smokers. The distribution of obesity measures was only significantly different between males with COPD and controls (37.07% vs. 29.34%, $p<0.05$). Table 4.6.2 shows the comparison of comorbidities between the four groups. In comparison to control and asthma groups, male participants in the ACO and COPD groups were more likely to report at least one of the comorbidities studied, with the differences being statistically significant ($p<0.001$). Compared to the control group, there were statistically significant increases in the proportion of heart disease, diabetes, osteoporosis, rheumatoid arthritis, and depression for both ACO and COPD groups. There was an increased proportion of underactive thyroid disease in the ACO group than in the control group ($p<0.05$). In the COPD group, there was a greater proportion of males with cancer ($p<0.05$), kidney disease ($p<0.01$), and a history of stroke ($p<0.001$) compared to controls. Males with asthma were more likely to have depression than the controls, but less likely than the ACO group. Compared to the asthma group, more males with ACO and COPD reported heart disease, diabetes, and a history of stroke, with the differences being statistically significant. There were also more males with cancer in the COPD group than the asthma or control group ($p<0.05$).

Table 4.6.1 Distribution of baseline characteristics for males among control, ACO, COPD only and asthma only groups.

	Control group (%)	ACO group (%)	COPD only group (%)	Asthma only group (%)	p-value*
Age Group (years)					<0.001
45-54	42.91	31.94 [a]	25.60 [c]	50.29 [c]	
55-64	30.88	31.35	33.06	30.97	
65-74	16.08	22.37	22.83	12.35	
75 years and above	10.13	14.34	18.51	6.39	
Ethnicity					<0.001
Caucasian	90.64	81.64 [c]	92.55	90.33	
Non-Caucasian, Non-Aboriginal	5.56	5.63	2.32	5.84	
Aboriginal	3.80	12.73	5.12	3.83	
Education					<0.001
Below Secondary	3.72	11.17 [c]	10.24 [c]	3.12	
Secondary and Certificate	41.48	54.82	56.82	37.58	
University Certificate and Above	54.80	34.01	32.94	59.31	
Marital Status					<0.001
Single	7.24	16.04 [c]	8.17 [c]	7.16	
Married	83.61	67.64	73.14	83.88	

Widowed, Divorced, Separated	9.15	16.32	18.70	8.96	
Household Income					<0.001
≤$19,999	2.70	10.77 [c]	8.67 [c]	3.00 [b]	
$20,000 - $49,999	13.92	24.58	23.22	10.76	
$50,000-$99,999	32.46	38.32	36.65	29.43	
≥$100,000	50.91	26.33	31.46	56.81	
Employed					<0.001
Yes	93.25	76.23 [c]	81.86 [c]	92.74	
No	6.75	23.77	18.14	7.26	
Province					<0.001
Eastern	16.05	14.38	21.04	14.94 [a]	
Quebec	20.57	20.46	16.48	16.30	
Ontario	21.45	25.34	19.88	23.00	
Prairies	21.47	21.21	21.55	22.79	
British Columbia	20.46	18.61	21.05	22.98	
Smoking Status					<0.001
Never smoker	48.91	18.88 [c]	17.41 [c]	51.84	
Current smoker	9.68	.27.16	27.41	7.74	
Former smoker	41.41	53.96	55.18	40.43	
Obesity					0.002

Underweight or Normal weight	24.22	20.96	24.08[a]	24.11
Overweight	46.45	39.11	38.85	45.91
Obese	29.34	39.92	37.07	29.98

* p-values from chi-squared for overall comparisons between control, ACO, COPD and asthma groups.
[a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$ from chi-squared statistics for comparison with controls after adjusting for multiple comparisons using Bonferroni's correction.

Table 4.6.2 Distribution of comorbidity characteristics for males among control, ACO, COPD only and asthma only groups.

	Control group (%)	ACO group (%)	COPD only group (%)	Asthma only group (%)	p-value*
Heart Disease	11.27	21.70 [c g]	24.37 [c g]	9.98	<0.001
Diabetes	16.68	27.68 [b f]	29.48 [c g]	16.75	<0.001
Cancer	11.78	13.58	16.32 [a f]	9.63	<0.001
Osteoporosis	1.71	5.69 [c]	4.55 [c]	2.48	<0.001
Rheumatoid Arthritis	1.96	5.73 [b]	4.49 [b]	2.77	<0.001
Depression	10.99	31.91 [c g]	22.46 [c]	16.36 [c]	<0.001
Kidney Disease	2.45	3.05	5.08 [b]	2.50	<0.001
Stroke	1.45	3.64 [f]	4.37 [c g]	0.90	<0.001
Underactive Thyroid Disease	5.12	10.10 [a]	7.47	6.27	<0.001
Any comorbidity	44.22	71.12 [c g]	69.10 [c g]	44.27	<0.001

* p-values obtained from logistic regression analysis after adjusting for age group and smoking.
[a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$ from chi-squared statistics for comparison with controls after adjusting for multiple comparisons using Bonferroni's correction.
[d]$p<0.05$, [e]<0.001 from chi-squared statistics for comparison with COPD after adjusting for multiple comparisons using Bonferroni's correction.
[f]$p<0.05$, [g]<0.001 from chi-squared statistics for comparison with asthma after adjusting for multiple comparisons using Bonferroni's correction.

4.7 Distribution of symptoms and airway obstruction for males in the respiratory health outcome groups.

Table 4.7.1 presents the distribution of symptoms and airway obstruction in the four health outcome groups for males. After adjusting for age and smoking, there were significant differences in the prevalence of all the symptoms among males with ACO, COPD, and asthma-only compared to the control group. The proportions of all reported symptoms were significantly greater in the ACO group than in the other groups. For males with ACO or COPD, there was an increased report of regular cough, cough with phlegm, shortness of breath while walking, wheeze during exertion, and wheeze in the last 12 months compared to males in the asthma and control groups. The proportion of subjects reporting wheeze in the last 12 months was the highest in the ACO group with the differences between the ACO group and the COPD group being statistically significant ($p<0.001$). There were significant differences in the distribution of responses to self-rated health between males with ACO or COPD to males in the asthma or control group after adjusting for age and smoking status. There were 7.6% of males with ACO and 5.7% of males with COPD that rated their health as "poor" compared to 1.2% and 1.5% in the control and asthma-only groups respectively. General self-rated health was not significantly different between males with asthma and males in the control group.

Distribution of airway obstruction measures for males are presented in Table 4.7.2. The proportion of male respondents that were classified as having definite CAO was the highest in the ACO group compared to all other respiratory groups, a consistent finding in females as well (42.48% in ACO group vs. 0.82% in control group, $p<0.001$). For males, the mean FEV_1, FVC and FEV_1/FVC predicted values were the lowest for participants reporting a diagnosis of ACO. The highest proportion of participants that met LLN criteria 1 and 2 were also from the ACO

group. Males with ACO were more likely to be classified as modified-GOLD stage III or IV than compared to all other outcome groups (7.10% vs 0.29% control).

Table 4.7.1 Distribution of respiratory symptoms and general health for males among control, ACO, COPD only and asthma only groups.

	Control group (%)	ACO group (%)	COPD only group (%)	Asthma only group (%)	p-value*
Regular cough	14.19	46.69 [b e]	39.42 [b e]	19.10 [b]	<0.001
Regular cough with phlegm	5.81	28.96 [b e]	27.51 [b e]	10.04 [b]	<0.001
Shortness of breath at rest	1.77	11.98 [b]	8.48 [b]	6.71 [b]	<0.001
Shortness of breath walking on flat surfaces	3.72	27.60 [b e]	24.48 [b e]	7.88 [b]	<0.001
Wheeze during exertion	4.85	38.82 [bc**e]	29.23 [b e]	16.50 [b]	<0.001
Wheeze in the last 12 months	12.11	64.18 [b d e]	50.47 [b]	44.97 [b]	<0.001
Perceived general health					<0.001
Very good/Excellent	62.29	27.02 [b e]	35.07 [b e]	58.48	
Good	29.86	39.17	37.82	30.94	
Fair	6.67	26.18	21.44	9.07	
Poor	1.18	7.63	5.67	1.51	

*p-values obtained after adjusting for age group and smoking using multinomial logistic and logistic regression analysis. The distribution of general health was compared between control and ACO, COPD only and asthma only groups.

[a]$p<0.05$, [b]$p<0.001$ for comparison with controls after adjusting for multiple comparisons using Bonferroni's correction.

[c]$p<0.05$, [d]$p<0.001$ for comparison with COPD after adjusting for multiple comparisons using Bonferroni's correction.

[e]$p<0.001$ for comparisons with asthma after adjusting for multiple comparisons using Bonferroni's correction.

** svy code was not used.

Table 4.7.2 Distribution of airway obstruction using modified GOLD and non-GOLD criteria for males among control, ACO, COPD only and asthma only groups.

	Control group	ACO group	COPD only group	Asthma only group	p-value*
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	
FEV_1 predicted (%)	98.00 (0.18)	83.44 [c] (2.26)	85.27 [c] (1.50)	91.19 [c] (0.59)	
FVC predicted (%)	96.46 (0.16)	89.93 [c] (1.60)	89.97 [c] (1.07)	93.53 [c] (0.50)	
FEV_1/FVC predicted (%)	101.0 (0.09)	91.77 [c] (1.70)	94.17 [c] (0.87)	96.55 [c] (0.32)	
	(%)	(%)	(%)	(%)	
Chronic Airway Obstruction (Definite)	0.82	42.48 [c]	26.86 [c]	24.29 [c]	<0.001
Non-GOLD staging criteria					
LLN Criteria 1	3.47	29.34 [c]	22.53 [c]	13.18 [c]	<0.001
LLN Criteria 2	1.76	19.72 [c]	15.86 [c]	7.51 [c]	<0.001
Modified-GOLD criteria					<0.001
No airflow limitation	91.74	57.04 [c]	67.28 [c]	76.48 [c]	
Stage I (mild)	4.38	12.01	4.94	10.03	
Stage II (moderate)	3.59	23.85	22.30	12.47	
Stage III, IV (severe and very severe)	0.29	7.10	5.48	1.03	

*p-values for overall comparison between ACO, COPD, asthma only groups and control subjects.
**Due to the small sample size, Stage III and IV were collapsed together in modified gold criteria.
[a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$ from chi-squared statistics for comparison with controls after adjusting for multiple comparisons using Bonferroni's correction.

4.8 Multivariable analysis of factors associated with respiratory health outcomes for females

The factors associated with respiratory outcomes from multivariable analysis are shown in Table 4.8 for females and the adjusted relative risk ratios and 95% CIs are also presented in the table. Aboriginal female participants were 1.80 (RRR: 1.80; 95% CI: [1.16, 2.79]; p<0.01) times more likely to have ACO, and 1.53 (RRR: 1.53; 95% CI: [1.21, 1.94]; p<0.001) times more likely to have asthma than white females, after controlling for all other variables). The risk of developing COPD compared to being healthy was 28.0% lower for those with a secondary school education or certificate compared to participants with less than a secondary school education, (RRR:0.72; 95% CI: [0.52, 0.99]; p=0.04). Likewise, the risk of reporting ACO and COPD among females that completed at least a university certificate was 39% and 44% lower than those who had less than a secondary school education, respectively (RRR: 0.61; 95% CI: [0.38, 0.96]; p<0.05) (RRR: 0.56; 95% CI: [0.40, 0.78]; p<0.01). A significant relationship between marital status and respiratory outcomes was found, with marriage having a protective effect against ACO, COPD, and asthma. Specifically, the risk of having ACO was 64% lower (RRR: 0.36; 95% CI: [0.25, 0.51]; p<0.001) for married females compared to females who were single. Similarly, the risk of having COPD was 36% lower for married females (RRR: 0.64; 95% CI: [0.46, 0.90]; p=0.006) and the risk of having asthma compared to no respiratory illness was 26% lower for married females than for single females, after controlling for all other variables (RRR: 0.74; 95% CI: [0.62, 0.88]; p=0.001). ACO and asthma were significantly associated with being divorced, separated or widowed. The risk of having ACO compared to no respiratory outcome was 46% lower for females that were divorced, separated, or widowed compared to females that were single (RRR: 0.54; 95% CI: [0.37, 0.77]; p=0.001). Likewise, the risk of having asthma

compared to being healthy was 24% lower for females that were divorced, separated, or widowed compared to females that were single after controlling for all other factors (RRR: 0.76; 95% CI: [0.63, 0.93]; p=0.001).

When comparing provinces in Canada, the risk of having ACO compared to reporting no respiratory illness was 1.53 times greater for females living in Quebec compared to females living in Eastern Canada (RRR:1.53; 95% CI: [1.04, 2.26]; p=0.032). However, females in Quebec had a 49% lower risk for having COPD compared to females living in Eastern Canada (RRR: 0.51; 95% CI: [0.37, 0.70]; p<0.001), after adjusting for all other variables listed in Table 4.8. Females in Ontario had 1.27 times greater risk for having asthma compared to females living in Eastern Canada, (RRR: 1.27; 95% CI: [1.07, 1.51]; p= 0.007). After adjusting for all other variables, the risk of reporting asthma was determined to be 1.30 times greater among females living in British Columbia compared to those living in Eastern Canada (RRR: 1.30; 95% CI: [1.09, 1.54]; p=0.004). ACO and COPD association with an overweight body mass index status compared to normal was not found to be statistically significant. However, after adjusting for all other variables, it was observed that the risk of having asthma compared to being healthy was 1.36 times greater for females that were overweight compared to females that were normal/underweight. This finding was statistically significant (RRR: 1.36; 95% CI: [1.19, 1.56]; p<0.001). When comparing females that were obese to females that were normal/underweight, a statistically significant association was found with ACO, COPD, and asthma. The risk of having ACO was 2.58 times greater (RRR: 2.58; 95% CI: [1.91, 3.50]; p<0.001), COPD was 1.40 times greater (RRR: 1.40; 95% CI: [1.11, 1.77]; p=0.005), and asthma was 1.87 times greater (RRR: 1.87; 95% CI: [1.62, 2.15]; p<0.001) for females that were obese compared to those that were normal/underweight. After adjusting for all other variables, only ACO and COPD had

statistically significant associations with current-smokers compared to never-smokers. The risk of having ACO compared to reporting no respiratory illness was 3.29 times greater (RRR: 3.29; 95% CI: [1.73, 6.24]; $p<0.001$) and the risk for COPD was 2.68 times greater (RR: 2.68; 95% CI: [1.56, 5.33]; $p=0.002$), when comparing female current smokers to never smokers. Former smoking was significantly associated with COPD. The risk of having COPD compared to being healthy was 1.76 times greater for females that were former smokers compared to females that were never smokers, after controlling for all other variables in the model (RRR: 1.76; 95% CI: [1.06, 3.21]; $p=0.05$). Current and former female smokers over the age of 55 were more likely to report having ACO or COPD than never smokers between the ages 45-54 years. The greatest risk for having COPD was among female current smokers 75 years and above which was 24.4 times greater than compared to never smokers in the 45-54 years age range (RRR: 24.44; 95% CI: [12.95, 46.15]; $p<0.001$). In each age group, current smokers were at a much greater risk for reporting ACO or COPD than former smokers, when compared to never smoking 45-54 years old females.

Table 4.8 Adjusted relative risk ratios for factors associated with ACO, COPD, and asthma for females in the final model: results from the multinomial logistic regression analysis.

	ACO group RRR (95% CI)	COPD only group RRR (95% CI)	Asthma only group RRR (95% CI)
Age Group (years)			
45-54	1.00	1.00	1.00
55-64	0.91 (0.51, 1.64)	0.95 (0.55, 1.65)	0.99 (0.83, 1.18)
65-74	0.90 (0.48, 1.68)	1.18 (0.68, 2.04)	0.88 (0.72, 1.07)
75+	1.43 (0.77, 2.64)	1.25 (0.25, 2.18)	0.62 [c] (0.48, 0.79)
Ethnicity			
White	1.00	1.00	1.00
Non-white, Non-Aboriginal	0.88 (0.44, 1.75)	1.52 (0.83, 2.78)	0.92 (0.70, 1.21)
Aboriginal	1.80 [b] (1.16, 2.79)	1.43 (0.91, 2.26)	1.53 [c] (1.21, 1.94)
Education			
Below secondary	1.00	1.00	1.00
Secondary and Certificate	0.78 (0.51, 1.19)	0.72[a] (0.52, 0.99)	0.97 (0.76, 1.23)
University Certificate and Above	0.61[a] (0.38, 0.96)	0.56 [b] (0.40, 0.78)	1.18 (0.92, 1.52)
Marital Status			
Single	1.00	1.00	1.00
Married	0.36 [c] (0.25, 0.51)	0.64 [b] (0.46, 0.90)	0.74 [c] (0.62, 0.88)

Widowed, Divorced, Separated	0.54 [b] (0.37, 0.77)	1.12 (0.80, 1.56)	0.76 [b] (0.63, 0.93)
Province			
Eastern	1.00	1.00	1.00
Quebec	1.53 [a] (1.04, 2.26)	0.51 [c] (0.37, 0.70)	0.94 (0.79, 1.13)
Ontario	1.38 (0.92, 2.07)	0.99 (0.73, 1.33)	1.27 [b] (1.07, 1.51)
Prairies	1.19 (0.77, 1.84)	0.74 (0.54, 1.02)	1.01 (0.84, 1.21)
British Columbia	1.48 (0.97, 2.25)	0.92 (0.68, 1.25)	1.30[b] (1.09, 1.54)
Smoking Status			
Never smoker	1.00	1.00	1.00
Current smoker	3.29[c] (1.73, 6.24)	2.68[c] (1.56, 5.33)	0.93 (0.67, 1.28)
Former smoker	0.94 (0.48, 1.82)	1.76[a] (1.06, 3.21)	1.03 (0.84, 1.27)
Obesity			
Underweight or Normal weight	1.00	1.00	1.00
Overweight	1.18 (0.84, 1.64)	0.90 (0.70, 1.15)	1.36[c] (1.19, 1.56)
Obese	2.58[c] (1.91, 3.50)	1.40[b] (1.11, 1.77)	1.87[c] (1.63, 2.15)
Age group (years) & smoking*			
45-54 and non-smoker	1.00	1.00	1.00
55-64 and current smoker	4.30[c] (2.35, 7.87)	7.11[c] (4.23, 11.94)	0.66[b] (0.46, 0.95)
55-64 and former smoker	2.23 [b] (1.32, 3.78)	2.74 [c] (1.72, 4.36)	0.93 (0.77, 1.12)

65-74 current smoker	6.48 [c] (3.03, 13.84)	14.80 [c] (8.43, 25.99)	1.03 (0.62, 1.71)
65-74 former smoker	2.91 [c] (1.71, 4,95)	4.34 [c] (2.76, 6.82)	0.79 [b] (0.64, 0.97)
75+ current smoker	4.62 [b] (1.41, 15.10)	24.44 [c] (12.95, 46.15)	0.25 (0.06, 1.03)
75+ former smoker	2.84 [c] (1.61, 5.00)	5.53 [c] (3.47, 8.80)	0.81 (0.63, 1.04)

In the multinomial logistic regression, ACO, COPD, and asthma groups were compared to the control group.
*Interaction term compares categories to female never smokers aged 45-54 years.
[a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$

4.9 Multivariable analysis of factors associated with respiratory health outcomes for males

The association between risk factors and respiratory outcomes from multivariable analysis are shown in Table 4.9 and the adjusted relative risk factors and 95%CIs are also provided in the table. For males, ethnicity, education, employment, and smoking were significant predictors for ACO, COPD and asthma. There was a statistically significant increased risk for ACO among Aboriginal males compared to white males. The risk of having ACO compared to being healthy was 3.30 times greater for Aboriginals compared to whites after controlling for other factors in the model (RRR: 3.30, 95% CI: [1.41, 7.74]; p=0.006). Compared to participants with less than a secondary school education, the risk of reporting a diagnosis of ACO was 73% lower (RRR: 0.27; 95% CI: [0.09, 0.78]; p=0.02), and a diagnosis of COPD was 65% lower for those with a secondary school graduation (RRR: 0.35; 95% CI: [0.15, 0.82]; p=0.02).

A significant relationship between employment and ACO and COPD was found, with employed males having a lower risk for these outcomes than unemployed. Employed males had a 61% lower risk for having ACO (RRR: 0.39; 95% CI: [0.19, 0.80]; p=0.01) and a 55% lower risk for having COPD compared to those who were unemployed (RRR: 0.45; 95% CI: [0.27, 0.73]; p<0.001). No association between employment and asthma was found.

For males, the risk of having ACO compared to being healthy was 5.12 times greater for current smokers compared to never smokers (RRR: 5.12; 95% CI: [2.15, 12.18]; $p<0.001$), and the risk of having COPD was 3.77 times greater for current smokers compared to never smokers, after controlling for all other factors in the model (RRR: 3.77; 95% CI: [2.24, 6.35]; $p<0.001$). The risk of having ACO compared to being healthy was 2.16 times greater for former smokers compared to never smokers, after controlling for all other factors in the model. This finding was not statistically significant. (RRR: 2.16; 95% CI: [0.94, 4.95]; $p=0.07$). The risk of having COPD compared to being healthy was 2.00 times greater for males that were former smokers compared to males that were never smokers, after controlling for all other variables in the model. This finding was statistically significant (RRR: 2.00; 95% CI: [1.24, 3.21]; $p=0.004$).

Table 1.9 Adjusted relative risk ratios for factors associated with ACO, COPD, and asthma for males in the final model: results from the multinomial logistic regression analysis.

	ACO group RRR (95% CI)	COPD only group RRR (95% CI)	Asthma only group RRR (95% CI)
Ethnicity			
White	1.00	1.00	1.00
Non-white, Non-Aboriginal	1.83 (0.46, 7.25)	0.71 (0.28, 1.77)	1.04 (0.74, 1.47)
Aboriginal	3.30[b] (1.41, 7.74)	1.20 (0.58, 2.51)	1.06 (0.71, 1.57)
Education			
Below secondary	1.00	1.00	1.00
Secondary and Certificate	0.39 (0.14, 1.05)	0.82 (0.37, 1.82)	1.07 (0.56, 2.04)
University Certificate and Above	0.27[a] (0.09, 0.78)	0.35[a] (0.15, 0.82)	1.23 (0.65, 2.35)
Employment			
No	1.00	1.00	1.00
Yes	0.39 [a] (0.19, 0.80)	0.45[b] (0.27, 0.73)	0.92 (0.66, 1.29)
Smoking Status			
Never Smoker	1.00	1.00	1.00
Current Smoker	5.12[c] (2.15, 12.18)	3.77[c] (2.24, 6.35)	0.81 (0.59, 1.10)
Former Smoker	2.16 (0.94, 4.95)	2.00[b] (1.24, 3.21)	0.95 (0.79, 1.15)

In the multinomial logistic regression, ACO, COPD, and asthma groups were compared to the control group.
[a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$

4.10 Association between environmental factors and respiratory health outcome groups

The distribution of environmental exposures among the respiratory outcomes studied are presented in Table 4.10.1 for females and Table 4.10.2 for males. Compared to the control group, the mean yearly exposure levels were significantly different for both males and females in the ACO, COPD, and asthma groups. With the exception of nitrogen dioxide (NO_2) estimates, mean exposure levels for sulphur dioxide (SO_2), fine inhalation particles of size 2.5 micron or less in diameter ($PM_{2.5}$), and ozone (O_3) were the highest in the ACO group for both males and females. Tables 4.10.3 and 4.10.4 presents the results of multinomial logistic regression models adjusted for significant factors identified in Sections 4.8 and 4.9 among males and females. In males, there was a significant association between NO_2 and asthma compared to the control group (RRR:1.04, 95% CI: [1.01, 1.07]; p=0.02). For every unit increase in annual average NO_2 exposure, the risk of having asthma versus no respiratory illness was 1.04 times greater among males. Other environmental factors (SO_2, $PM_{2.5}$, and O_3) were not associated with any of the respiratory health outcomes in males. No statistically significant association was found between environmental exposure and respiratory outcomes in females after adjusting for all other variables in the model.

The association between environmental factors and respiratory health outcomes were examined in non-smokers. Among male non-smokers, there was a statistically significant association between asthma in male non-smokers and ozone. Male non-smokers had a 4.0% lower risk of reporting asthma for every unit increase in annual average exposure levels of ozone (RRR: 0.96; 95% CI: [0.93-0.98]; p=0.007). For female non-smokers, a statistically significant relationship between COPD and SO_2 was found. For every unit increase in annual average SO_2 exposure, the

risk of having COPD versus no respiratory illness was 1.49 times greater for female non-smokers (RRR: 1.49; 95% CI: [1.07-2.08]; p=0.02).

Table 4.10.1 Distribution of average yearly environmental exposure for females among control, ACO, COPD-only, and asthma only groups.

	Control group Mean (SD)	ACO group Mean (SD)	COPD only group Mean (SD)	Asthma only group Mean (SD)
SO_2 (ppb)	1.03 (0.009)	1.11 (0.051)[c]	1.10(0.047) [c]	1.03 (0.022) [c]
$PM_{2.5}$, ($\mu g/m^3$)	6.63(0.013)	6.70 (0.079) [c]	6.57 (0.068) [c]	6.67 (0.035) [c]
O_3 (ppb)	24.60(0.035)	24.75 (0.224) [c]	24.65 (0.184) [c]	24.29 (0.099) [c]
NO_2 (ppb)	8.36(0.029)	8.30 (0.179) [c]	8.12 (0.134) [c]	8.398 (0.076) [c]

[a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$ from chi-squared statistics for comparison with controls after adjusting for multiple comparisons using Bonferroni's correction.

Table 4.10.2 Distribution of environmental exposure for males among control, ACO, COPD-only, and asthma-only groups.

	Control group Mean (SD)	ACO group Mean (SD)	COPD only group Mean (SD)	Asthma only group Mean (SD)
SO_2 (ppb)	1.01 (0.008)	1.09 (0.075) [c]	0.99 (0.051) [c]	0.97 (0.027) [c]
$PM_{2.5}$ ($\mu g/m^3$)	6.71 (0.014)	6.82 (0.099) [c]	6.65 (0.072) [c]	6.77 (0.042) [c]
O_3 (ppb)	24.46 (0.036)	24.94 (0.288) [c]	24.58 (0.193) [c]	24.13 (0.119) [c]
NO_2 (ppb)	8.60 (0.031)	8.50 (0.270) [c]	8.17 (0.169) [c]	8.68 (0.101) [c]

[a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$ from chi-squared statistics for comparison with controls after adjusting for multiple comparisons using Bonferroni's correction.

Table 4.10.3 Adjusted relative risk ratios for environmental factors associated with ACO, COPD, and asthma for females in the final model: results from the multinomial logistic regression analysis. *

	ACO group RRR (95% CI)	COPD only group RRR (95% CI)	Asthma only group RRR (95% CI)
SO_2 (ppb)	0.94 (0.78, 1.13)	1.07 (0.91, 1.25)	0.92 (0.85, 1.01)
$PM_{2.5}$ ($\mu g/m^3$)	1.02 (0.89, 1.17)	1.01 (0.90, 1.13)	1.01 (0.95, 1.07)
O_3 (ppb)	0.97 (0.93, 1.02)	1.01 (0.97, 1.05)	0.98 (0.96, 1.00)
NO_2 (ppb)	0.97 (0.91, 1.04)	0.99 (0.95, 1.04)	1.01 (0.98, 1.03)

*Relative risk ratios for three groups after controlling for age, ethnicity, education, marital status, province, obesity, smoking status, and the interaction between age by smoking.
No statistically significant association detected.

Table 4.10.4 Adjusted relative risk ratios for environmental factors associated with ACO, COPD, and asthma for males in the final model: results from the multinomial logistic regression analysis. *

	ACO group RRR (95% CI)	COPD only group RRR (95% CI)	Asthma only group RRR (95% CI)
SO_2 (ppb)	1.03 (0.68, 1.57)	0.95 (0.72, 1.24)	0.98 (0.87, 1.10)
$PM_{2.5}$ ($\mu g/m^3$)	1.05 (0.87, 1.28)	1.08 (0.93, 1.25)	1.07 (0.997, 1.14)
O_3 (ppb)	1.06 (0.98, 1.13)	0.98 (0.93, 1.03)	0.98 (0.96, 1.00)
NO_2 (ppb)	1.02 (0.91, 1.14)	0.96 (0.89, 1.04)	1.04 (1.01, 1.07)$^{0.024}$

*Relative risk ratios for three groups after controlling for ethnicity, education, employment, and smoking.

Chapter 5

Discussion and Conclusion

5.1 Summary of Findings

Differences between males and females regarding various factors related to the risk of ACO, COPD, and asthma were examined in this thesis. Such factors included social, physical, and environmental predictors, respiratory symptoms, perceived general health, and lung functioning measured by spirometry. We carried out statistical analysis of the baseline data from the Canadian Longitudinal Study on Aging (CLSA), using a cross-sectional population study. This study found that the overall prevalence for ACO, COPD, and asthma in this population were 1.80%, 3.05%, and 11.74%, respectively. Furthermore, 37.1% of COPD respondents reported an additional diagnosis of asthma, while only 13.3% of asthma respondents reported having an additional diagnosis of COPD. Prevalence estimates were higher among females than males for all three respiratory conditions (ACO: 2.17% vs. 1.41%; COPD: 3.22% vs. 2.87%; asthma 13.31% vs. 10.11%). Risk factors for the respiratory outcomes differed between male and female participants. For females, age, ethnicity, education, marital status, province, obesity, and smoking were associated with ACO, COPD, or asthma. While for males, ethnicity, education, employment, and smoking were associated with ACO, COPD, or asthma. Males with ACO and COPD had more severe airflow obstruction than females. Participants with ACO or COPD were more likely to have comorbidities, experience respiratory symptoms, and rate their perceived general health as "poor" than participants with asthma or no respiratory illness, regardless of sex. No statistically significant associations were observed between environmental exposure and

respiratory outcomes for females. However, nitrogen dioxide exposure was associated with an increased risk of asthma among males.

5.2 Importance of Study

The motivation for this research was to better understand the incongruent trends between men and women regarding the prevalence, morbidity, and mortality of ACO and COPD in Canada. In Canada, the number of COPD cases has increased from 1.1 million to approximately 2 million between 2000 and 2013 (Dai et al., 2018). Secular trends such as aging and increased smoking rates over time are often associated as contributing to this increase in cases. However, according to the Public Health Agency of Canada 2018 surveillance report on COPD, the age-standardized prevalence of COPD in Canada increased from 7.1% in 2001 to 9.5% in 2012. The age-standardized prevalence for males and females differed, with females showing a greater increase over the same period (Dai et al., 2018). For females in Canada, the age-standardized prevalence of COPD increased from 6.4% in 2001 to 9.2% in 2012, while for males, it increased from 8.1% in 2001 to 10.0% in 2012 (Dai et al., 2018), a bigger increase for females. Death due to COPD has declined in males in both Canada and the U.S., however for females, COPD death rates have increased (Gershon et al., 2010; Nicolini et al., 2018). Undoubtedly smoking trends have increased over a number of decades, particularly among females. Despite this, a significant proportion of individuals with COPD were non-smokers, suggesting that other factors may be contributing to this rise in prevalence. Some researchers have found that women were more likely than men to have ACO (de Marco et al., 2013; Ekerljung et al., 2018; Kauppi et al., 2011; Koleade et al., 2019; Senthilselvan & Beach, 2018; Wheaton et al., 2018), although a systematic review found no significant difference in prevalence between the sexes (Alshabanat et al., 2015).

This suggests that females may be potentially more susceptible to risk factors for ACO and underscores the importance of examining sex-specific differences in risk factors related to environmental impact, physical health, and social demographics.

The prevalence of ACO in our study was 1.8%, which is higher than another Canadian-based study which reported a prevalence of 1.6% (Senthilselvan & Beach, 2018). However, it was lower than findings from cross-sectional studies conducted in the U.S. (3.2%) and Sweden (3.4%) (Ekerljung et al., 2018; Kumbhare et al., 2016). We found that ACO prevalence is greater among females than males, and this finding is compatible with several studies in the literature (de Marco et al., 2013; Ekerljung et al., 2018; Koleade et al., 2019; Senthilselvan & Beach, 2018; Wheaton et al., 2018). Similar to findings by de Marco et al., and Senthilselvan & Beach, we observed that the prevalence of ACO and COPD increased with age, whereas the prevalence of asthma decreased with age (de Marco et al., 2013; Senthilselvan & Beach, 2018). Our study further adds that this trend is consistent for both males and females. Comparable to findings by Sin et al., we also found that participants with COPD were more likely to be classified as having ACO than participants with asthma (37.1% COPD group vs. 13.3% asthma group) (Sin et al., 2016). Our estimate for ACO among patients with COPD (37.1%) is higher than that in a systematic review and meta-analysis, which reported a 27.0% pooled prevalence of ACO among patients with COPD (Alshabanat et al., 2015). Our research findings add a sex-specific component to this, and our analysis determined that more females with COPD reported a diagnosis of asthma than males with COPD (40.3% vs. 33.0%). Additionally, more females with asthma reported a diagnosis of COPD than males with asthma. However, this finding was not statistically significant.

Ethnicity in our study population was categorized into three groups, Caucasian, Aboriginal, and Non-Caucasian, Non-Aboriginal. The majority of participants were Caucasian. Of the 30,097 participants, 91.9% were Caucasian, followed by 4.5% non-Caucasian and non-Aboriginal group, and 3.8% Aboriginal. Aboriginal ethnicity was a risk factor for respiratory disease among female and male subjects. This study found that both Aboriginal females and males were more likely to be diagnosed with ACO than Caucasian males and females. Aboriginal females were also more likely to develop asthma than Caucasian females, however this was not observed among males. Our study supports the finding that Aboriginal ethnicity is significantly associated with an increased risk of ACO in Canada, and Aboriginal females also have a greater risk for asthma than white females. A systematic review and meta-analysis on asthma and COPD prevalence comparing Aboriginal and non-Aboriginal participants from New Zealand, Australia, and Canada, found that overall, Aboriginal subjects were more likely to report having asthma than non-Aboriginals, and this was greater among Canadian Aboriginals compared to Canadian non-Aboriginals (Ospina et al., 2012). No sex-specific differences between asthma prevalence were identified in the review. In this analysis however, sex-specific difference was observed, and the association between asthma and Aboriginal identity was only found among Aboriginal females and not males. As part of the CLSA study recruitment, residents from the Canadian territories, some remote regions, Federal First Nation reserves, and other provincial First Nations settlements were excluded from the study. Therefore, these findings may not be generalizable to all Indigenous Peoples in Canada and may not adequately reflect respiratory risk estimates for Indigenous people living on-reserve.

The proportion of subjects reporting ACO and COPD among those who completed at least a university certificate was lower than those who have had less than secondary school education.

This is consistent for both males and females. The finding corresponds with many studies that observed a protective effect of higher education against ACO and COPD (de Marco et al., 2013; Kim et al., 2019; Senthilselvan & Beach, 2018; Wheaton et al., 2018). Furthermore, lower educational attainment was significantly associated with COPD incidence in females with asthma (To et al., 2018). These findings may be explained by healthier lifestyle choices, access to health information and resources, or possibly working in less hazardous workplace settings for participants who completed higher education than those who completed less than secondary school education.

In the literature, obesity has been consistently identified as a risk factor for ACO, COPD, and asthma (Franssen et al., 2008; Fuller-Thomson et al., 2018; Kumbhare et al., 2016; Lambert et al., 2017; Peters et al., 2018; Senthilselvan & Beach, 2018; Sood, 2011). This study also confirmed significant associations between obesity, ACO, COPD, and asthma among females. Female subjects who were obese were 2.58 times more likely to develop ACO, 1.40 times more likely to develop COPD, and 1.87 times more likely to develop asthma than females in the normal/underweight category. Additionally, asthma was more likely to be reported by overweight females as well. Obesity was not associated with ACO, COPD, or asthma for males. A number of epidemiological studies have found that obese females have a greater risk for asthma compared to obese males (Cadeddu et al., 2016; Guerra et al., 2002; Sood, 2011; Wang et al., 2015) and COPD (Franssen et al., 2008; Fuller-Thomson et al., 2018; Lambert et al., 2017). To et al. reported that obesity was associated with a greater cumulative incidence of COPD among female subjects with asthma. However, this study did not include male subjects, therefore a sex-specific comparison cannot be made (To et al., 2018). Wheaton et al., in a study on sex-specific differences for obstructive lung diseases in a U.S. population reported that obesity was

associated with current asthma for males only and ACO for both females and males (Wheaton et al., 2018). The present study supports the findings by Wheaton et al. on the association between obesity and ACO among females. Unlike Wheaton et al., this study did not observe an association between obesity and asthma or ACO among males. These divergent conclusions regarding the association among males in this current study and Wheaton et al. may be due to differences in the age distribution of the two study populations. Wheaton et al. included subjects over the age of 18, while in this study, the CLSA data includes participants 45 years of age and above. Age is an important risk modifier for asthma. Among younger age groups, asthma is more predominant in males than females, while in older age groups, females are disproportionately burdened by asthma than males. Lastly, since this is a cross-sectional study, implications on causality cannot be confirmed. The association between obesity and obstructive lung disease may, in part, be due to a more sedentary lifestyle or differences in expressing symptoms such as dyspnea that limit exercise tolerance (Franssen et al., 2008; Pitta et al., 2005). A study by Lambert et al. reported that among subjects with COPD, those that are more obese exhibited reduced exercise capacity than compared to normal-weight subjects with COPD (Lambert et al., 2017). Patients with COPD are progressively limited in their ability to undertake normal daily activities due to shortness of breath with exertion and peripheral muscle weakness. Peripheral muscle weakness is a known contributor in reducing exercise capacity for patients with COPD (Rausch-Osthoff et al., 2014). This has a cascading effect leading to activity avoidance, reduced quality of life, and early development of comorbidities (Thomas et al., 2013). A study using the data from the Canadian Longitudinal Study on Aging found that lung function was associated with physical activity and sedentary time among subjects with asthma or COPD (Dogra et al., 2018). Furthermore, evidence from a randomized control trial determined that endurance

exercise and strength training improve health outcomes among obese adults with asthma (Freitas et al., 2017). The finding that obesity is associated with obstructive lung disease in females only and not males suggest that sex hormones, such as estrogen and progesterone, may influence the risk for obstructive lung disease. The sex-specific difference in the association between obesity and ACO warrants further research across additional Canadian and other population-based studies.

This study examined current employment status as a potential factor associated with ACO, COPD, and asthma. Current employment was associated with respiratory disease for males only and not females in this study. Employed males had a 61% reduction in the risk of having ACO and a 55% reduction in the risk of having COPD than those who were unemployed. Being employed was a protective factor against COPD and ACO for males. The sex-specific association between current employment status and respiratory outcome, exhibits that 76% of males with ACO and 82% of males with COPD were currently employed. This is comparably lower than the 93% of males in the control group, and 93% of males with asthma who reported being employed. By changing the reference category in our regression analysis, the data suggests that unemployed males have 2.60 times the likelihood of reporting ACO than employed males. They also have 2.23 times the likelihood of reporting COPD compared to employed males. A similar finding was observed by To et al., but this association was found among females with asthma, and the study population did not include males (To et al., 2018). An explanation for this could be tied to disease severity. ACO- and COPD-related symptoms and exacerbations could hinder an individual's ability to work, to seek out employment, or to maintain a job if it risks worsening symptoms and overall respiratory health. This could lead to those with ACO or COPD being 'selected' out of work. Studies have shown that individuals with ACO are more likely to

experience worse health-related quality of life, more frequent respiratory exacerbations, rapid decline in lung function, higher mortality, and greater utilization of healthcare resources than compared to patients with COPD or asthma alone (de Marco et al., 2013; Global Initiative for Asthma, 2020; Tommola et al., 2017). Similarly, people living with COPD experience impaired participation in daily life, school, work, and social activities (Dai et al., 2018). This may result in an increased likelihood of unemployment in the ACO and COPD groups that we observed in this study.

Marital status was associated with ACO, COPD, and asthma only among females. For married females, the risk for ACO, COPD, and asthma was lower than compared to single females. Females who were previously married (divorced, separated, or widowed) also had a lower risk for ACO and asthma than females who were single. This data describes a protective effect of marriage or previous marriage on the risk of these lung diseases. This finding is consistent with the results from other studies, which found marriage or a history of prior marriage having a protective effect against ACO (Koleade et al., 2019) and COPD (Noda et al., 2009) for females as well. This may be explained by changes brought on through marriage such as elevated socioeconomic status, increase in household income, or improved health behaviours such as reduced smoking habits.

Residing in some provinces was associated with respiratory illness only among females. Compared to Eastern provinces, females from Quebec were more likely to have ACO and less likely to have COPD. Females from Ontario or British Columbia were more likely to report asthma than females living in the Eastern provinces. Senthilselvan & Beach found no association between provincial residence and ACO, COPD, or asthma (Senthilselvan & Beach, 2018). Very few studies in the literature looked at sex-specific differences for obstructive lung disease in

specific Canadian provinces. To et al. reported a high incidence of ACO among females with asthma residing in Ontario. Female subjects were followed between 1992 to 2015, and over 40% of females with asthma developed COPD during the 23-year study period (To et al., 2018). However, this study only included females from Ontario, therefore meaningful comparisons between different provinces cannot be adequately made.

This study did not observe any significant associations between SO_2, $PM_{2.5}$, O_3, NO_2, and respiratory disease among females. This suggests that the relationship between respiratory health risk and province may be related to other reasons apart from pollution and the environmental factors studied, such as variable access to health, different provincial health policies and resources, built environments, or improvements in public health interventions such as smoking cessation.

Smoking is a significant risk factor for respiratory diseases. In this study, current smoking was significantly associated with ACO and COPD among both females and males. However, current smoking was not associated with asthma. There was no significant association between ACO and being a former smoker in this study. This contrasts with findings from other studies, which found that both current and former smoking was associated with ACO (de Marco et al., 2013; Senthilselvan & Beach, 2018). However, this study does agree with de Marco et al. and Senthilselvan & Beach in finding that both current and former smoking were associated with COPD (de Marco et al., 2013; Senthilselvan & Beach, 2018). This finding was consistent across sexes. Furthermore, we observed that more females with ACO or COPD reported being never smokers than males with ACO or COPD. A systematic review and meta-analysis on the published literature on ACO found that subjects with ACO had less smoking history than patients with COPD (Alshabanat et al., 2015).

The distribution of comorbidities in the female population found that depression was the most commonly reported comorbidity, followed by underactive thyroid disease, diabetes, cancer, and osteoporosis, heart disease, and stroke. For males in our study population, diabetes was the most commonly reported comorbidity, followed by depression, cancer and heart disease, underactive thyroid disease, osteoporosis, and stroke. The apparent disparities between the sexes for osteoporosis (12.3% females vs. 1.9% males), hypothyroidism (18.5% females vs. 5.4% males), heart disease (6.7% females vs. 11.2% males), and depression (20.7% females vs. 12.2% males) are notable. Several studies have reported a high number of comorbidities among patients with ACO than patients with COPD (Alshabanat et al., 2015; Kumbhare et al., 2016; Senthilselvan & Beach, 2018) or asthma alone (Tommola et al., 2017). This study agrees with these findings from other studies and also observed that participants with ACO or COPD were more likely to report having a comorbidity than those with asthma only or no respiratory disease, irrespective of sex. The largest proportion of comorbidities was found in the ACO group, followed by the COPD group. Females with COPD were more likely to report having depression, while for males with COPD, diabetes was the most common comorbidity reported. Previous research on COPD also observed a greater prevalence of depression for females with COPD than males (Han et al., 2007). Unlike the COPD group, depression was the most common comorbidity reported by both females and males with ACO. A higher proportion of depression was reported by females with ACO than males with ACO. The finding that females with ACO are more likely to report depression than males is compatible with other studies in the literature (Dal Negro et al., 2015; Kang et al., 2019; Nicolini et al., 2018; Wheaton et al., 2018).

Following depression, the next most common comorbidity reported by females with ACO was underactive thyroid disease, while males were more likely to report having diabetes. To the best

of our knowledge, this is the only study to look at underactive thyroid disease (also known as hypothyroidism) and ACO in this population. Hypothyroidism was significantly associated with ACO for both males and females however it was not associated with COPD. When the distribution of comorbidities was compared between the ACO group and COPD group, apart from hypothyroidism in females, the distribution of all other comorbidities was similar between the two disease groups. In other words, the only significant difference in the distribution of comorbidities between the COPD group and ACO group was observed for hypothyroidism among females. Although more males with ACO reported hypothyroidism than males with COPD, the difference in the distribution between the two respiratory groups was not statistically significant. In addition, hypothyroidism among male and female participants with COPD was not significantly different from the expected distribution in the control group and the asthma group. This is the only comorbidity in the COPD group to demonstrate this finding. All other comorbidities studied were significantly different than distributions in the control group in particular. Based on the baseline distribution of the overall study population, 18.5% of females reported having underactive thyroid disease, while 5.36% of males reported this. In short, participants with ACO are more likely to have hypothyroidism, and the proportion is higher among females. This finding supports the hypothesis that hormones may play a key role in ACO development and differentiation of ACO and COPD (Han et al., 2007; Postma, 2007; Shah & Newcomb, 2018; Townsend et al., 2012). It may also potentially help explain the female predominance and disparities we see in ACO prevalence.

Perceived general self-rated health was assessed in this study. Statistically significant differences between the respiratory groups studied and general self-rated health for males and females were observed. Participants who reported their health as “poor” were more likely to have ACO. More

males than females with ACO or COPD reported their self-rated health as “poor”. Male and female participants with ACO were less likely than other groups to report their health as “Very good/Excellent”. This is consistent with Senthilselvan & Beach finding that subjects reporting poor health were highest among participants with ACO, followed by participants with COPD (Senthilselvan & Beach, 2018).

After adjusting for smoking and age, the ACO group had the highest proportion of subjects reporting respiratory symptoms, which was consistent for males and females. This finding is supported by other population studies (de Marco et al., 2013; Menezes et al., 2014; Miravitlles et al., 2013; Senthilselvan & Beach, 2018; Sin, 2017) and two systematic reviews of the literature on ACO (Alshabanat et al., 2015; Nielsen et al., 2015). This current study found that wheezing in the last 12 months was the most common respiratory symptom reported, followed by regular cough and shortness of breath walking on flat surfaces. Henriksen et al. (2018) reported that wheezing attacks were the most frequently reported symptom in the ACO, COPD-only, and asthma-only group. Senthilselvan & Beach found that most subjects reporting wheeze were in the ACO group, while most subjects reporting shortness of breath were in the COPD group. In this study, both wheeze and shortness of breath were more frequently reported by subjects with ACO than subjects with COPD. Sex-specific differences in the proportions of respiratory symptoms reported were observed. Among participants with ACO, the proportion of females reporting symptoms of wheeze or dyspnea was greater than reported by males, while the proportion of subjects with ACO reporting regular cough and coughing with phlegm symptoms was higher in males than females. In subjects with COPD, more males reported symptoms of wheeze, shortness of breath while walking, coughing and coughing with phlegm than females.

Based on lung obstruction measures, the highest proportion of participants that met the lower limit of normal criteria (LLN 1 and LLN 2) were in the ACO group, irrespective of sex. Similarly, the highest proportion of participants experiencing lung obstruction according to the GOLD criteria was from the ACO and COPD groups. Patients with ACO have an increased risk of FEV_1 decline (Sin, 2017). This is observed in the current study, whereby the mean FEV_1, FVC, and FEV_1/FVC percent-predicted values were lowest for participants reporting an ACO diagnosis for both males and females. Males with ACO and COPD had more severe airflow obstruction than females. Using the chronic airflow algorithm (CAO) validated by the CLSA, this study observed a greater proportion of airflow obstruction in the ACO group than the COPD-only or asthma-only group. This is congruent with many studies in the literature that found that patients with ACO experience greater obstruction and severity of symptoms. In terms of sex-specific differences, males with ACO or COPD were more likely to report severe stages of lung obstruction than females. Notably, a significant proportion of females and males in the ACO and COPD group did not exhibit evidence of airway limitation as determined by the modified-GOLD criteria using pre-bronchodilator lung function measurements. In this study, less than 30% of females and 33% of males in the COPD group have COPD as defined by the modified GOLD criteria. This finding is similar to the results reported by Senthilselvan & Beach, which found that less than 50% of their study population in the COPD group had modified-GOLD-defined COPD (Senthilselvan & Beach, 2018). It is possible for significant airflow limitation to occur without the presence of chronic dyspnea, cough and sputum production, and for respiratory symptoms to occur without the presence of airflow limitation (Global Initiative for Chronic Obstructive Lung Disease, 2020).

Our study found no statistically significant association between environmental exposure and respiratory outcomes among females. A Canadian study on ACO among females also reported no association between fine particulate matter, an important air pollutant, and ACO (To et al., 2018). It has been proposed in the literature that women are more likely to spend more time indoors for cooking and subsequently at greater risk of exposure to biomass fuels than men (Nicolini et al., 2018), as such, they may have a greater susceptibility to the harmful effects of air pollution (Cadeddu et al., 2016). However, we did not observe this in our study population for females. Alternatively, this study did find an association with males, specifically regarding exposure to NO_2 and increased asthma risk.

5.3 Strengths and Limitations

A number of significant findings have been elucidated through this research. To our knowledge, this is the first study looking at sex-specific differences for ACO in the general Canadian adult population. Similar studies include sex-specific differences in ACO, COPD, and asthma in a U.S. adult population (Wheaton et al., 2018), and a Canadian study focused on sex-specific differences in risk factors for ACO among Indigenous Peoples (Koleade et al., 2019). A major strength of this study was the use of the CLSA dataset. This dataset has a large sample size, detailed participant-level risk factor data, and physical measurements such as spirometry estimates. The large sample size improves the generalizability of our results to the Canadian adult population. One of the limitations of this study is the nature of a cross-sectional study design whereby causality between respiratory diseases and risk factors cannot be confirmed. Although we analyzed the baseline data of the CLSA dataset, the CLSA is a prospective cohort study, therefore future studies may be able to expand on the findings elucidated by this analysis.

Another limitation was that the history of asthma, COPD, and ACO was determined from a self-report of a physician diagnosis. Self-reported asthma has acceptable validity, however, self-reported COPD has been shown to have low sensitivity and high specificity (Murgia et al., 2014; A. Senthilselvan et al., 1993). The self-report diagnosis was not independently validated, and therefore misclassification is possible. However, there was a significant association between the prevalence of ACO, COPD, and asthma and airway obstruction determined using lung function measurements. Participant data were also collected by self-report and may be subjected to response or recall bias. Furthermore, post-bronchodilator spirometry values were not available, therefore overestimation of airflow obstruction severity cannot be ruled out.

5.4 Conclusion

This thesis discusses important differences between males and females on social, physical, and environmental risk factors for asthma, COPD, and asthma-COPD overlap (ACO). In the Canadian adult population studied, the prevalence of asthma, COPD, and ACO was greater among females than males. Risk factors significant for both males and females include Aboriginal ethnicity, smoking, and less education. However, this study observed some risk factors that were associated with females or males only. Marital status, province, age, and obesity were associated with asthma, COPD, or ACO among females but not males. While for males, unemployment was a significant factor for obstructive lung disease, which was not significant in females. We also observed that males with ACO and COPD had more severe lung obstruction than females. The most frequently reported comorbidity among participants with ACO, irrespective of sex, was depression. To the best of our knowledge, this is the first study to look at sex-specific differences regarding hypothyroidism (also referred to as underactive thyroid

disease) and ACO. Participants with ACO are more likely to have hypothyroidism, and the proportion is higher among females. Hypothyroidism was not significant for males or females with COPD. Taken together, this supports the observation that hormones may be implicated in ACO development and may play a role in differentiating ACO and COPD patients. It may also potentially help explain the female predominance and disparities we see in ACO prevalence. Participants who rated their general health as "poor" were more likely to have ACO or COPD. More males with ACO or COPD reported their health as being "poor" than females with these diseases. Participants with ACO or COPD also experienced more respiratory symptoms than subjects with asthma or no respiratory disease. Males with ACO were likely to report having more coughing and coughing with phlegm symptoms than females, and females with ACO were more likely than males to report shortness of breath and wheeze. Environmental exposures to sulphur dioxide, fine particulate matter, ozone, or nitrogen dioxide were not associated with respiratory diseases for females. However, for males, asthma was associated with nitrogen dioxide exposure. Asthma, COPD, and ACO pose a substantial economic burden and necessitate a large allocation of healthcare resources to manage. This current study helps identify and contextualize sex-specific differences in prevalence and associated risk factors for ACO, COPD, and asthma in the Canadian adult population. Understanding sex-specific differences provide helpful information regarding the influence of sex and gender on disease prevalence, comorbidities, respiratory symptoms, lung obstruction, and other social, behavioural, and physical factors. The findings identified in this study may be used to support future research and public health programs aimed at addressing the disproportionate burden of ACO and COPD mortality and morbidity among females in Canada. Early identification of disease prompts earlier

management of symptoms. This will improve overall health outcomes, mitigate the risk for severe disease, and help reduce the burden of COPD, asthma, and ACO in Canada.

References:

1. Alshabanat, A., Zafari, Z., Albanyan, O., Dairi, M., & Fitzgerald, J. M. (2015). Asthma and COPD overlap syndrome (ACOS): A systematic review and meta-analysis. *PLoS ONE*, *10*(9), 1–15. https://doi.org/10.1371/journal.pone.0136065

2. Cadeddu, C., Capizzi, S., Colombo, D., Nica, M., & De Belvis, A. G. (2016). Literature review of gender differences in respiratory conditions: a focus on asthma and Chronic Obstructive Pulmonary Disease (COPD). *Igiene e Sanita Pubblica*, *72*(5), 481–504.

3. Dai, S., Bancej, C., Loukine, L., Waters, C., & Baclic, O. (2018). Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Canada, 2018. *Report from the Canadian chronic disease surveillance system*, *31(1).*

4. Dal Negro, R. W., Bonadiman, L., & Turco, P. (2015). Prevalence of different comorbidities in COPD patients by gender and GOLD stage. *Multidisciplinary Respiratory Medicine*, *10*(1), 1–9. https://doi.org/10.1186/s40248-015-0023-2

5. de Marco, R., Pesce, G., Marcon, A., Accordini, S., Antonicelli, L., Bugiani, M., Casali, L., Ferrari, M., Nicolini, G., Panico, M. G., Pirina, P., Zanolin, M. E., Cerveri, I., & Verlato, G. (2013). The Coexistence of Asthma and Chronic Obstructive Pulmonary Disease (COPD): Prevalence and Risk Factors in Young, Middle-aged and Elderly People from the General Population. *PLoS ONE*, *8*(5), 1–7. https://doi.org/10.1371/journal.pone.0062985

6. Dogra, S., Good, J., Buman, M. P., Gardiner, P. A., Copeland, J. L., & Stickland, M. K. (2018). Physical activity and sedentary time are related to clinically relevant health outcomes among adults with obstructive lung disease. *BMC Pulmonary Medicine*, *18*(1), 1–13. https://doi.org/10.1186/s12890-018-0659-8

7. Ekerljung, L., Mincheva, R., Hagstad, S., Bjerg, A., Telg, G., Stratelis, G., & Lötvall, J.

(2018). Prevalence, clinical characteristics and morbidity of the Asthma-COPD overlap in a general population sample. *Journal of Asthma*, *55*(5), 461–469. https://doi.org/10.1080/02770903.2017.1339799

8. Franssen, F. M. E., O'Donnell, D. E., Goossens, G. H., Blaak, E. E., & Schols, A. M. W. J. (2008). Obesity and the lung: Obesity and COPD. *Thorax*, *63*(12), 1110–1117. https://doi.org/10.1136/thx.2007.086827
9. Freitas, P. D., Ferreira, P. G., Silva, A. G., Stelmach, R., Carvalho-Pinto, R. M., Fernandes, F. L. A., Mancini, M. C., Sato, M. N., Martins, M. A., & Carvalho, C. R. F. (2017). The role of exercise in a weight-loss program on clinical control in obese adults with Asthma: A randomized controlled trial. *American Journal of Respiratory and Critical Care Medicine*, *195*(1), 32–42. https://doi.org/10.1164/rccm.201603-0446OC
10. Fuller-Thomson, E., Howden, K. E. N., Fuller-Thomson, L. R., & Agbeyaka, S. (2018). A Strong Graded Relationship between Level of Obesity and COPD: Findings from a National Population-Based Study of Lifelong Nonsmokers. *Journal of Obesity*, *2018*. https://doi.org/10.1155/2018/6149263
11. Gershon, A. S., Wang, C., Wilton, A. S., Raut, R., & To, T. (2010). Trends in chronic obstructive pulmonary disease prevalence, incidence, and mortality in Ontario, Canada, 1996 to 2007: A population-based study. *Archives of Internal Medicine*, *170*(6), 560–565. https://doi.org/10.1001/archinternmed.2010.17
12. Global Initiative for Asthma. (2020). Global strategy for asthma management and prevention: Socioeconomics. *Global Initiative for Asthma*, *36*(6), 685–704. https://doi.org/10.1016/S0335-7457(96)80056-6
13. Global Initiative for Chronic Obstructive Lung Disease (2020). GOLD 2020 Report. *Global*

Initiative for Chronic Obstructive Lung Disease.

14. Guerra, S., Sherrill, D. L., Bobadilla, A., Martinez, F. D., & Barbee, R. A. (2002). The Relation of Body Mass Index to Asthma, Chronic Bronchitis, and Emphysema. *Chest, 122*(4), 1256-1263.

15. Han, M. L. K., Postma, D., Mannino, D. M., Giardino, N. D., Buist, S., Curtis, J. L., & Martinez, F. J. (2007). Gender and chronic obstructive pulmonary disease: Why it matters. *American Journal of Respiratory and Critical Care Medicine*, *176*(12), 1179–1184. https://doi.org/10.1164/rccm.200704-553CC

16. Kang, H. R., Hong, S. H., Ha, S. Y., Kim, T. B., & Lee, E. K. (2019). Differences in the risk of mood disorders in patients with asthma-COPD overlap and in patients with COPD alone: A nationwide population-based retrospective cohort study in Korea. *Respiratory Research*, *20*(1), 1–13. https://doi.org/10.1186/s12931-019-1039-5

17. Kauppi, P., Kupiainen, H., Lindqvist, A., Tammilehto, L., Kilpeläinen, M., Kinnula, V. L., Haahtela, T., & Laitinen, T. (2011). Overlap syndrome of asthma and COPD predicts low quality of life. *Journal of Asthma*, *48*(3), 279–285. https://doi.org/10.3109/02770903.2011.555576

18. Kim, M., Tillis, W., Patel, P., Davis, R. M., & Asche, C. V. (2019). Association between asthma/chronic obstructive pulmonary disease overlap syndrome and healthcare utilization among the U.S. adult population. *Current Medical Research and Opinion*, *35*(7), 1191–1196. https://doi.org/10.1080/03007995.2019.1565531

19. Koleade, A., Farrell, J., Mugford, G., & Gao, Z. (2019). Female-specific risk factors associated with risk of ACO (asthma COPD overlap) in aboriginal people. *Journal of Asthma*, *57*(9), 1–8. https://doi.org/10.1080/02770903.2019.1621890

20. Kumbhare, S., Pleasants, R., Ohar, J. A., & Strange, C. (2016). Characteristics and prevalence of asthma/chronic obstructive pulmonary disease overlap in the United States. *Annals of the American Thoracic Society*, *13*(6), 803–810. https://doi.org/10.1513/AnnalsATS.201508-554OC

21. Lambert, A. A., Putcha, N., Drummond, M. B., Boriek, A. M., Hanania, N. A., Kim, V., Kinney, G. L., McDonald, M. L. N., Brigham, E. P., Wise, R. A., McCormack, M. C., & Hansel, N. N. (2017). Obesity Is Associated With Increased Morbidity in Moderate to Severe COPD. *Chest*, *151*(1), 68–77. https://doi.org/10.1016/j.chest.2016.08.1432

22. Menezes, A. M. B., De Oca, M. M., Pérez-Padilla, R., Nadeau, G., Wehrmeister, F. C., Lopez-Varela, M. V., Muiño, A., Jardim, J. R. B., Valdivia, G., & Tálamo, C. (2014). Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype : COPD-Asthma. *Chest*, *145*(2), 297–304. https://doi.org/10.1378/chest.13-0622

23. Miravitlles, M., Soriano, J. B., Ancochea, J., Muñoz, L., Duran-Tauleria, E., Sánchez, G., Sobradillo, V., & García-Río, F. (2013). Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. *Respiratory Medicine*, *107*(7), 1053–1060. https://doi.org/10.1016/j.rmed.2013.03.007

24. Murgia, N., Brisman, J., Claesson, A., Muzi, G., Olin, A. C., & Torén, K. (2014). Validity of a questionnaire-based diagnosis of chronic obstructive pulmonary disease in a general population-based study. *BMC Pulmonary Medicine*, *14*(1), 1–7. https://doi.org/10.1186/1471-2466-14-49

25. Nicolini, A., Barbagelata, E., Tagliabue, E., Colombo, D., Monacelli, F., & Braido, F. (2018). Gender differences in chronic obstructive pulmonary diseases: A narrative review. *Panminerva Medica*, *60*(4), 192–199. https://doi.org/10.23736/S0031-0808.18.03463-8

26. Nielsen, M., Bårnes, C. B., & Ulrik, C. S. (2015). Clinical characteristics of the asthma–COPD overlap syndrome – A systematic review. *International Journal of COPD*, *10*(1), 1443–1454. https://doi.org/10.2147/COPD.S85363

27. Noda, T., Ojima, T., Hayasaka, S., Hagihara, A., Takayanagi, R., & Nobutomo, K. (2009). The health impact of remarriage behavior on chronic obstructive pulmonary disease: Findings from the U.S. longitudinal survey. *BMC Public Health*, *9*, 1–6. https://doi.org/10.1186/1471-2458-9-412

28. Ospina, M. B., Voaklander, D. C., Stickland, M. K., King, M., Senthilselvan, A., & Rowe, B. H. (2012). Prevalence of asthma and chronic obstructive pulmonary disease in Aboriginal and non-Aboriginal populations: A systematic review and meta-analysis of epidemiological studies. *Canadian Respiratory Journal*, *19*(6), 355–360. https://doi.org/10.1155/2012/825107

29. Peters, U., Dixon, A., & Forno, E. (2018). Obesity and Asthma. *Physiology & Behavior*, *176*(5), 139–148. https://doi.org/10.1016/j.jaci.2018.02.004

30. Pitta, F., Troosters, T., Spruit, M. A., Probst, V. S., Decramer, M., & Gosselink, R. (2005). Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, *171*(9), 972–977. https://doi.org/10.1164/rccm.200407-855OC

31. Postma, D. S. (2007). Gender Differences in Asthma Development and Progression. *Gender Medicine*, *4*(Suppl. 2), 133–146. https://doi.org/10.1016/S1550-8579(07)80054-4

32. Senthilselvan, A., Dosman, J. A., & Chen, Y. (1993). Relationship between pulmonary test variables and asthma and wheezing: A validation of self-report of asthma. *Journal of Asthma*, *30*(3), 185–193. https://doi.org/10.3109/02770909309054516

33. Senthilselvan, A., & Beach, J. (2018). Characteristics of asthma and COPD overlap syndrome (ACOS) in the Canadian population. *Journal of Asthma*, *56*(11), 1129–1137. https://doi.org/10.1080/02770903.2018.1531997

34. Shah, R., & Newcomb, D. C. (2018). Sex Bias in Asthma Prevalence and Pathogenesis. *Frontiers in Immunology*, *9*(12), 2997. https://doi.org/10.3389/fimmu.2018.02997

35. Sin, D. D. (2017). Asthma-COPD overlap syndrome: What we know and what we don't. *Tuberculosis and Respiratory Diseases*, *80*(1), 11–20. https://doi.org/10.4046/trd.2017.80.1.11

36. Sin, D. D., Miravitlles, M., Mannino, D. M., Soriano, J. B., Price, D., Celli, B. R., Leung, J. M., Nakano, Y., Park, H. Y., Wark, P. A., & Wechsler, M. E. (2016). What is asthma COPD overlap syndrome? Towards a consensus definition from a round table discussion. *European Respiratory Journal*, *48*(3), 664–673. https://doi.org/10.1183/13993003.00436-2016

37. Sood, A. (2011). Sex differences: Implications for the obesity-asthma association. *Exercise and Sport Sciences Reviews*, *39*(1), 48–56. https://doi.org/10.1097/JES.0b013e318201f0c4

38. To, T., Zhu, J., Gray, N., Feldman, L. Y., Villeneuve, P. J., Licskai, C., Gershon, A., & Miller, A. B. (2018). Asthma and chronic obstructive pulmonary disease overlap in women incidence and risk factors. *Annals of the American Thoracic Society*, *15*(11), 1304–1310. https://doi.org/10.1513/AnnalsATS.201802-078OC

39. Tommola, M., Ilmarinen, P., Tuomisto, L. E., Lehtimäki, L., Haanpää, J., Niemelä, O., & Kankaanranta, H. (2017). Differences between asthma - COPD overlap syndrome and adult-onset asthma. *European Respiratory Journal*, *49*(5), 1–10. https://doi.org/10.1183/13993003.02383-2016

40. Townsend, E. A., Miller, V. M., & Prakash, Y. S. (2012). Sex differences and sex steroids in lung health and disease. *Endocrine Reviews*, *33*(1). https://doi.org/10.1210/er.2010-0031

41. Wang, L., Wang, K., Gao, X., Paul, T. K., Cai, J., & Wang, Y. (2015). Sex difference in the association between obesity and asthma in U.S. adults: Findings from a national study. *Respiratory Medicine*, *109*(8), 955–962. https://doi.org/10.1016/j.rmed.2015.06.001

42. Wheaton, A., Pleasants, R. A., Croft, J. B., Ohar, J. A., Heidari, K., Mannino, D. M., Liu, Y., & Strage, C. (2018). Gender and Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome. *Physiology & Behavior*, *176*(1), 139–148. https://doi.org/10.1016/j.physbeh.2017.03.040

Bibliography

Alshabanat, A., Zafari, Z., Albanyan, O., Dairi, M., & FitzGerald, J. M. (2015). Asthma and COPD overlap syndrome (ACOS): A systematic review and meta analysis. *PLoS ONE*, *10*(9), 1–15. https://doi.org/10.1371/journal.pone.0136065

Aryal, S., Diaz-Guzman, E., & Mannino, D. M. (2014). Influence of sex on chronic obstructive pulmonary disease risk and treatment outcomes. *International Journal of COPD*, *9*, 1145–1154. https://doi.org/10.2147/COPD.S54476

Banderali, G., Martelli, A., Landi, M., Moretti, F., Betti, F., Radaelli, G., Lassandro, C., & Verduci, E. (2015). Short and long term health effects of parental tobacco smoking during pregnancy and lactation: A descriptive review. *Journal of Translational Medicine*, *13*(1), 1–7. https://doi.org/10.1186/s12967-015-0690-y

Barczyk, A., Maskey-Warzęchowska, M., Górska, K., Barczyk, M., Kuziemski, K., Śliwiński, P., Batura-Gabryel, H., Mróz, R., Kania, A., Obojski, A., Tażbirek, M., Celejewska-Wójcik, N., Guziejko, K., Brajer-Luftmann, B., Korzybski, D., Damps-Kostańska, I., & Krenke, R. (2019). Asthma-COPD Overlap—A Discordance Between Patient Populations Defined by Different Diagnostic Criteria. *Journal of Allergy and Clinical Immunology: In Practice*, *7*(7), 2326-2336. https://doi.org/10.1016/j.jaip.2019.04.022

Barnes, P. J., Burney, P. G. J., Silverman, E. K., Celli, B. R., Vestbo, J., Wedzicha, J. A., & Wouters, E. F. M. (2015). Chronic obstructive pulmonary disease. *Nature Reviews Disease Primers*, *1*(12), 1–22. https://doi.org/10.1038/nrdp.2015.76

Bischoff, E. W. M. A., Schermer, T. R. J., Bor, H., Brown, P., Van Weel, C., & Van Den Bosch, W. J. H. M. (2009). Trends in COPD prevalence and exacerbation rates in Dutch primary care. *British Journal of General Practice*, *59*(569), 927–933.

https://doi.org/10.3399/bjgp09X473079

Bloomfield, S. F., Rook, G. A. W., Scott, E. A., Shanahan, F., Stanwell-Smith, R., & Turner, P. (2016). Time to abandon the hygiene hypothesis: New perspectives on allergic disease, the human microbiome, infectious disease prevention and the role of targeted hygiene. *Perspectives in Public Health*, *136*(4), 213–224. https://doi.org/10.1177/1757913916650225

Bosonea, A. M., Sharpe, H., Wang, T., Bakal, J. A., Befus, A. D., Svenson, L. W., & Vliagoftis, H. (2020). Developments in asthma incidence and prevalence in Alberta between 1995 and 2015. *Allergy, Asthma and Clinical Immunology*, *16*(1), 1–11. https://doi.org/10.1186/s13223-020-00485-3

Bryan, S., & Navaneelan, T. (2015). Deaths from Chronic Obstructive Pulmonary Disease in Canada , 1950 to 2011. *Health at a Glance*, *82*, 1–8.

Buist, A. S., McBurnie, M. A., Vollmer, W. M., Gillespie, S., Burney, P., Mannino, D. M., Menezes, A. M., Sullivan, S. D., Lee, T. A., Weiss, K. B., Jensen, R. L., Marks, G. B., Gulsvik, A., & Nizankowska-Mogilnicka, E. (2007). International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study. *Lancet*, *370*(9589), 741–750. https://doi.org/10.1016/S0140-6736(07)61377-4

Cadeddu, C., Capizzi, S., Colombo, D., Nica, M., & De Belvis, A. G. (2016). Literature review of gender differences in respiratory conditions: a focus on asthma and Chronic Obstructive Pulmonary Disease (COPD). *Igiene e Sanita Pubblica*, *72*(5), 481–504.

Canadian Institutes of Health Research. (2020). What is gender? What is sex? Retrieved online July 3, 2020. https://cihr-irsc.gc.ca/e/48642.html

Canadian Urban Environmental Health Research Consortium. (2018). CIHR Operating Grant for

CANUE Data: Webinar. Retrieved from https://canue.ca/cihr-operating-grant-for-canue-data-webinar/

Chambliss, J. M., Sur, S., & Tripple, J. W. (2018). Asthma versus chronic obstructive pulmonary disease, the Dutch versus British hypothesis, and role of interleukin-5. *Current Opinion in Allergy and Clinical Immunology*, *18*(1), 26–31. https://doi.org/10.1097/ACI.0000000000000409

Chung, J. W., Kong, K. A., Lee, J. H., Lee, S. J., Ryu, Y. J., & Chang, J. H. (2014). Characteristics and self-rated health of overlap syndrome. *International Journal of COPD*, *9*, 795–804. https://doi.org/10.2147/COPD.S61093

Chung, W. S., Lin, C. L., & Kao, C. H. (2015). Comparison of acute respiratory events between: Asthma-COPD overlap syndrome and COPD patients. *Medicine (United States)*, *94*(17), e755. https://doi.org/10.1097/MD.0000000000000755

Col, L., & Freiler, J. F. (2015). The Asthma-COPD Overlap Syndrome. *Federal Practitioner*, *32*(Suppl. 10), 19–23.

Coates, AL., Wong, SL., Tremblay, C., & Hankinson, JL. (2015). Reference Equations for Spirometry in the Canadian Population. *Annals of the American Thoracic Society,* 13(6):833-841.

Comberiati, P., Di Cicco, M. E., D'Elios, S., & Peroni, D. G. (2017). How much asthma is atopic in children? *Frontiers in Pediatrics*, *5*(5), 5–8. https://doi.org/10.3389/fped.2017.00122

Dai, S., Bancej, C., Loukine, L., Waters, C., & Baclic, O. (2018). Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Canada, 2018. *Report from the Canadian chronic disease surveillance system*, *31(1).*

Dal Negro, R. W., Bonadiman, L., & Turco, P. (2015). Prevalence of different comorbidities in

COPD patients by gender and GOLD stage. *Multidisciplinary Respiratory Medicine*, *10*(1), 1–9. https://doi.org/10.1186/s40248-015-0023-2

de Marco, R., Pesce, G., Marcon, A., Accordini, S., Antonicelli, L., Bugiani, M., Casali, L., Ferrari, M., Nicolini, G., Panico, M. G., Pirina, P., Zanolin, M. E., Cerveri, I., & Verlato, G. (2013). The Coexistence of Asthma and Chronic Obstructive Pulmonary Disease (COPD): Prevalence and Risk Factors in Young, Middle-aged and Elderly People from the General Population. *PLoS ONE*, *8*(5), 1–7. https://doi.org/10.1371/journal.pone.0062985

Dogra, S., Good, J., Buman, M. P., Gardiner, P. A., Copeland, J. L., & Stickland, M. K. (2018). Physical activity and sedentary time are related to clinically relevant health outcomes among adults with obstructive lung disease. *BMC Pulmonary Medicine*, *18*(1), 1–13. https://doi.org/10.1186/s12890-018-0659-8

Dransfield, M. T., Davis, J. J., Gerald, L. B., & Bailey, W. C. (2006). Racial and gender differences in susceptibility to tobacco smoke among patients with chronic obstructive pulmonary disease. *Respiratory Medicine*, *100*(6), 1110–1116. https://doi.org/10.1016/j.rmed.2005.09.019

Ekerljung, L., Mincheva, R., Hagstad, S., Bjerg, A., Telg, G., Stratelis, G., & Lötvall, J. (2018). Prevalence, clinical characteristics and morbidity of the Asthma-COPD overlap in a general population sample. *Journal of Asthma*, *55*(5), 461–469. https://doi.org/10.1080/02770903.2017.1339799

Eva Prescott, J. V. (1999). Socioeconomic status and chronic obstructive pulmonary disease. *TAF Preventive Medicine Bulletin*, *12*(1), 87–96. https://doi.org/10.5455/pmb.1-1331198324

Franssen, F. M. E., O'Donnell, D. E., Goossens, G. H., Blaak, E. E., & Schols, A. M. W. J.

(2008). Obesity and the lung: Obesity and COPD. *Thorax*, *63*(12), 1110–1117. https://doi.org/10.1136/thx.2007.086827

Freitas, P. D., Ferreira, P. G., Silva, A. G., Stelmach, R., Carvalho-Pinto, R. M., Fernandes, F. L. A., Mancini, M. C., Sato, M. N., Martins, M. A., & Carvalho, C. R. F. (2017). The role of exercise in a weight-loss program on clinical control in obese adults with Asthma: A randomized controlled trial. *American Journal of Respiratory and Critical Care Medicine*, *195*(1), 32–42. https://doi.org/10.1164/rccm.201603-0446OC

Fuller-Thomson, E., Howden, K. E. N., Fuller-Thomson, L. R., & Agbeyaka, S. (2018). A Strong Graded Relationship between Level of Obesity and COPD: Findings from a National Population-Based Study of Lifelong Nonsmokers. *Journal of Obesity*, *2018*. https://doi.org/10.1155/2018/6149263

Fuseini, H., & Newcomb, D. C. (2017). Mechanisms driving gender differences in asthma. *Physiology & Behavior*, *17*(13), 100–106. https://doi.org/10.1007/s11882-017-0686-1

Gerhardsson De Verdier, M., Andersson, M., Kern, D. M., Zhou, S., & Tunceli, O. (2015). Asthma and Chronic Obstructive Pulmonary Disease Overlap Syndrome: Doubled Costs Compared with Patients with Asthma Alone. *Value in Health*, *18*(6), 759–766. https://doi.org/10.1016/j.jval.2015.04.010

Gershon, A. S., Wang, C., Wilton, A. S., Raut, R., & To, T. (2010). Trends in chronic obstructive pulmonary disease prevalence, incidence, and mortality in Ontario, Canada, 1996 to 2007: A population-based study. *Archives of Internal Medicine*, *170*(6), 560–565. https://doi.org/10.1001/archinternmed.2010.17

Global Initiative for Asthma. (2020). Global strategy for asthma management and prevention: Socioeconomics. *Global Initiative for Asthma*, *36*(6), 685–704.

https://doi.org/10.1016/S0335-7457(96)80056-6

Global Initiative for Asthma. (2019). *Global Strategy for Asthma Management and Prevention*. Retrieved from www.ginasthma.org

Global Initiative for Asthma. (2017). *Diagnosis and initial treatment of asthma, COPD, and asthma - COPD overlap : A joint project of GINA and GOLD updated April 2017*. *April*. https://ginasthma.org/wp-content/uploads/2019/11/GINA-GOLD-2017-overlap-pocket-guide-wms-2017-ACO.pdf

Global Initiative for Chronic Obstructive Lung Disease (2020). GOLD 2020 Report. *Global Initiative for Chronic Obstructive Lung Disease*.

Global Initiative for Chronic Obstructive Lung Disease. (2017) Pocket Guide to COPD Diagnosis, Management, and Prevention. Online. Retrieved from https://bit.ly/3sOwqiY

Guerra, S., Sherrill, D. L., Bobadilla, A., Martinez, F. D., & Barbee, R. A. (2002). The Relation of Body Mass Index to Asthma, Chronic Bronchitis, and Emphysema. *Chest, 122*(4), 1256-1263.

Gut-Gobert, C., Cavaillès, A., Dixmier, A., Guillot, S., Jouneau, S., Leroyer, C., Marchand-Adam, S., Marquette, D., Meurice, J. C., Desvigne, N., Morel, H., Person-Tacnet, C., & Raherison, C. (2019). Women and COPD: Do we need more evidence? *European Respiratory Review*, *28*(151). https://doi.org/10.1183/16000617.0055-2018

Haghighi, A., Cone, J. E., Li, J., & de la Hoz, R. E. (2020). Asthma-COPD overlap in World Trade Center Health Registry enrollees, 2015–2016. *Journal of Asthma*, 2015–2016. https://doi.org/10.1080/02770903.2020.1817935

Han, M. L. K., Postma, D., Mannino, D. M., Giardino, N. D., Buist, S., Curtis, J. L., & Martinez, F. J. (2007). Gender and chronic obstructive pulmonary disease: Why it matters. *American*

Journal of Respiratory and Critical Care Medicine, *176*(12), 1179–1184. https://doi.org/10.1164/rccm.200704-553CC

Hardin, M., Cho, M., McDonald, M.-L., Beaty, T., Ramsdell, J., Bhatt, S. P., van Beek, E. J. R., Make, B. J., Crapo, J. D., Silverman, E. K., & Hersh, C. P. (2014). The clinical and genetic features of the COPD asthma overlap syndrome. *European Respiratory Journal*, *44*(2), 341–350. https://doi.org/10.1183/09031936.00216013.

Hardin, M., Silverman, E. K., Barr, R. G., Hansel, N. N., Schroeder, J. D., Make, B. J., Crapo, J. D., & Hersh, C. P. (2011). The clinical features of the overlap between COPD and asthma for the COPDGene Investigators. *Respiratory Research*, *12*(127), 1–8. https://respiratory-research.biomedcentral.com/track/pdf/10.1186/1465-9921-12-127?site=respiratory-research.biomedcentral.com

Hardin, M., Silverman, E. K., Barr, R. G., Hansel, N. N., Schroeder, J. D., Make, B. J., Crapo, J. D., Hersh, C. P., Curtis, J., Kazerooni, E., Hanania, N., Alapat, P., Bandi, V., Guntupalli, K., Guy, E., Mallampalli, A., Trinh, C., Atik, M., DeMeo, D., Allen, A. (2011). The clinical features of the overlap between COPD and asthma. *Respiratory Research*, *12*(1), 127. https://doi.org/10.1186/1465-9921-12-127

Harris, R. E. (2019). *Epidemiology of Chronic Disease*. Jones & Bartlett Learning.

Hayden, L. P., Cho, M. H., Raby, B. A., Beaty, T. H., Silverman, E. K., & Hersh, C. P. (2018). Childhood asthma is associated with COPD and known asthma variants in COPDGene: A genome-wide association study. *Respiratory Research*, *19*(1), 1–11. https://doi.org/10.1186/s12931-018-0890-0

Hankinson JL, Odencrantz JR, & Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159(1):179-187.

Henriksen, A. H., Langhammer, A., Steinshamn, S., Mai, X. M., & Brumpton, B. M. (2018a). The Prevalence and Symptom Profile of Asthma–COPD Overlap: The HUNT Study. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, *15*(1), 27–35. https://doi.org/10.1080/15412555.2017.1408580

Henriksen, A. H., Langhammer, A., Steinshamn, S., Mai, X. M., & Brumpton, B. M. (2018b). The Prevalence and Symptom Profile of Asthma–COPD Overlap: The HUNT Study. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, *15*(1), 27–35. https://doi.org/10.1080/15412555.2017.1408580

Hines, K. L., & Peebles, R. S. (2017). Management of the Asthma-COPD Overlap Syndrome (ACOS): a Review of the Evidence. *Current Allergy and Asthma Reports*, *17*(3), 4–9. https://doi.org/10.1007/s11882-017-0683-4

Holgate, S. T., Wenzel, S., Postma, D. S., Weiss, S. T., Renz, H., & Sly, P. D. (2015). Asthma. *Nature Reviews Disease Primers*, *1*(9), 1–22. https://doi.org/10.1038/nrdp.2015.25

Hosseini, M., Almasi-Hashiani, A., Sepidarkish, M., & Maroufizadeh, S. (2019). Global prevalence of asthma-COPD overlap (ACO) in the general population: A systematic review and meta-analysis. *Respiratory Research*, *20*(1), 4–13. https://doi.org/10.1186/s12931-019-1198-4

Hystad P, Setton E, Cervantes A, Poplawski K, Deschenes S, Brauer M, van Donkelaar A, Lamsal L, Martin R, & Jerrett M, Demers P. (2011). Creating national air pollution models for population exposure assessment in Canada. *Environmental Health Perspectives*, 119(8), 1123-1129. https://doi.org/10.1289/ehp.1002976.

Institute of Health Metrics and Evaluation. (2020a). Asthma. *The Lancet*, *396*, 108–109.

Institute of Health Metrics and Evaluation. (2020b). Global burden of disease 2019-Chronic

obstructive pulmonary disease. *The Lancet*, *396*, S106–S107. https://www.thelancet.com/pb-assets/Lancet/gbd/summaries/diseases/copd.pdf

Izbicki, G., Teo, V., Liang, J., Russell, G. M., Holland, A. E., Zwar, N. A., Bonevski, B., Mahal, A., Eustace, P., Paul, E., Phillips, K., Wilson, S., George, J., & Abramson, M. J. (2019). Clinical characteristics of patients with asthma COPD overlap (ACO) in Australian primary care. *International Journal of COPD*, *14*, 2745–2752. https://doi.org/10.2147/COPD.S220346

Kanervisto, M., Vasankari, T., Laitinen, T., Heliövaara, M., Jousilahti, P., & Saarelainen, S. (2011). Low socioeconomic status is associated with chronic obstructive airway diseases. *Respiratory Medicine*, *105*(8), 1140–1146. https://doi.org/10.1016/j.rmed.2011.03.008

Kang, H. R., Hong, S. H., Ha, S. Y., Kim, T. B., & Lee, E. K. (2019). Differences in the risk of mood disorders in patients with asthma-COPD overlap and in patients with COPD alone: A nationwide population-based retrospective cohort study in Korea. *Respiratory Research*, *20*(1), 1–13. https://doi.org/10.1186/s12931-019-1039-5

Kang, J., Yao, W., Cai, B., Chen, P., Ling, X., & Shang, H. (2016). Current situation of asthma-COPD overlap syndrome (ACOS) in chinese patients older than 40 years with airflow limitation: Rationale and design for a multicenter, cross-sectional trial (study protocol). *Journal of Thoracic Disease*, *8*(12), 3744–3751. https://doi.org/10.21037/jtd.2016.12.108

Kant, S. (2013). Socio-economic dynamics of asthma. *Indian Journal of Medical Research*, *138*(10), 446–448.

Kauppi, P., Kupiainen, H., Lindqvist, A., Tammilehto, L., Kilpeläinen, M., Kinnula, V. L., Haahtela, T., & Laitinen, T. (2011). Overlap syndrome of asthma and COPD predicts low quality of life. *Journal of Asthma*, *48*(3), 279–285.

https://doi.org/10.3109/02770903.2011.555576

Kim, M. A., Noh, C. S., Chang, Y. J., Hong, Y. K., Lee, J. S., Lee, S. W., Lee, S. D., & Oh, Y. M. (2015). Asthma and COPD overlap syndrome is associated with increased risk of hospitalization. *International Journal of Tuberculosis and Lung Disease*, *19*(7), 864–869. https://doi.org/10.5588/ijtld.14.0327

Kim, M., Tillis, W., Patel, P., Davis, R. M., & Asche, C. V. (2019). Association between asthma/chronic obstructive pulmonary disease overlap syndrome and healthcare utilization among the US adult population. *Current Medical Research and Opinion*, *35*(7), 1191–1196. https://doi.org/10.1080/03007995.2019.1565531

Koleade, A., Farrell, J., Mugford, G., & Gao, Z. (2019). Female-specific risk factors associated with risk of ACO (asthma COPD overlap) in aboriginal people. *Journal of Asthma*, *57*(9), 1–8. https://doi.org/10.1080/02770903.2019.1621890

Kumbhare, S., Pleasants, R., Ohar, J. A., & Strange, C. (2016). Characteristics and prevalence of asthma/chronic obstructive pulmonary disease overlap in the United States. *Annals of the American Thoracic Society*, *13*(6), 803–810. https://doi.org/10.1513/AnnalsATS.201508-554OC

Lambert, A. A., Putcha, N., Drummond, M. B., Boriek, A. M., Hanania, N. A., Kim, V., Kinney, G. L., McDonald, M. L. N., Brigham, E. P., Wise, R. A., McCormack, M. C., & Hansel, N. N. (2017). Obesity Is Associated With Increased Morbidity in Moderate to Severe COPD. *Chest*, *151*(1), 68–77. https://doi.org/10.1016/j.chest.2016.08.1432

Lee, H., Kim, S. H., Kim, B. K., Lee, Y., Lee, H. Y., Ban, G. Y., Kim, M. H., Kim, J. H., Kwon, J. W., Park, S. Y., Jung, J. W., Park, S. Y., Park, C. S., Rhee, C. K., Lee, T., Lee, J. H., Kim, S. R., Park, J. S., Park, H. W., Yoon, H. J. (2020). Characteristics of Specialist-

Diagnosed Asthma-COPD Overlap in Severe Asthma: Observations from the Korean Severe Asthma Registry (KoSAR). *Allergy: European Journal of Allergy and Clinical Immunology*, *March 2020*, 223–232. https://doi.org/10.1111/all.14483

Lee, Y. M., Lee, J. H., Kim, H. C., & Ha, E. (2020). Effects of PM10 on mortality in pure COPD and asthma-COPD overlap: difference in exposure duration, gender, and smoking status. *Scientific Reports*, *10*(1), 1–10. https://doi.org/10.1038/s41598-020-59246-2

Lomauro, A., & Aliverti, A. (2018). Sex differences in respiratory function. *Breathe*, *14*(2), 131–140. https://doi.org/10.1183/20734735.000318

Long, J.S., & Freese, J. (2014). *Regression Models for Categorical Dependent Variables Using Stata*. College Station, TX: Stata Press.

Lõpez-Campos, J. L., Tan, W., & Soriano, J. B. (2016). Global burden of COPD. *Respirology*, *21*(1), 14–23. https://doi.org/10.1111/resp.12660

Louie, S., Zeki, A. A., Schivo, M., Chan, A. L., Yoneda, K. Y., Morrissey, B. M., & Albertson, T. E. (2013). *The asthma–chronic obstructive pulmonary disease overlap syndrome: pharmacotherapeutic considerations*. *6*(2), 197–219. https://doi.org/10.1586/ecp.13.2.The

Lung Association of Saskatchewan. (2017). *COPD Fact Sheet*. Retrieved from https://sk.lung.ca/about-us/news-room/backgrounders-and-information-sheets/copd-fact-sheet

Maselli, D. J., & Hanania, N. A. (2018). Asthma COPD overlap: Impact of associated comorbidities. *Pulmonary Pharmacology and Therapeutics*, *52*(6), 27–31. https://doi.org/10.1016/j.pupt.2018.08.006

Menezes, A. M. B., De Oca, M. M., Pérez-Padilla, R., Nadeau, G., Wehrmeister, F. C., Lopez-Varela, M. V., Muiño, A., Jardim, J. R. B., Valdivia, G., & Tálamo, C. (2014). Increased

risk of exacerbation and hospitalization in subjects with an overlap phenotype : COPD-Asthma. *Chest*, *145*(2), 297–304. https://doi.org/10.1378/chest.13-0622

Milne, S., Mannino, D., & Sin, D. D. (2020). Asthma-COPD Overlap and Chronic Airflow Obstruction: Definitions, Management, and Unanswered Questions. *Journal of Allergy and Clinical Immunology: In Practice*, *8*(2), 483–495. https://doi.org/10.1016/j.jaip.2019.10.044

Miravitlles, M., Soriano, J. B., Ancochea, J., Muñoz, L., Duran-Tauleria, E., Sánchez, G., Sobradillo, V., & García-Río, F. (2013). Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. *Respiratory Medicine*, *107*(7), 1053–1060. https://doi.org/10.1016/j.rmed.2013.03.007

Murgia, N., Brisman, J., Claesson, A., Muzi, G., Olin, A. C., & Torén, K. (2014). Validity of a questionnaire-based diagnosis of chronic obstructive pulmonary disease in a general population-based study. *BMC Pulmonary Medicine*, *14*(1), 1–7. https://doi.org/10.1186/1471-2466-14-49

Nicolini, A., Barbagelata, E., Tagliabue, E., Colombo, D., Monacelli, F., & Braido, F. (2018). Gender differences in chronic obstructive pulmonary diseases: A narrative review. *Panminerva Medica*, *60*(4), 192–199. https://doi.org/10.23736/S0031-0808.18.03463-8

Nielsen, M., Bårnes, C. B., & Ulrik, C. S. (2015). Clinical characteristics of the asthma–COPD overlap syndrome – A systematic review. *International Journal of COPD*, *10*(1), 1443–1454. https://doi.org/10.2147/COPD.S85363

Noda, T., Ojima, T., Hayasaka, S., Hagihara, A., Takayanagi, R., & Nobutomo, K. (2009). The health impact of remarriage behavior on chronic obstructive pulmonary disease: Findings from the US longitudinal survey. *BMC Public Health*, *9*, 1–6. https://doi.org/10.1186/1471-2458-9-412

Oremus, M., Postuma, R., Griffith, L., Balion, C., Wolfson, C., Kirkland, S., Patterson, C., Shannon, H., CLSA Algorithms Validation Group, & Raina, P. (2013). Validating Chronic Disease Ascertainment Algorithms for Use in the Canadian Longitudinal Study of Aging. *Canadian Journal on Aging, 32*(3):232-239.

Ospina, M. B., Voaklander, D. C., Stickland, M. K., King, M., Senthilselvan, A., & Rowe, B. H. (2012). Prevalence of asthma and chronic obstructive pulmonary disease in Aboriginal and non-Aboriginal populations: A systematic review and meta-analysis of epidemiological studies. *Canadian Respiratory Journal*, *19*(6), 355–360. https://doi.org/10.1155/2012/825107

Pauwels, R., Buist, S., Calverley, P., Jenkins, C., & Hurd, S. (2001). Global strategy for the diagnosis, management and prevention of Chronic Obstructive Pulmonary Disease. NHBLI/WHO global initiative for Chronic Obstructive Lung Disease (GOLD) workshop summary. *Revista Portuguesa de Pneumologia*, *7*(4–5), 398–400. https://doi.org/10.1016/s0873-2159(15)30846-1

Pellegrino, R., Viegl, G., Brusasco, V., Crapo, R.O., Burgos, F., Casaburi, R., Coates, A., C. P. M. van der Grinten, P. Gustafsson, J. Hankinson, R. Jensen, D. C. Johnson, N. MacIntyre, R. McKay, M. R. Miller, D. Navajas, O. F. Pedersen, & Wanger, J. (2005) Interpretive strategies for lung function tests. *European Respiratory Journal*, *26*(5): 948:968.

Peters, U., Dixon, A., & Forno, E. (2018). Obesity and Asthma. *Physiology & Behavior*, *176*(5), 139–148. https://doi.org/10.1016/j.jaci.2018.02.004

Pitta, F., Troosters, T., Spruit, M. A., Probst, V. S., Decramer, M., & Gosselink, R. (2005). Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, *171*(9), 972–977.

https://doi.org/10.1164/rccm.200407-855OC

Postma, D. S. (2007). Gender Differences in Asthma Development and Progression. *Gender Medicine*, *4*(Suppl. 2), 133–146. https://doi.org/10.1016/S1550-8579(07)80054-4

Prescott, E., Bjerg, A. M., Andersen, P. K., Lange, P., & Vestbo, J. (1997). Gender difference in smoking effects on lung function and risk of hospitalization for COPD: Results front a Danish longitudinal population study. *European Respiratory Journal*, *10*(4), 822–827. https://doi.org/10.1183/09031936.97.10040822

Qian Zhang, Huie Jing, and H. C. S. (2017). Prevalence and Features of Asthma-COPD Overlap in the U.S. 2007-2012. *Physiology & Behavior*, *176*(5), 139–148. https://doi.org/10.1016/j.physbeh.2017.03.040

Rausch-Osthoff, A. K., Kohler, M., Sievi, N. A., Clarenbach, C. F., & Van Gestel, A. J. R. (2014). Association between peripheral muscle strength, exercise performance, and physical activity in daily life in patients with Chronic Obstructive Pulmonary Disease. *Multidisciplinary Respiratory Medicine*, *9*(1), 1–7. https://doi.org/10.1186/2049-6958-9-37

Raina, P. (2014). CLSA as a Platform for Studying Disease and Disability in an Aging Population. Online. Retrieved from https://bit.ly/2NsaTgO

Raina, P. (2014). CLSA Follow-up 1. Online. Retrieved from https://clsa-elcv.ca/doc/519

Raina, P., Wolfson, C., & Kirkland, S. (2016). CLSA Protocol. Retrieved from https://clsa-elcv.ca/doc/511.

Raina, P., Wolfson, C., Kirkland, S., & Griffith, L.E. (2018). The Canadian Longitudinal Study on Aging (CLSA) Report on Health and Aging in Canada: Findings from Baseline Data Collection 2010-2015. Online. Retrieved from https://clsa-elcv.ca/stay-informed/new-clsa/2018/canadian-longitudinal-study-aging-releases-first-report-health-and-aging

Raina, P., Wolfson, C., Kirkland, S., Griffith, L.E., Balion, C., Cossette, B., Dionne, I., Hofer, S., Hogan, D., Heuval, ER., Liu-Ambrose, T., Menec, V., Mugford, G., Patterson, C., Payette, H., Richards, B., Shannon, H., Sheets, D., Taler, V., Thompson, M., Tuokko, H., Wister, A., Wu, C., Young, L. (2019). Cohort Profile: The Canadian Longitudinal Study on Aging. *International Journal of Epidemiology, 48*(6), 1752:1753j.

Robichaud, A., & Ménard R. (2014). Multi-year objective analyses of warm season ground-level ozone and PM2.5 over North America using real-time observations and the Canadian operational air quality models. *Atmospheric Chemistry and Physics*, *14*(4), 1769-1800; https://doi.org/10.5194/acp-14-1769-2014

Romanet-Manent, S., Charpin, D., Magnan, A., Lanteaume, A., & Vervloet, D. (2002). Allergic vs nonallergic asthma: What makes the difference? *Allergy: European Journal of Allergy and Clinical Immunology*, *57*(7), 607–613. https://doi.org/10.1034/j.1398-9995.2002.23504.x

Salvi, S. S., & Barnes, P. J. (2009). Chronic obstructive pulmonary disease in non-smokers. *The Lancet*, *374*(9691), 733–743. https://doi.org/10.1016/S0140-6736(09)61303-9

Sears, M. R. (2015). Smoking, asthma, chronic airflow obstruction and COPD. *European Respiratory Journal*, *45*(3), 586–588. https://doi.org/10.1183/09031936.00231414

Senthilselvan, A., Dosman, J. A., & Chen, Y. (1993). Relationship between pulmonary test variables and asthma and wheezing: A validation of self-report of asthma. *Journal of Asthma*, *30*(3), 185–193. https://doi.org/10.3109/02770909309054516

Senthilselvan, Ambikaipakan, & Beach, J. (2018). Characteristics of asthma and COPD overlap syndrome (ACOS) in the Canadian population. *Journal of Asthma*, *56*(11), 1129–1137. https://doi.org/10.1080/02770903.2018.1531997

Shantakumar, S., Pwu, R. F., D'Silva, L., Wurst, K., Kuo, Y. W., Yang, Y. Y., Juan, Y. C., & Chan, K. A. (2018). Burden of asthma and COPD overlap (ACO) in Taiwan: A nationwide population-based study. *BMC Pulmonary Medicine*, *18*(1), 1–12. https://doi.org/10.1186/s12890-017-0571-7

Shah, R., & Newcomb, D. C. (2018). Sex Bias in Asthma Prevalence and Pathogenesis. *Frontiers in Immunology*, *9*(12), 2997. https://doi.org/10.3389/fimmu.2018.02997

Silverman, E. K., Weiss, S. T., Drazen, J. M., Chapman, H. A., Carey, V., Campbell, E. J., Denish, P., Silverman, R. A., Celedon, J. C., Reilly, J. J., Ginns, L. C., & Speizer, F. E. (2000). Gender-related differences in severe, early-onset chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, *162*(6), 2152–2158. https://doi.org/10.1164/ajrccm.162.6.2003112

Sin, D. D. (2017). Asthma-COPD overlap syndrome: What we know and what we don't. *Tuberculosis and Respiratory Diseases*, *80*(1), 11–20. https://doi.org/10.4046/trd.2017.80.1.11

Sin, D. D., Miravitlles, M., Mannino, D. M., Soriano, J. B., Price, D., Celli, B. R., Leung, J. M., Nakano, Y., Park, H. Y., Wark, P. A., & Wechsler, M. E. (2016). What is asthma COPD overlap syndrome? Towards a consensus definition from a round table discussion. *European Respiratory Journal*, *48*(3), 664–673. https://doi.org/10.1183/13993003.00436-2016

Sood, A. (2011). Sex differences: Implications for the obesity-asthma association. *Exercise and Sport Sciences Reviews*, *39*(1), 48–56. https://doi.org/10.1097/JES.0b013e318201f0c4

Soriano, J. B., Abajobir, A. A., Abate, K. H., Abera, S. F., Agrawal, A., Ahmed, M. B., Aichour, A. N., Aichour, I., Eddine Aichour, M. T., Alam, K., Alam, N., Alkaabi, J. M., Al-Maskari,

F., Alvis-Guzman, N., Amberbir, A., Amoako, Y. A., Ansha, M. G., Antó, J. M., Asayesh, H., Vos, T. (2017). Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet Respiratory Medicine*, *5*(9), 691–706. https://doi.org/10.1016/S2213-2600(17)30293-X

Soriano, J. B., Kendrick, P. J., Paulson, K. R., Gupta, V., Abrams, E. M., Adedoyin, R. A., Adhikari, T. B., Advani, S. M., Agrawal, A., Ahmadian, E., Alahdab, F., Aljunid, S. M., Altirkawi, K. A., Alvis-Guzman, N., Anber, N. H., Andrei, C. L., Anjomshoa, M., Ansari, F., Antó, J. M., Vos, T. (2020). Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Respiratory Medicine*, *8*(6), 585–596. https://doi.org/10.1016/S2213-2600(20)30105-3

Spindel, E. R., & McEvoy, C. T. (2016). The role of nicotine in the effects of maternal smoking during pregnancy on lung development and childhood respiratory disease: Implications for dangers of e-cigarettes. *American Journal of Respiratory and Critical Care Medicine*, *193*(5), 486–494. https://doi.org/10.1164/rccm.201510-2013PP

Stapleton, M., Howard-Thompson, A., George, C., Hoover, R. M., & Self, T. H. (2011). Smoking and asthma. *Journal of the American Board of Family Medicine*, *24*(3), 313–322. https://doi.org/10.3122/jabfm.2011.03.100180

Stringer, W. W., Porszasz, J., Bhatt, S. P., McCormack, M. C., Make, B. J., & Casaburi, R. (2019). Physiologic insights from the COPD genetic epidemiology study. *Chronic Obstructive Pulmonary Diseases*, *6*(3), 256–266.

https://doi.org/10.15326/jcopdf.6.3.2019.0128

The Canadian Longitudinal Study on Aging. (2014). Data Collection Site Questionnaires. Online. Retrieved from https://clsa-elcv.ca/doc/1122

The Canadian Longitudinal Study on Aging. (2014). Standard Operating Procedure Spirometry. Online. Retrieved from https://clsa-elcv.ca/doc/523

The Canadian Longitudinal Study on Aging. (2017). CLSA Technical Document: Sampling and Computation of Response Rates and Sample Weights for the Tracking Participants and Comprehensive Participants. Online. Retrieved from https://www.clsa-elcv.ca/doc/1041

The Canadian Longitudinal Study on Aging. (2017). Data Support Materials Air Pollution and Meteorological Exposure Measurements. Online. Retrieved from https://www.clsa-elcv.ca/doc/1905

The Canadian Longitudinal Study on Aging. (2016). Standard Operating Procedure Standing Height and Weight User Guide. Online. Retrieved from https://www.clsa-elcv.ca/doc/1112

The Canadian Longitudinal Study on Again. (2018). In-Home Questionnaire – Baseline Comprehensive. Online. Retrieved from https://clsa-elcv.ca/doc/1048

The Canadian Longitudinal Study on Aging. (2020). Physical Assessment in the CLSA Baseline and Follow-up 1 Data Collection. Online. Retrieved from https://www.clsa-elcv.ca/doc/3653

The Canadian Longitudinal Study on Aging. (2021). Data Collection. Online. Retrieved from https://www.clsa-elcv.ca/researchers/data-collection

Thomas, M., Decramer, M., & O'Donnell, D. E. (2013). No room to breathe: The importance of lung hyperinflation in COPD. *Primary Care Respiratory Journal*, *22*(1), 101–111. https://doi.org/10.4104/pcrj.2013.00025

Thomson, N. C., Chaudhuri, R., & Livingston, E. (2004). Asthma and cigarette smoking. *European Respiratory Journal*, *24*(5), 822–833. https://doi.org/10.1183/09031936.04.00039004

To, T., Zhu, J., Gray, N., Feldman, L. Y., Villeneuve, P. J., Licskai, C., Gershon, A., & Miller, A. B. (2018). Asthma and chronic obstructive pulmonary disease overlap in women incidence and risk factors. *Annals of the American Thoracic Society*, *15*(11), 1304–1310. https://doi.org/10.1513/AnnalsATS.201802-078OC

Tommola, M., Ilmarinen, P., Tuomisto, L. E., Lehtimäki, L., Haanpää, J., Niemelä, O., & Kankaanranta, H. (2017). Differences between asthma - COPD overlap syndrome and adult-onset asthma. *European Respiratory Journal*, *49*(5), 1–10. https://doi.org/10.1183/13993003.02383-2016

Townsend, E. A., Miller, V. M., & Prakash, Y. S. (2012). Sex differences and sex steroids in lung health and disease. In *Endocrine Reviews*, *33*(1). https://doi.org/10.1210/er.2010-0031

Trivedi, M., & Denton, E. (2019). Asthma in children and adults—what are the differences and what can they tell us about asthma? *Frontiers in Pediatrics*, *7*(6), 1–15. https://doi.org/10.3389/fped.2019.00256

van Boven, J. F. M., Román-Rodríguez, M., Palmer, J. F., Toledo-Pons, N., Cosío, B. G., & Soriano, J. B. (2016). Comorbidome, pattern, and impact of asthma-COPD overlap syndrome in real life. *Chest*, *149*(4), 1011–1020. https://doi.org/10.1016/j.chest.2015.12.002

van Donkelaar A, Martin RV, Brauer M, & Boys BL. (2015). Use of satellite observations for long-term exposure assessment of global concentrations of fine particulate matter. *Environmental Health Perspect*ive, *123*,135–143. https://doi.org/10.1289/ehp.1408646

Vestbo, J., Hurd, S. S., Agustí, A. G., Jones, P. W., Vogelmeier, C., Anzueto, A., Barnes, P. J., Fabbri, L. M., Martinez, F. J., Nishimura, M., Stockley, R. A., Sin, D. D., & Rodriguez-Roisin, R. (2013). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease GOLD executive summary. *American Journal of Respiratory and Critical Care Medicine*, *187*(4), 347–365. https://doi.org/10.1164/rccm.201204-0596PP

Vonk, J. M., Postma, D. S., Boezen, H. M., Grol, M. H., Schouten, J. P., Koëter, G. H., & Gerritsen, J. (2004). Childhood factors associated with asthma remission after 30 year follow up. *Thorax*, *59*(11), 925–929. https://doi.org/10.1136/thx.2003.016246

Wang, L., Wang, K., Gao, X., Paul, T. K., Cai, J., & Wang, Y. (2015). Sex difference in the association between obesity and asthma in U.S. adults: Findings from a national study. *Respiratory Medicine*, *109*(8), 955–962. https://doi.org/10.1016/j.rmed.2015.06.001

Wheaton, A. G., Liu, Y., Croft, J. B., VanFrank, B., Croxton, T. L., Punturieri, A., Postow, L., & Greenlund, K. J. (2019). Chronic Obstructive Pulmonary Disease and Smoking Status — United States, 2017. *Morbidity and Mortality Weekly Report*, *68*(24), 533–538. https://doi.org/10.15585/mmwr.mm6824a1

Wheaton, A., Pleasants, R. A., Croft, J. B., Ohar, J. A., Heidari, K., Mannino, D. M., Liu, Y., & Strage, C. (2018). Gender and Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome. *Physiology & Behavior*, *176*(1), 139–148. https://doi.org/10.1016/j.physbeh.2017.03.040

Willett, L. J., Hashim, S. A. F., Tompson, R. V., & Loyalka, S. K. (1999). Effect of surface heterogeneities on condensation on an aerosol particle. *Journal of Aerosol Science*, *30*(5), 569–585. https://doi.org/10.1016/S0021-8502(98)00741-1

World Health Organization. (2020). *Asthma*. Retrieved from https://www.who.int/news-

room/fact-sheets/detail/asthma

World Health Organization. (2010). Global status report on noncommunicable diseases. *World Health Organization*, *53*(9), 1689–1699. https://doi.org/10.1017/CBO9781107415324.004

World Health Organization. (2018). *WHO - The top 10 causes of death*. Retrieved from http://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death

Xu, X., Weiss, S. T., Rijcken, B., & Schouten, J. P. (1994). Smoking, changes in smoking habits, and rate of decline in FEV1: New insight into gender differences. *European Respiratory Journal*, *7*(6), 1056–1061. https://doi.org/10.1183/09031936.94.07061056

Zhou, X. L., & Zhao, L. Y. (2021). Comparison of clinical features and outcomes for asthma-COPD overlap syndrome vs. COPD patients: A systematic review and meta-analysis. *European Review for Medical and Pharmacological Sciences*, *25*(3), 1495–1510. https://doi.org/10.26355/eurrev_202102_24857

Appendix

Ethics approval for the study from the University of Alberta

Notification of Approval (Renewal)

Date:	February 21, 2021
Amendment ID:	Pro00091377_REN2
Principal Investigator:	Ambikaipakan Senthilselvan
Study ID:	MS2_Pro00091377
Study Title:	Sex-specific environmental and genetic determinants of COPD in middle-aged and older Canadian adults: An analysis of CLSA data
Sponsor/Funding Agency:	CIHR - Canadian Institutes for Health Research CIHR

RSO-Managed Funding:

	Project ID	Title	Grant Status	Program	Project Start Date	Project End Date	Purpose	Other Information
View	RES0042683							Sponsor: Memorial University

Approval Expiry Date: Friday, February 18, 2022

Thank you for submitting this renewal application. Your application has been reviewed and approved.

This re-approval is valid for another year. If your study continues past the expiration date as noted above, you will be required to complete another renewal request. Beginning at 30 days prior to the expiration date, you will receive notices that the study is about to expire. If you do not renew on or before the renewal expiry date, you will have to re-submit an ethics application.

All study related documents should be retained so as to be available to the Health REB upon request. They should be kept for the duration of the project and for at least 5 years following study completion.

Approval by the Research Ethics Board does not encompass authorization to recruit and/or interact with human participants at this time. Researchers still require operational approval as applicable (eg AHS, Covenant Health, ECSD etc) and where in-person interactions are proposed, institutional and operational requirements as outlined in the Resumption of Human Participant Research - June 24, 2020 must be met.

Sincerely,

Charmaine Kabatoff, REB Consultant, for

Anthony S. Joyce, PhD.
Chair, Health Research Ethics Board - Health Panel

Note: This correspondence includes an electronic signature (validation and approval via an online system).