# The Role of Chronic Obstructive Pulmonary Disease in the Relationship Between Air Pollution and Cardiovascular Disease

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**ABSTRACT**

Background- Cardiovascular diseases (CVD), which are the second leading cause of death in Canada, are associated with ambient air pollution, such that air pollution increases the risk of cardiovascular morbidity and mortality. Moreover, CVD have also been linked to chronic obstructive pulmonary disease (COPD). It is unknown whether COPD influences the association between ambient air pollution and CVD. The study objectives of this thesis were as follows: (1) to examine the relationship between ambient air pollution, and more particularly, $PM_{2.5}$ (fine particulate matter air pollution), and ischemic heart disease (IHD) in the aging, Canadian population; and (2) to determine whether COPD and severity of airflow obstruction effects the relationship between ambient air pollution and IHD.

Methods- A cross-sectional study was completed using the Canadian Longitudinal Study on Aging database. Of the 30,098 participants, 18,118 were included in analyses. Multiple logistic regressions between air pollution metrics, $PM_{2.5}$, $NO_2$, and $O_3$, and IHD were completed. An interaction model considering COPD and air pollution, and the effect on IHD was also conducted. Covariates include sociodemographic variables, such as age, sex, BMI, education, and income, diet, and smoking status, in addition to the main independent (air pollution and COPD) and dependent variables (IHD).

Results- An association between air pollution and IHD was found. $PM_{2.5}$ exposure yielded a 6% increase in the odds of ischemic heart disease ($p<0.001$). There was no combined effect of COPD and air pollution on cardiovascular outcome, i.e. IHD. Furthermore, there was no change in this finding, wherein there was no effect of COPD and air pollution, when an alternative cardiovascular outcome, i.e. myocardial infarction, was utilized.

Conclusion- The study findings support literature evidence, ascertaining the relationship between air pollution and IHD. Further exploration, via longitudinal studies and a greater sub-group sample size of COPD participants, should be considered to examine the link between COPD, air pollution, and CVD before we can be more definitive on our conclusion.

**RÉSUMÉ**

Contexte- Les maladies cardiovasculaires (MCV) sont la deuxième cause de décès en importance au Canada. Les MCV sont associées à la pollution atmosphérique, de sorte que la pollution de l'air augmente le risque de morbidité et de mortalité cardiovasculaires. De plus, les MCV sont également associées à la maladie pulmonaire obstructive chronique (MPOC). Il n'est pas connu si la MPOC a une influence sur l'association entre la pollution atmosphérique et les MCV. Les objectifs de cette thèse étaient les suivants: (1) évaluer la relation entre la pollution atmosphérique, et plus particulièrement les particules fines (PM2,5), et les cardiopathies ischémiques dans la population canadienne vieillissante; et (2) déterminer si la MPOC et la gravité de l'obstruction des voies respiratoires affectent la relation entre la pollution atmosphérique et les cardiopathies ischémiques.

Méthodes- Une étude transversale a été réalisée à l'aide de la base de données de l'Étude longitudinale canadienne sur le vieillissement. Sur les 30 098 participants, 18 118 ont été inclus dans les analyses. Des modèles de régressions logistiques multiples ont été effectuées afin d'estimer les associations entre les paramètres de pollution atmosphérique (PM2,5, NO2 et O3) et les cardiopathies ischémiques. Un modèle d'interaction tenant compte de la MPOC et de la pollution atmosphérique, ainsi que de l'effet sur les cardiopathies ischémiques, a également été réalisé. Les covariables incluaient des variables sociodémographiques, telles que l'âge, le sexe, l'IMC, l'éducation et le revenu, l'alimentation et le tabagisme, en plus des principales variables indépendantes (pollution de l'air et MPOC) et dépendantes (cardiopathies ischémiques).

Résultats- Une association entre la pollution atmosphérique et les cardiopathies ischémiques a été trouvée. L'exposition aux PM2,5 a entraîné une augmentation de 6% de la probabilité de cardiopathie ischémique ($p < 0,001$). Il n'y avait pas d'effet combiné de la MPOC et de la pollution

atmosphérique sur les issues cardiovasculaires. En outre, les résultats étaient inchangés, c'est à dire qu'il n'y avait aucun effet de la MPOC et de la pollution de l'air, en utilisant spécifiquement l'infarctus du myocarde et non toutes les cardiopathies ischémiques.

Conclusions- Les résultats de l'étude appuient les preuves de la littérature, établissant la relation entre la pollution de l'air et les cardiopathies ischémiques. Une exploration plus approfondie, via des études longitudinales et une plus grande taille d'échantillon de sous-groupes de participants ayant la MPOC, devrait être envisagée pour examiner le lien entre la MPOC, la pollution atmosphérique et les maladies cardiovasculaires avant que nous puissons être plus définitifs sur notre conclusion.

## PREFACE

*Contributions of Authors*

With the expert guidance of Dr. Jean Bourbeau (MSc thesis supervisor), I have completed this thesis. The contribution to the manuscript is specified below.

Dr. Jean Bourbeau, Dr. Dany Doiron, and Kerman Sekhon contributed to research protocol preparation. Data analysis was completed by Kerman Sekhon with the assistance of a data analyst, Pei Zhi Li. Manuscript preparation and thesis writing was completed by Kerman Sekhon, with support and expert feedback from Dr. Bourbeau and Dr. Doiron. Chapters 1, 2, 3, 4, and 5 were written by Kerman Sekhon, with expert feedback from Dr. Jean Bourbeau and Dr. Dany Doiron, as well as support from Pei Zhi Li for 'Sample Size Calculation' section in Chapter 4. The Section of Tables and Figures was written by Kerman Sekhon and Pei Zhi Li, with expert feedback from Dr. Jean Bourbeau and Dr. Dany Doiron.

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## Chapter 1: Introduction

The worldwide burden of CVD is enormous and growing. Simultaneously, the body of knowledge linking ambient air pollution and CVD is escalating. Air pollution has been associated with CVD morbidity and mortality (Dockery et al. N Engl J Med 1993;329:1753-1759; Pope et al. Am J Resp Crit Care Med 1995;151:669- 674; Pope et al. Circulation 2004;109:71-77). Of the various components of air pollution, fine particulate matter (PM2.5) is thought to be the largest contributor to CVD related morbidity and mortality (Rajagopalan, Al-Kindi & Brook, 2018). The well-established causal associations between active and passive smoking with heart disease support the plausibility of an adverse effect of PM on the cardiovascular system (Leone, 2012). The PM component of air pollution is especially of interest, as its association with CVD mortality is independent of other pollution components such as sulfur dioxide, nitrogen dioxide, etc. and is independent of smoking status (Bell et al., 2008). Furthermore, it has been found that an increase of 10 ug/cm3 of particulate matter air pollution results in a 1.04% increase in mortality (Atkinson et al., 2014). In 2015, 4.2 million deaths were attributable to ambient PM2.5 air pollution exposure, of which, cardiovascular disease-related mortality was significant (Cohen et al., 2017).

The subclinical pathway through which air pollution and CVD are associated is believed to be the inflammatory response and resulting cytokine release, as well as atherosclerosis and thrombosis, among others (Hamanaka & Mutlu, 2018). The first hypothesized mechanism through which CVD and air pollution are thought to be associated is the inflammatory response due to air pollution, which can induce CVD such as atherosclerosis and thrombosis (Brook et al., 2010; Chin et al., 2015; Cosselman, Navas-Acien & Kaufman, 2015; Franklin, Brook & Pope,

2015). This is thought to occur through inflammatory cytokine production which is dependent on reactive oxygen species (i.e. oxidative stress response) (Brook et al., 2010; Chin et al., 2015; Cosselman, Navas-Acien & Kaufman, 2015; Franklin, Brook & Pope, 2015). An animal model study, found that the atherosclerotic plaque in rabbits exposed to PM had much larger plaque, and the PM induced the inflammatory pathway which further increased atherosclerosis in the rabbits' arteries (Suwa, Hogg, Quinlan, Ohgami, Vincent & van Eden, 2002). An additional hypothesized mechanism through which PM induces CVD is through sensory receptors in the lung (Brook et al., 2010; Chin et al., 2015; Cosselman, Navas-Acien & Kaufman, 2015; Franklin, Brook & Pope, 2015). It is suggested that the activation of the sympathetic pathway in the autonomic nervous system and the hypothalamic pituitary adrenal axis has a role in this (Brook et al., 2010; Chin et al., 2015; Cosselman, Navas-Acien & Kaufman, 2015; Franklin, Brook & Pope, 2015). The third hypothesized mechanism is the possibility of translocation of PM air pollution particles, whereby, introduction into the circulatory system may induce inflammation (Brook et al., 2010; Chin et al., 2015; Cosselman, Navas-Acien & Kaufman, 2015; Franklin, Brook & Pope, 2015).

There is growing interest of the potential link of CVD with chronic respiratory illnesses. In the past, respiratory and cardiovascular researchers have largely stayed in "silos." However, emerging data strongly indicate an independent relationship between the two diseases (Nishiyama et al., 2010), Chronic Obstructive Pulmonary Disease (COPD) and CVD, and between lung inflammation and injury, and cardiovascular disease. Numerous epidemiological studies have shown that COPD, independent of cigarette smoking and aging, increases the risk of CVD hospitalization and death (Finkelstein, Cha & Scharf, 2009; Agusti et al., 2012; Onishi,

2017; GOLD, 2017). Inflammatory mediators found in COPD patients are thought to contribute to atherosclerotic plaque build-up and in turn, a higher risk of CVD morbidity and mortality (Hill et al., 2011; Danesh et al., 2008). However, lung function impairment is well established as a risk factor for CVD, independent of other factors such as smoking or breathlessness (Friedman, Klatsky & Siegelaub, 1976; Sin & Man, 2005; Sin, Wu & Man, 2005; Onishi, 2017). Furthermore, acute exacerbation, which is a major component of COPD, has been shown to be associated to an increased risk of myocardial infarction and stroke, respectively 2.27 and 1.26 times higher than those without exacerbation (Donaldson, Hurst, Smith, Hubbard & Wedzicha, 2010).

More recently, it has been demonstrated that COPD prevalence was associated with higher concentrations of PM, most particularly PM2.5 (Doiron et al., 2019). Higher exposures to air ambient pollutant were significantly associated with lower lung function. Knowing that the presence of air pollution (e.g. fine particulate matter, PM2.5) increases the risk of CVD, and that ambient air pollution is also associated with lower lung function and increased COPD prevalence, whether the risk of CVD is independent and/or amplified by the presence of COPD remains unknown (Di, Dai, Wang, et al., 2017; Di, Wang, Zanobetti, et al., 2017) and a topic of great interest.

# Chapter 2: Literature Review

## 1. Definition, Clinical Presentation, Diagnosis and Classification

### 1.1 Chronic Obstructive Pulmonary Disease (COPD)

*Definition*- Chronic Obstructive Pulmonary Disease (COPD) is a chronic respiratory disease characterized as persistent airflow obstruction (GOLD, 2017; Soriano & Lamprecht, 2012). It is a result of abnormalities in the airway (bronchioles) and alveoli (GOLD, 2017). It is said that these abnormalities are commonly the result of significant exposure to tissue-damaging stimuli (GOLD, 2017). These stimuli include reactive oxygen species and proteolytic enzymes (Rabe & Watz, 2017). The two most common airway diseases are Emphysema (parenchymal damage) and Obstructive Bronchiolitis (airway disease) (GOLD, 2017). Clinically, spirometry is required to diagnose a patient for COPD (GOLD, 2017). Often times, there are some key risk factors and symptoms that are red flags and initiate diagnosis for COPD, including chronic coughing, mucus (sputum) production and dyspnea, or shortness of breath (GOLD, 2017). The Tiffeneau-Pinelli Index ($FEV_1$/FVC) is used in spirometric diagnosis. $FEV_1$/FVC refers to the ratio between the forced expiratory volume in one second (FEV1) and the forced vital capacity (FVC) (i.e. full expiratory volume). If the post bronchodilator $FEV_1$/FVC is less than 0.7, this confirms that there is non completely reversible airflow obstruction (GOLD, 2017). The Tiffeneau-Pinelli Index in combination with common COPD symptoms, risk factors and known exposure to stimuli allow clinicians to establish the diagnosis of COPD (GOLD, 2017).

*Clinical presentation*- COPD clinically presents itself mostly in individuals over the age of 40 (GOLD, 2017). The symptoms of COPD are said to slowly and progressively worsen

(GOLD, 2017). COPD exacerbation refers to the worsening of COPD-related symptoms. Furthermore, mucus (sputum) production, chronic coughing (including wheezing), dyspnea (which is persistent and increase with exercise) and a history of smoke exposure are all characteristics of patients with COPD (GOLD, 2017). Airflow obstruction is classified into different severities by GOLD: non-COPD and COPD GOLD 2+, where $FEV_1$ is less than 80%. Furthermore, an alternative definition for COPD is adopted in this study, wherein, the post-bronchodilator definition is not used.

*Diagnosis and classification*- COPD assessment should include beyond spirometry the patient's risk for exacerbations and symptom burden. Symptoms are assessed using validated tool such as the mMRC score – Modified medical research council dyspnea score, the CAT assessment – COPD Assessment Test and the CCQ – COPD Control Questionnaire, in order to have a standard assessment and better understand the resulting impairment of health status in COPD patients (GOLD, 2017). This modern approach of classifying COPD patients has been redefined as the ABCD classification.

In a new model of classifying COPD, patients are first diagnosed using spirometry, followed by an assessment of airflow limitation severity using post-BD (bronchodilator) $FEV_1$, e.g., GOLD 1 to 4. The exacerbation history in the previous year (risk of exacerbation), of the patient is taken and a formal symptomatic assessment is conducted using CAT and/or mMRC. These results (symptomatic assessment classification, exacerbation history) are all used to classify patients into one of four categories (A, B, C or D). On the basis of this classification, individual therapies and patient symptom management is informed for each

patient. Defining treatable traits of symptom burden and/or risk of exacerbations allows for a more personalized treatment decision for a given patient.

## 1.2 Cardiovascular Disease (CVD)

*Definition*- Cardiovascular Disease (CVD) is an umbrella term for a broad range of diseases that affect the circulatory system (i.e. blood vessels or heart), including ischemic heart disease and myocardial infarction (National Heart, Lung and Blood Institute). Ischemic heart disease, also known as coronary artery disease, is the most common type of heart disease (National Heart, Lung and Blood Institute). It is a result of plaque buildup on the walls of the heart's arteries, which is called atherosclerosis (Cardiovascular Disability: Updating the Social Security Listings, 2010). The plaque prevents sufficient blood circulation, resulting in inadequate amounts of rich oxygen being delivered to the heart (Cardiovascular Disability: Updating the Social Security Listings, 2010).

Due to the decreased blood supply, heart muscle cells sometimes begin to die (Cardiovascular Disability: Updating the Social Security Listings, 2010). This is also known as myocardial infarction (Cardiovascular Disability: Updating the Social Security Listings, 2010). Often times, if the blood vessel is not constricted to less than 50% its original size, the individual is less likely to experience any symptoms (Cardiovascular Disability: Updating the Social Security Listings, 2010). However, symptoms may arise progressively overtime, especially during increased blood circulation demand (e.g. during exercise or stress) (Cardiovascular Disability: Updating the Social Security Listings, 2010).

*Clinical presentation*- The symptoms of ischemic heart disease include discomfort/pain in the shoulder, chest, arm, jaw or back, which is known as angina or angina pectoris (Cardiovascular Disability: Updating the Social Security Listings, 2010). Angina can be classified into four different categories on the basis of the Canadian Cardiovascular Society Scheme (Cardiovascular Disability: Updating the Social Security Listings, 2010). Class I is angina that occurs as a result of excessive exertion due to work or recreation (not including physical activity: e.g. cycling, skating, chopping wood, etc.) (Cardiovascular Disability: Updating the Social Security Listings, 2010). Class II refers to angina as a result of ordinary activity with some added stress (e.g. walking uphill after a meal or in the cold) (Cardiovascular Disability: Updating the Social Security Listings, 2010). Class III is angina that is a result of ordinary activity such as walking around the block, completing household chores, etc. (Cardiovascular Disability: Updating the Social Security Listings, 2010). Finally, Class IV refers to angina that is a result of any physical activity completed and may also be prevalent during periods of non-movement (i.e. rest) (Cardiovascular Disability: Updating the Social Security Listings, 2010).

*Diagnosis and classification*- Most often, myocardial infarction is diagnosed on the basis of cardiac biomarkers (Thygesen, Alpert & White, 2007). This biomarker is usually troponin (Thygesen, Alpert & White, 2007). Symptoms of ischaemia or ECG changes in combination with fluctuation in the concentration of troponin (above the $99^{th}$ percentile upper reference limit) is a basis for diagnosis (Thygesen, Alpert & White, 2007). Myocardial infarction, which is a manifestation of ischemic heart disease, can be classified into five different categories (Thygesen, Alpert & White, 2007). Type 1 is myocardial infarction due to a

coronary event such as plaque rupture (Thygesen, Alpert & White, 2007). Type 2 is myocardial infarction due to an increase in the demand for oxygen (e.g. hypertension) (Thygesen, Alpert & White, 2007). Type 3 is symptoms of myocardial infarction simultaneously with sudden cardiac arrest (Thygesen, Alpert & White, 2007). Type 4 and Type 5 refers to myocardial infarction in association with stent thrombosis and coronary artery bypass grafting, respectively (Thygesen, Alpert & White, 2007).

## 2. Disease burden

### 2.1 COPD

COPD is considered a global burden on healthcare (Rabe & Watz, 2017). COPD is the 4$^{th}$ leading cause of death globally, and is predicted to become the 3$^{rd}$ leading cause of death (GOLD, 2017, 5; Soriano & Lamprecht, 2012). Determining prevalence is difficult due to the different approaches of determining the impact of COPD on the population (i.e. spirometry, surveys, etc.) (GOLD, 2017). For example, in 2015, the Global Burden of Disease Study approximated that 174 million are affected globally due to COPD (Systematic analysis for the Global Burden of Disease Study 2015). However, in 2010 a study found that there are 384 million cases globally on the basis of spirometry (Adeloye et al., 2015).

COPD is often compared with asthma due to their similar symptomology (GBD 2015 Chronic Respiratory Disease Collaborators, 2017). A study on the global burden of diseases discovered that in 2015, death due to COPD was 8 times higher than death due to asthma. Furthermore, of all the diseases contributing to disability-adjusted life years (DALYs), COPD caused 2.6%, whereas, asthma caused 1.1%. COPD is the eighth leading cause of

disease burden, on the basis of DALYs. In 2015, approximately 170 million men and women were affected by COPD globally.

COPD is increasingly prevalent among older individuals and in less-developed countries. Overall, COPD receives less medical attention and significance in comparison with other non-communicable diseases such as cardiovascular disease and cancer. Less physical activity and smoking have also been linked with COPD mortality and increased burden due to COPD.

## 2.2 CVD

CVD (i.e. heart disease) is the 2nd leading cause of death in Canada (Statistics Canada: Heart Disease in Canada, 2017). Heart disease (ischemic) is one of many CVD, including, myocardial infarction, cerebrovascular disease and congestive heart disease (Public Health Agency of Canada: Chronic Disease and Injury Indicator Framework, 2016). Risk of mortality is three times higher in the 2.4 million Canadians, age 20 and older, diagnosed with heart disease than the average Canadian without heart disease (Statistics Canada: Heart Disease in Canada, 2017).

Cardiovascular disease has been declining, however, this is mainly limited to regions with a higher sociodemographic index (i.e. greater income, higher education and reproduction) (Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015). In 2015, there were 422.7 million cases of CVD globally (Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015). In 1990, 12.5 million deaths were attributed to CVD, whereas, in 2015, 17.9 million deaths were due to CVD (Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes,

1990 to 2015). As the sociodemographic index increases in a region, CVD mortality rates seem to become higher among men than women in that region (Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015).

In countries with a sociodemographic index that is greater than 0.75, CVD mortality decreases greatly (Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015). CVD in individuals age 40 and older was largely dominated by the prevalence of ischemic heart disease in 2015 (Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015). Globally, it was estimated that there were 7.29 and 110.55 million cases of myocardial infarction and ischemic heart disease, respectively (Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015). The prevalence of ischemic heart disease was 290 cases per 100,000 people for those aged 40 to 44, whereas, the ratio was much higher at 11,203 cases per 100,000 for those aged 75-79 (Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015). CVD was responsible for a third of all deaths globally in 2015. CVD mortality and sociodemographic index shift from 2015 shows that in regions with a higher sociodemographic index, mortality due to CVD is higher in men than women, whereas, the opposite holds true in areas with lower sociodemographic index.

## 3. Clinical management

### 3.1 Management of COPD

#### 3.1.1 Goal of Treatment

The goal of treatment is three-fold: (1) to reduce disease progression, (2) symptom burden and (3) risk of exacerbations and mortality. As COPD is a progressive disease, the condition

worsens over time. The importance of pharmacological and non-pharmacological treatment is to help manage symptom, primarily dyspnea, and treat or prevent acute events (i.e. exacerbation) in patients with COPD (Martinez, Han, Flaherty & Curtis, 2006; GOLD, 2017).

### 3.1.2 Pharmacological therapy

The treatment of stable COPD, in particular, treatment targeting alleviation of symptoms and preventative measures against exacerbation include bronchodilation, azithromycin, and mucolytics, such as N-acetylcysteine (Miravitlles, M., D'Urzo, A., Singh, D., & Koblizek, V., 2016). Management of COPD exacerbation, which refers to worsening respiratory symptoms, can be done based on the classification of the exacerbation (GOLD, 2017; Criner et al., 2015). Mild, moderate and severe exacerbations are treated with different pharmacological therapies (GOLD, 2017; Criner et al., 2015). Mild exacerbations are treated with short acting bronchodilators (SABDs), whereas, moderate exacerbation are treated with both SABDs and antibiotics/corticosteroids (GOLD, 2017). Severe exacerbations may require hospitalization. Antibiotics and corticosteroids improve recovery time and lung function, respectively (GOLD, 2017). Various pharmacological treatments can also be used to reduce symptoms and increase exercising abilities, in addition to managing/reducing exacerbations (Bourbeau et al., 2019).

### 3.1.3 Non-pharmacological therapy

Respiratory support can be provided as non-pharmacological therapy (GOLD, 2017). This includes oxygen therapy, ventilator support and invasive/non-invasive mechanical ventilation

(GOLD, 2017). Oxygen therapy refers to the provision of supplemental oxygen during hospitalization in order to ensure blood oxygen saturation levels are maintained (GOLD, 2017). The most important non-pharmacological therapy is pulmonary rehabilitation as well as self-management interventions such as physical activity (Pulmonary rehabilitation: official statement of the American Thoracic Society, 159; Dechman et al., 2019). Pulmonary rehabilitation can be defined using the official statement by the American Thoracic Society, which identifies pulmonary rehabilitation as any program created and adapted for the unique needs of each COPD patient with the ultimate goal of efficiently increasing physical and social wellbeing as well as autonomy (Pulmonary rehabilitation: official statement of the American Thoracic Society, 159; Dechman et al., 2019). Pulmonary rehabilitation beyond improving exercise capacity includes but is not limited to: using communication to increase adherence to therapy and improve lifestyle choices (i.e. nutrition) for a healthier lifestyle, as well as increase physical activity through education, therapy and training.

#### 3.1.4 Preventative Approach

Smoking cessation is considered a key component in "influenc[ing] the natural history of COPD" (GOLD, 2017, p. 10). Using counselling and other resources to quit smoking is recommended. Vaccinations are also important in preventing risk of exacerbations, hospital admission, mortality and illness due to COPD (GOLD, 2017). This includes the influenza vaccine and pneumococcal vaccine (GOLD, 2017).

## 3.2 Management of CVD

### 3.2.1 Goal of Treatment

The goal of treatment is to reduce cardiovascular events (i.e. stroke, etc.), reduce mortality, for symptom management and increase both survival and quality of life (Zieman & Malasky, 2005). Diet and physical activity have been shown to play a role in preventing cardiovascular disease in the elderly. Pharmacological and non-pharmacological treatments such as B-blockers and rehabilitation, respectively, can be used as treatment.

### 3.2.2 Pharmacological Therapy

Pharmacological therapy is dependent on the presence of disease, meaning that the therapy differs if there are multiple diseases (Zieman & Malasky, 2005). For example, patients with ischemic heart disease are treated with B-blockers (Farjo, Patel, Shah, Badami, Regner, Stansbury & Schmidt, 2018). B-blockers are also used post-myocardial infarction, however, a selective aldosterone antagonist is used in patients post-myocaridal infarction who also have left ventricular dysfunction (Zieman & Malasky, 2005; McKenna et al., 2012). In addition to this, a diuretic is used if there are signs of heart failure. ACE inhibitors are used for patients with diabetes (Johnson & Spurney, 2015). The JNC-7 guidelines should be used to determine the therapy, however, often 2 or more agents are used in order to initiate treatment especially when the patient has an abnormal systolic and diastolic blood pressure reading (Zieman & Malasky, 2005; Karmali et al., 2016).

### 3.2.3 Non-pharmacological Therapy

Cardiac rehabilitation is a non-pharmacological therapy used to limit the impact of cardiac illness on physiological well-being, reduce risk of mortality due to CVD, decrease cardiac disability, control CVD symptoms and prevent further atherosclerosis (Zieman & Malasky,

2005). Cardiac rehabilitation has decreased CVD mortality as much as 25% in some studies, which are limited by their lack of inclusion of individuals over the age of 65 (Zieman & Malasky, 2005).

Exercise training is one component of cardiac rehabilitation. When using exercise training as a part of cardiac rehabilitation in the elderly, comorbidities and functional capabilities of patients, especially those with cardiac disabilities, must be taken into consideration. Peak aerobic capacity is considered a marker for physical function (Zieman & Malasky, 2005). If an individual's peak aerobic capacity is impaired, training may improve the same which in turn lowers risk of mortality (Zieman & Malasky, 2005). As such, the purpose of exercise training should be to improve physical function and increase disability-free survival (Zieman & Malasky, 2005). Resistance training has been recognized as a useful exercise training tool in addition to aerobic exercise training (Zieman & Malasky, 2005). Interestingly, women are less likely than men to be referred to cardiac rehabilitation that includes exercise training by physicians (Ades et al., 1992).

It is predicted that smoking cessation would be able to prevent around 600,000 strokes that occur annually (Zieman & Malasky, 2005). Smoking cessation would substantially reduce CVD related morbidity and mortality for those over the age of 70 (Zieman & Malasky, 2005). It has been found that patients with myocardial infarction have a 20-50% reduced likelihood of mortality due to smoking cessation (Sparrow & Dawber, 1978).

### 3.2.4. Preventative Approach

Both diet and physical activity play important roles in preventing CVD (Zieman & Malasky, 2005). Exercise controls the presence of high density and low density lipoprotein, weight and

blood pressure/hypertension (Zieman & Malasky, 2005). Furthermore, exercise can have a beneficial impact on the disease burden of CVD, perhaps reducing hospitalization rates and costs for CVD-based disability (Zieman & Malasky, 2005).

## 4. Risk factors

### 4.1 Risk factors for COPD

***Genetic factors-*** Alpha-1 antitrypsin deficiency (AATD) has been identified as a the only known genetic risk factor for COPD (Stroller & Aboussouan, 2005). It has been found that smokers with AATD deficiency, which is severe and hereditary, are more likely to have early onset COPD than smokers without AATD deficiency (Holm et al., 2013).

***Lung development-*** Factors that may affect lung growth during childhood and gestational period (i.e. infections, birth weight, premature birth, etc.) may increase risk of COPD in the long-term (GOLD, 2017). Furthermore, if there is a history of respiratory infections throughout childhood this is related to a decrease in lung function (de Marco et al., 2011).

***Exposure to particulate-***

**Smoking (cigarette, second-hand, marijuana)**

Smoking is a shared risk factor for both COPD and CVD. Please see the shared risk factor section (*Section 4.3.3*) below.

**Biomass fuel**

Biomass fuel, also referred to as indoor air pollution, is the pollution caused by the use of oils in cooking (GOLD, 2017). When used in small spaces with poor ventilation, this exposure is a risk factor for COPD (GOLD, 2017). This is also one the main reasons that COPD is thought as becoming more prevalent among women globally, as, predominately, they are being exposed to this source of indoor pollution (developing countries) (GOLD, 2017). It is estimated that 35% of COPD incidents in low and middle-income countries are due to biomass fuel exposure (Mannino & Buist, 2007). Ambient air pollution is a shared risk factor for both COPD and CVD (see section 4.3.4).

**Asthma and airway hyper-reactivity** Asthma, in comparison to COPD, has early onset (i.e. usually diagnosed at a younger age). Furthermore, asthma is not as consistent in symptomology as COPD. Obesity, eczema, arthritis and allergy are also commonly coexisting with asthma. Asthma and airway hyper-reactivity are considered risk factors for COPD. The Dutch hypothesis is one of the explanations that link the pathogenesis of COPD with that of asthma (Postma, Weiss, van den Berge, Kerstjens & Koppelman, 2015). In particular, when originally formulated in 1961, the Dutch Hypothesis brought to light the significance of phenotyping genetic and environmental factors, age, sex, and other variables, that may influence diagnosis of asthma, COPD, or a combination syndrome, which in turn impacts management in clinical settings.

**Ambient Air Pollution**

Ambient air pollution is a shared risk factor for both COPD and CVD (see *Section 4.3.4*).

## 4.2 Risk factors for CVD

***Genetic Factors-*** High sensitivity C-reactive protein is a biomarker for inflammation (Silva & de Lacerda, 2012). It is a risk factor for cardiovascular heart disease among elderly women. High sensitivity C-reactive protein has a role in regulating, inducing and upregulating expression in the atherosclerosis pathway (Silva & de Lacerda, 2012). It has been found that C-reactive protein has genetic determinants (Hersh CP, Miller DT, Kwiatkowski DJ, Silverman EK., 2006). The concentration of high sensitivity C-reactive protein is related to smoking, obesity, hypertension, diabetes and other risk factors of CVD (Saito, Ishimitsu, Minami, Ono, Ohrui & Matsuoka, 2003). However, high sensitivity C-reactive protein is also an independent risk factor for CVD (Koenig, 2013). High sensitivity C-reactive protein is associated with an increase in CVD related mortality and cardiovascular heart disease events (Fonseca & Izar, 2016).

***Hypertension and High Blood Pressure-*** It has been found that hypertension, which is increasingly prevalent with age, is a risk factor for CVD (Petrie, Guzik & Touyz, 2018). Over 60% of individuals over the age of 65 have either a high blood pressure or hypertension (Zieman & Malasky, 2005). CVD and systolic blood pressure are associated with one another, as are systolic blood pressure and myocardial infarction, angina and sudden death due to CVD (Zieman & Malasky, 2005). There is also an increase in vascular events with increased systolic blood pressure in the elderly population (Zieman & Malasky, 2005). Blood pressure measures may sometimes be false due to calcification in arteries (i.e. pseudohypertension) (Feng, Zang, Huang & Huang, 2018). Thus, it is recommended that hypertension be considered in addition to any organ damage, such as left ventricular

hypertrophy, which is both associated with hypertension and also an independent risk factor, for CVD (Corbett, Naqvi & Bajwa, 2020).

***Left Ventricular Hypertrophy***- The prevalence of left ventricular hypertrophy, which is determined by EKG, increases with age (Wachtell & Okin, 2016). For example, the prevalence of left ventricular hypertrophy is 4.2 and 4.9% for men and women, aged 75-84, respectively, however, it is 5.9 and 9.4% for men and women aged 85-94, respectively (Zieman & Malasky, 2005). Left ventricular hypertrophy is a risk factor for cardiovascular heart disease events in the elderly (Zieman & Malasky, 2005; Wachtell & Okin, 2016).

***High Body Mass Index (BMI) and Obesity***- It has been found that body mass index (BMI) increases with age until the age of 65-70 years-old (Poehlman et al., 1995; Cooper, Popham, Santanasto, Glynn & Kuh, 2017). It is unclear if BMI is an independent risk factor for CVD (Zieman & Malasky, 2005). However, BMI is associated with other well-known risk factors such as dysplipidemia and hypertension (Zieman & Malasky, 2005). Furthermore, the waist-to-hip ratio for abdominal obesity has been recognized as an important measure to determine insulin resistance which contributes to the diabetes and CVD association (Bando, Kato, Sakamoto, Ogawa, Bando & Yonei, 2017; Scicali et al., 2018). Abdominal obesity, or the waist-to-hip ratio is considered a CVD risk factor in the elderly, especially for women.

***Dysplipidemia***- Overall, high cholesterol levels have been identified as a risk factor for cardiovascular events in the elderly (Nadrowski et al., 2016). Total cholesterol, low-density lipoprotein and high-density lipoprotein are all predictors of myocardial infarction (Zieman &

Malasky, 2005). High-density lipoprotein is also a risk factor for CVD (Nadrowski et al., 2016). The association between total cholesterol and cardiovascular heart disease does not hold with increasing age, however, high-density lipoprotein continues to be a risk factor for cardiovascular heart disease events as age increases (i.e. including those over 80) (Zieman & Malasky, 2005).

***Diabetes***- The prevalence of type II diabetes increases with age. Heart and blood vessel related diseases are responsible for 75% of mortality among diabetes patients (Zieman & Malasky, 2005). The risk of death due to cardiovascular heart disease is between one to four times higher for individuals with diabetes as compared to those without (Zieman & Malasky, 2005; Liu, Simon, Shi, Mallhi & Eisen, 2016). Furthermore, this association is more defined in women than men (Abbott, Donahue, Kannel & Wilson, 1988). It has been found that the risk for cardiovascular heart disease was 1.8 and 4.6 times more for men and women, respectively, for those who have diabetes (Zieman & Malasky, 2005). Diabetes is also a risk factor for coronary events in the elderly (Vestberg, Rosengren, Eeg-Olofsson, Miftaraj, Franzen, Svensson & Lind, 2018). Moreover, there is an increased likelihood of adverse outcomes post-diagnosis of coronary disease among individuals with diabetes (Zieman & Malasky, 2005).

**Pre-existing Atherosclerosis**- Pre-existing atherosclerosis is one of the biggest risk factors for new coronary events (Zieman & Malasky, 2005). For example, a history of myocardial infarction increases the likelihood of CVD based mortality by 2.1 times (Simons, Simons, Friedlander & McCallum, 2002).

**Carotid Intima-Media Thickness**- Carotid intima-media thickness, which is measured using ultrasound is associated with increased risk for myocardial infarction and stroke in the elderly population (Berkman et al., 2003). As carotid intima-media thickness increases, the risk for both myocardial infarction and stoke increases (Berkman et al., 2003).

**Sleep Apnea**- Sleep apnea has been found to increase with age. In particular, 4% and 13% of women and men, respectively, over the age of 65, have the disorder (Shochat & Pillar, 2000). Sleep disorder is also associated with hypertension (Peppard, Young, Palta & Skatrud, 2000). Sleep apnea is an independent risk factor for cardiovascular heart disease events and CVD mortality in older individuals (Zieman & Malasky, 2005). Furthermore, this association is more defined for women than men (Zieman & Malasky, 2005).

**Exposure to particulate-**

**Smoking (cigarette, second-hand, marijuana)**

Smoking is a shared risk factor for both CVD and COPD. Please see the shared risk factor section (*Section 4.3.3*) below.

**Ambient Air Pollution**

Ambient air pollution is a shared risk factor for both CVD and COPD (see *Section 4.3.4*).

## 4.3 Shared risk factors COPD and CVD

### 4.3.1 Age and Sex

Despite the fact that COPD has historically been more common in men than women, this is thought to be changing currently (Adeloye et al., 2015). As women may be more susceptible to airflow limitation, the risk of COPD is predicted to increase in women (Han et al., 2007; Sorheim et al., 2010; Luoto, Elmstahl, Wollmer & Pihlsgard, 2016). COPD is considered a part of the multimorbidity of aging (Rabe & Watz, 2017). Aging is a risk factor for COPD as 28% of Canadian over the age of 80 is at risk of having COPD (Gershon et al., 2011). Cardiovascular heart disease is considered a disease of elderly women due to its high prevalence among this population (Zieman & Malasky, 2005). Furthermore, age is associated with CVD, such that the prevalence of cardiovascular heart disease, myocardial infarction, etc. is predicted to increase with the aging population (Zieman & Malasky, 2005). Disability due to CVD is also an increasingly prevalent concern, due to the close association between CVD and age (Zieman & Malasky, 2005). Coronary artery disease in the elderly is more severe in its presentation and affect (i.e. angiographic disease, left ventricular stiffness, etc.) as compared to in younger populations (Zieman & Malasky, 2005). The higher rates of disability among elderly CVD patients further contributes to reduced exercise which, in turn, is a risk factor for CVD and CVD events (Huang, Duong, Killian, Raina, Xie, Dragoman & Chen, 2018). Furthermore, women are more likely to report disability than men, especially among those with cardiovascular heart disease.

### 4.3.2 Socioeconomic status

The evidence shows that individuals with lower socioeconomic status are at a higher risk of developing COPD (GOLD, 2017; de Marco et al., 2011). What is unclear in this relation is the role of air pollution (indoor and outdoor), nutrition, infection and other factors related to

socioeconomic status (GOLD, 2017). Socioeconomic status also seems to play a role in the prevalence of CVD. Wherein, racial and socioeconomic differences are reflected in the prevalence of CVD and related risk factors such as diabetes, whereby, disadvantaged groups are more highly affected (Zieman & Malasky, 2005). This also stands true for the association between air pollution and CVD, whereby, non-white communities generally are exposed to higher levels of air pollution (Clark, Millet & Marshall, 2017).

### 4.3.3 Health habits

***Physical Activity***- Physical activity is seen to reduce the risk of COPD, even in elderly populations with less vigorous activity (Garcia-Aymerich, Lange, Benet, Schnohr & Anto, 2007; Garcia-Aymerich, Lange, Serra, Schnohr & Anto, 2008). Physical activity not only reduces the risk of COPD, but hospitalizations and mortality related to COPD causes (Garcia-Aymerich, Lange, Serra, Schnohr & Anto, 2008). Higher levels of frequent physical activity are associated with reduced risk for COPD among smokers (Garcia-Aymerich, Lange, Benet, Schnohr & Anto, 2007). Physical inactivity is a leading risk factor for CVD related mortality (Yusuf et al., 2004). In this study, it was found that of all patients with myocardial infarction, approximately 12% of these myocardial infarction cases are due to physical inactivity (Yusuf et al., 2004). Furthermore, physical inactivity is accountable for 18% and 10% of hypertension and diabetes patients, respectively, which are two of the risk factors for CVD (Yusuf et al., 2004).

***Diet***- A diet, consisting of vegetables, fish, fruit and cereal was found to be associated, positively, with $FEV_1$ (Shaheen et al., 2010). Furthermore, a meal richer in these

aforementioned components was associated with lower prevalence of COPD (Shaheen et al., 2010). It was hypothesized that these results may suggest that a healthier diet can help prevent COPD and lung impairment (Shaheen et al., 2010). In particular, this study hypothesizes that this diet plan may prevent lung impairment, COPD as well as CVD due to the shared link to $FEV_1$ and mortality rates (Shaheen et al., 2010).

It was also suggested, in the literature review of this study, that certain components of these 'healthy' foods are the underlying factor in the relation between diet and COPD (Shaheen et al., 2010). They also mentioned components of food, such as certain types of fatty acids, which have been linked to reduced risk for COPD and CVD in some studies (Shaheen et al., 2010). A review, which was conducted to determine the influence of nutrition on COPD, found that certain components of nutrition such as antioxidant vitamins (e.g. Vitamin C and Vitamin E) may play a role in the prevention of initiation and progression of lung impairment and related diseases such as Obstructive Lung Diseases (Mosallanezhad, Jalali, Eftekhari & Ahmadi, 2019).

### 4.3.4 Exposure to Particulate Matter

**Smoking**- Tobacco smoke is considered the most common risk factor for COPD globally (GOLD, 2017). Other forms of tobacco and marijuana are also risk factors which includes, cigar, pipes and water pipes (GOLD, 2017). This may also include environmental tobacco smoke (i.e. second hand smoking) (GOLD, 2017). This is a shared risk factor among COPD and CVD.

Despite the fact that smoking generally decreases with age, there is still a risk of myocardial infarction or death for individuals who have a history of smoking (Hermanson, Omenn,

Kronmal & Gersh, 1988). However, this risk is higher in the elderly population that is still currently smoking (Hermanson, Omenn, Kronmal & Gersh, 1988). It was found that the risk of death for smokers (previous or current) over the age of 75, was 3.3 times higher for those who currently smoke as compared to those who have a history of smoking (Hermanson, Omenn, Kronmal & Gersh, 1988).

In a different study conducted with those over the age of 65, the risk of CVD related death was approximately two times higher in those who currently smoked as compared to those who had never smoked (LaCroix et al., 1991). Furthermore, smoking increases the likelihood of CVD events by approximately 2 times in CVD patients in long term care facilities (Zieman & Malasky, 2005). Smoking is considered the second most important risk factor after hypertension for stroke (Zieman & Malasky, 2005).

***Air ambient pollution***- Air pollution (outdoor) is another risk factor for COPD (GOLD, 2017). It is thought to increase the damage to the lungs by increasing the burden on the lungs due to inhaled small particulate matter (GOLD, 2017). It's affect as a risk factor is thought to be less in comparison to other known risk factors (e.g. smoking) (GOLD, 2017). Particulate matter air pollution exposure, including chronic and acute exposures, have been associated with a higher risk of CVD related mortality (Hamanaka & Mutlu, 2018). This includes CVDs such as ischemic (coronary) heart disease, stroke and heart failure (Hamanaka & Mutlu, 2018). Furthermore, air pollution has been found to be an important factor contributing to the development of diabetes and obesity, which, in turn, are risk factors for CVD (Hamanaka & Mutlu, 2018). Please see section 5.

## 5. Air ambient pollution, COPD and CVD

### 5.1 Air Pollution

#### 5.1.1 Definition

As the composition of air pollution includes gases such as nitrogen dioxide, sulfur dioxide, ozone, $PM_{2.5}$ (particulate matter less than 2.5 micrometers), etc., the sources of these various different components are diverse (i.e. traffic pollution, ozone, 'indoor pollution', natural sources, industrial sources) (Hamanaka & Mutlu, 2018). Please see the Table A for a breakdown of the various sources and components of air pollution. Particulate matter, in particular, has been found to have profound effects on health outcomes in comparison with other gaseous components of air pollution (Hamanaka & Mutlu, 2018). Rapidly growing cities and developing countries seem to be most affected by air pollution and the effects on health (Cohen et al., 2005).

#### 5.1.2 Burden of Air Pollution

Air pollution, and in particular, PM2.4, caused 4.2 million deaths in 2015 alone, wherein, significant death can be attributed to cardiovascular disease-related mortality (Cohen et al., 2017). This can be estimated to contribute to 6.4 million years of lost life (Cohen et al., 2005). The burden of air pollution on health and survival is especially defined in developing countries, such as those in Asia (65% of air pollution burden) (Cohen et al., 2005). It is also estimated that, in terms of air pollution burden based on morbidity, the disability-adjusted life years is 20% higher for cardiopulmonary disease (Cohen et al., 2005). Please see Figure 1 for the differences in air pollution concentrations between Canadian cities and worldwide.

Air pollution, especially fine particulate matter air pollution, is associated with numerous diseases, disease-related deaths and disease adjusted life years (Cohen et al., 2005). Particulate matter air pollution is associated with lung cancer and various other cardiopulmonary-causes related mortality (Cohen et al., 2005). Fine particulate air pollution ($PM_{2.5}$) causes mortality related to cancer of the respiratory system (i.e. bronchus, trachea and lungs) (5%), cardiopulmonary diseases (3%) and respiratory infection (1%) (Cohen et al., 2005).

Higher levels of particulate matter air pollution has been known to have adverse outcomes on health. One example of the same was the London, UK smog incident in 1952, in which 4,000 people died due to the smog and 100,000 suffered other severe health effects (Logan, 1953). Previously, it has been found that an increase of 10 $ug/cm^3$ of particulate matter air pollution results in a 1.04% increase in mortality (Atkinson et al., 2014). Furthermore, hospitalization for cardiopulmonary and respiratory diseases also goes up with an increase in particulate matter air pollution (Hamanaka & Mutlu, 2018). The effect of particulate matter air pollution on mortality was greater in cities with more traffic caused particulate matter air pollution (Hamanaka & Mutlu, 2018).

### 5.1.3 Effect of Air Pollution on CVD morbidity and mortality

***5.1.3.1 Epidemiology-*** $PM_{2.5}$ has been associated with increased CVD risk (Brook et al., 2010). Traffic caused particulate matter air pollution has been found to cause myocardial infarction, as does physical activity and alcohol in CVD patients (Nawrot et al., 2011). Furthermore, this association between particulate matter air pollution

and mortality is independent of other pollution components such as sulfur dioxide, nitrogen dioxide, etc. (Bell et al., 2008). Recently, a short-term exposure study conducted shows that as $PM_{2.5}$ level increases approximately 10 ug/$cm^3$, CVD mortality increases by 0.47% (Newell, Kartsonaki, Lam & Kurmi, 2017). This is a finding limited to low and middle income countries, whereas, an alternative meta-analysis considering over 110 peer reviewed articles globally, finds that the same increase of $PM_{2.5}$ levels, increases mortality by 1.04% (Atkinson et al., 2014).

In terms of long-term exposure, this association between $PM_{2.5}$ and mortality still stands, with a 1.26 increased risk of mortality in more polluted cities as compared to less polluted cities (Dockery et al., 1993). A study conducted with over 552,000 participants on long term air pollution exposure ($PM_{2.5}$ and $SO_2$ exposure,) found that mortality due to lung cancer and cardiopulmonary reasons was 8% and 6% higher, respectively, with 10 ug/$cm^3$ increment increases in air pollution (Pope et al., 1995; Pope et al., 2002).

The increased likelihood of CVD mortality due to air pollution is linked to pre-existing heart disease, smoking, socioeconomic status and older age (Hamanaka & Mutlu, 2018). Disadvantaged populations, such as unemployed individuals as well as elderly individuals are more likely to be effected by health issues due to air pollution (Samoli et al., 2008). The association between $PM_{2.5}$ and ischemic heart disease related mortality was not affected by the smoking status of the population (i.e. the association stood true for previous smokers, current smokers and non-smokers) (Pope et al., 2004). Whereas, the association between $PM_{2.5}$ and risk of mortality due to arrhythmia, cardiac arrest and heart failure was higher only in the current and

previous smoker population, and not for non-smokers (Pope et al., 2004). Furthermore, this association between CVD and air pollution is particularly defined among women. In a women's only study, it was found that a 10 ug/$cm^3$ increase in $PM_{2.5}$ increased CVD events by 76% and coronary heart disease by 43% (Di, Dai, Wang, et al., 2017; Di, Wang, Zanobetti, et al., 2017). Globally, this disproportionate risk for women seems even more significant with higher exposure to indoor air pollution in developing countries (biomass fuels used to cook indoors) (Landrigan et al., 2018).

Air pollution, thus, seems to play a role in exacerbation of CVD, mortality due to CVD and development of CVDs (Hamanaka & Mutlu, 2018). $PM_{2.5}$ is associated with heart failure, cerebrovascular disease and other CVD such as ischemic heart disease (Hamanaka & Mutlu, 2018). Myocardial infarction and ischemic heart disease are related to both short-term and long-term exposure to air pollution (Hamanaka & Mutlu, 2018).

***5.1.3.2 Subclinical Association and Plausible Mechanisms: Cell Biology and Animal In Vivo Studies-*** $PM_{2.5}$ exposures can induce systemic inflammation (Ghio, Kim & Devlin, 2000). Biomarkers of inflammation are increasingly produced after just 2 hours of exposure to high concentrations of $PM_{2.5}$ (Ghio, Kim & Devlin, 2000). These biomarkers include C-reactive protein, pulmonary neutrophils, fibrinogen, interleukin-6 and tumor necrosis factor-a (van Eden et al., 2001; Moller & Loft, 2010; Huang et al., 2012). Biomarkers of oxidative stress are oxidized lipids, which are an atherogenic precursor (van Eden et al., 2001; Moller & Loft, 2010; Huang et al.,

2012). Carotid artery intima-media thickness is a surrogate marker for atherosclerotic progression (Kunzli et al., 2005; Diez et al., 2008; Bauer et al., 2010; Adar et al., 2013). Furthermore, PM exposure in mice with atherosclerosis have higher amounts of low density lipoproteins (Sun et al., 2005; Araujo et al., 2008; Campen et al., 2010; Bai et al., 2011). The study by Sun et al. (2005), considered mice assigned randomly to PM2.5 exposure and filtered air exposure groups. It was found that there was significantly higher plaque development in the PM2.5 exposure group (Sun et al., 2005).

Other CVDs and risk factors related to the PM air pollution response include myocardial infarction, insulin resistance and obesity (Xu et al., 2012; Liu et al., 2014; Marchini et al., 2016; Hamanaka & Mutlu, 2018). There is an effect of PM on insulin resistance in mice models (Sun et al., 2009; Liu et al., 2014; Liu et al., 2014).

A study conducted by Liu et al. (2014), using mice models, found that PM2.5 exposure modulates insulin resistance through the mediation of visceral adipose tissue inflammation responses, both independent and dependent of CC-chemokine receptor 2 (which is known to be involved in inflammatory responses). Furthermore, this PM-related insulin resistance seems to increase the likelihood of PM-related endothelial dysfunction (O'Neill et al., 2005). A study by Xu et al. (2010), finds that early life exposure to fine particulate matter, in mice models, results in insulin resistance and obesity. In the mice model, PM2.5 exposure has also been linked to myocardial infarction through cytokine release from lung macrophages (Marchini et a., 2016).

***5.1.3.3 Subclinical Association and Plausible Mechanisms: Cell Biology and In Vitro Studies-*** It is believed that $PM_{2.5}$ exposure results in the release of reactive oxygen species and in turn, oxidative stress responses. In particular, several markers of oxidative stress are associated with $PM_{2.5}$ exposure (Moller & Loft, 2010; Jacobs et al., 2011; Huang et al., 2012). Various airway, nose and lungs cells, respond to $PM_{2.5}$ with an increase in reactive oxygen species and oxidative stress markers. This includes epithelial cells (Mutlu et al., 2006; Soberanes, Panduri, Mutlu, Ghio, Bundinger & Kamp, 2006; Manzo, LaGier, Slade, LedBetter, Richards & Dye, 2012; Hong et al., 2016; Wang et al., 2017), endothelial cells (Li et al., 2009; Montiel-Davalos, Ibarra-Sanchez, Ventura-Gallegos, Alfaro-Moreno & Lopez-Marure, 2010), macrophages (Li et al., 2003; Ohyama et al., 2008; Zhao et al., 2016) and cardiomyocytes (Cao et al., 2016; Yang et al., 2018).

***5.1.3.4 Clinical Association and Plausible Mechanism: Human Studies-*** Particulate matter air pollution is associated not just with the prevalence and risk of CVD and CVD related mortality, but also with clinical pathologies of CVD (Ghio, Kim & Devlin, 2000). This includes inflammation, arrhythmia, atherosclerosis, thrombosis, oxidative stress and endothelial dysfunction (Hamanaka & Mutlu, 2018).
Vascular function is also seen to be impacted by exposure to PM. For example, arterial vasoconstriction is one result of exposure to diesel exhaust (Brook et al., 2002). Furthermore, long-term exposure to PM air pollution is associated with hypertension (Coogan et al., 2012; Chen et al., 2014). It is suggested that

hypertension, as well as vasoconstriction, that results due to long-term air pollution exposure, can exacerbate heart failure (Van Hee et al., 2009; Leary et al., 2014). Cardiac arrhythmias and increased heart rate have also been found to be associated with pollution exposure (Riediker et al., 2004; Dockery et al., 2005; Rich et al, 2006; Link et al., 2013; Folino et al., 2017). PM and insulin resistance have also been linked, whereby, it is suggested that PM is a modifiable risk for diabetes mellitus (Brook et al., 2013; Thiering et al., 2013; Wolf et al., 2016).

The increased likelihood of thrombosis as a result of air pollution exposure is shown to cause arterial and venous thrombotic events such as ischemic cerebrovascular events, myocardial infarction and deep venous thrombosis (Hamanaka & Mutlu, 2018). Important coagulation factors, Plasminogen Activator Inhibitor-1 and Plasminogen Activator, are up-regulated and inhibited, respectively, as a result of PM exposure (Hamanaka & Mutlu, 2018; Liu et al., 2017; Mills et al., 2005; Chuang et al., 2007; Mills et al., 2007).

The biological mechanisms underlying the association between CVD and air pollution are hypothesized to be three-fold (Hamanaka & Mutlu, 2018; Brook et al., 2010; Chin et al., 2015; Cosselman, Navas-Acien & Kaufman, 2015; Franklin, Brook & Pope, 2015). The first hypothesized mechanism through which CVD and air pollution are thought to be associated is the inflammatory response, which is a result of air pollution, and can induce CVD such as atherosclerosis, thrombosis and endothelial dysfunction (Brook et al., 2010; Chin et al., 2015; Cosselman, Navas-Acien & Kaufman, 2015; Franklin, Brook & Pope, 2015). This is thought to occur through inflammatory cytokine production which is dependent on reactive oxygen

species (i.e. oxidative stress response) (Brook et al., 2010; Chin et al., 2015; Cosselman, Navas-Acien & Kaufman, 2015; Franklin, Brook & Pope, 2015). It is also hypothesized that the second mechanism through which PM induces CVD is through sensory receptors in the lung (Brook et al., 2010; Chin et al., 2015; Cosselman, Navas-Acien & Kaufman, 2015; Franklin, Brook & Pope, 2015). It is suggested that the activation of the sympathetic pathway in the autonomic nervous system and the hypothalamic pituitary adrenal axis has a role in this (Brook et al., 2010; Chin et al., 2015; Cosselman, Navas-Acien & Kaufman, 2015; Franklin, Brook & Pope, 2015). The third hypothesized mechanism is the possibility of translocation of PM air pollution particles, whereby, introduction into the circulatory system may induce inflammation (Brook et al., 2010; Chin et al., 2015; Cosselman, Navas-Acien & Kaufman, 2015; Franklin, Brook & Pope, 2015).

Epigenetics are also an important consideration to better understand the association between air pollution and CVD, though little is known about the biological mechanism. Mice model studies have shown that early-life exposure to air pollution can have long term effects (Weldy, Liu, Liggitt & Chin, 2014). Methylation and histone modification seem to be epigenetic mechanisms that are a result of exposure to air pollution (Yauk et al., 2008; Baccarelli et al., 2009; Baccarelli et al., 2010; Madrigano et al., 2011). A complete understanding of the epigenetic changes as a result of the association between CVD and air pollution is still limited.

## 5.2 Relationship between COPD and CVD

### *5.2.1* Epidemiology

An association between impaired lung function and CVD has been determined since as early as 1970 (Friedman, Klatsky & Siegelaub, 1976; Sin, Wu & Man, 2005). Lung function impairment, which is determined through spirometry measurement, is a risk factor for CVD independent of other factors such as smoking or breathlessness (Friedman, Klatsky & Siegelaub, 1976; Sin & Man, 2005; Onishi, 2017). In 2013, a paper stated that COPD increases the risk of CVD independent of common confounders (Mullerova, Agusti, Erqou & Mapel, 2013). Furthermore, it was also found that based on various studies on the association between CVD and COPD, the prevalence of CVD among COPD patients was anywhere from 28% to 70% (Mullerova, Agusti, Erqou & Mapel, 2013). Moreover, for COPD patients the prevalence of ischemic heart disease, heart failure, stroke and arrhythmia, is 20-60%, 10-30%, 10-20+% and 10-15%, respectively.

Impaired lung function is also strongly associated with mortality due to ischemic heart disease (Hole et al., 1996). In fact, impaired lung function was among the highest factors contributing to mortality due to ischemic heart disease (Hole et al., 1996). For example, the risk of ischemic heart disease mortality due to smoking, hypertension and impaired lung function was 38%, 30% and 26% in men and 32%, 40% and 24% in women (Hole et al., 1996).

A decade long longitudinal study found that approximately 50% of all hospitalizations of COPD patients were due to CVD related events (Anthonisen et al., 1994). CVD was the second leading cause of death for these patients and ischemic heart disease was estimated to be accountable for approximately two-third of all these cases (Anthonisen, Connett, Enright & Manfreda, 2001). Observational studies found

that the morbidity and mortality due to CVD is over twice as high in COPD patients as compared to non-COPD patients (Global Initiative for Chronic Obstructive Lung Disease, 2019; Chen, Thomas, Sadatsafavi & Fitzgerald, 2015).

Furthermore, patients with exacerbation due to COPD are at increased risk for a major CVD event such as stroke or myocardial infarction (Crisan et al., 2019; Global Initiative for Chronic Obstructive Lung Disease, 2019; Chen, Thomas, Sadatsafavi & Fitzgerald, 2015). CVD risk factors such as hypertension, smoking, etc. are also prevalent among COPD patients while inducing both major CVD events and COPD exacerbation (Crisan et al., 2019; Global Initiative for Chronic Obstructive Lung Disease, 2019; Chen, Thomas, Sadatsafavi & Fitzgerald, 2015; Kunisaki et al., 2018). The prediction of mortality in COPD patients improved as much as 17.1% after accounting for CVD risk (Lee et al., 2012).

In another study, it was found that the risk of myocardial infarction and stroke went up by 2.27 and 1.26 times, respectively, post-COPD exacerbation (Donaldson, Hurst, Smith, Hubbard & Wedzicha, 2010). A study with 13,471 participants found that the risk of sudden death due to cardiac reasons was twice as high in COPD patients as compared to non-COPD patients, whereas, the risk of sudden cardiac death was three times as high in patients with more frequent COPD exacerbations (Lahousse et al., 2015).

***5.2.2 Subclinical Association and Plausible Mechanisms: Cell Biology and Animal In Vivo Studies***- There is a lack of animal, in vivo studies considering the subclinical association between COPD and cardiovascular diseases. However, the effect of e-

cigarette uses in mice and the effect on cardiovascular outcome has indeed been explored (Olfert et al., 2018). Increased arterial stiffness and vasculature reactivity was impaired by long-term exposure to e-cigarettes (Olfert et al., 2018). Monocytes have been found to play a role in inflammatory responses, as seen in mice models (Tacke et al., 2007). Animal studies find that inflammation in the lungs affects systemic circulation through macrophages that induce inflammation (van Eden et al., 2001; Terashima et al., 1997). A study by Smith et al. (1989), conducted in dogs and sheep, finds that lung proteins enter circulation.

***5.2.3 Subclinical Association and Plausible Mechanisms: Cell Biology and In Vitro Studies***- The inflammatory response during COPD is thought to be linked to atherosclerosis through monocytic cells (Tacke et al., 2007). Post-cytokine release, cells such as monocytes, mast cells and T-cells are abundant (Liuzzo et al., 2000; Kovanen, Kaartinen & Paavonen, 1995; Tacke et al., 2007). Oxidative stress-related damage and inflammation due to COPD is thought reduce the length of telemores of cells in circulation (Savale, Chaouat, Bastuji-Garin, Marcos, Boyer, Maitre, Sarni, Housset, Weitzenblum, Matrat, Corvoisier, Rideau, Boczkowski, Dubois-Rande, Chouaid & Adnot, 2009; Tsuji, Aoshiba & Nagai, 2006). This is believed to have a potential effect on immunity and risk of cardiac outcomes (Savale, Chaouat, Bastuji-Garin, Marcos, Boyer, Maitre, Sarni, Housset, Weitzenblum, Matrat, Corvoisier, Rideau, Boczkowski, Dubois-Rande, Chouaid & Adnot, 2009; Tsuji, Aoshiba & Nagai, 2006).

***5.2.4 Clinical Association and Plausible Mechanisms: Human Studies***- The mechanism through which COPD increases the risk of CVD events, morbidity and mortality is not fully understood, but there are several proposed mechanisms, including inflammation and mechanical (hyperinflation). The likelihood of hyperinflation in COPD patients is thought to contribute to increased diastolic blood pressure and reduce left and right ventricular contractility, which is known to increase the risk of CVD (Smith et al., 2013). COPD patients often display endothelial dysfunction, inflammation (myocardial) and artery stiffness, which are signs of blood circulation related inflammatory responses (Paulus & Tschope, 2013; Patel et al., 2013; Luehrs et al., 2018). Inflammatory mediators found in COPD patients are thought to contribute to atherosclerotic plaque build-up and in turn, a higher risk of CVD morbidity and mortality (Hill et al., 2011; Danesh et al., 2008). It is believed that the inflammatory pathway and cytokines may have a role to play (Crisan et al., 2019). A theoretical model created to predict the mechanism through which smoking and other risk factors cause CVD illustrated that inflammatory mediators in the circulatory system causing plaque initiation and in turn, CVD, may also play a role in macrophage-related inflammatory responses in the lung (van Eden, Leipsic, Man & Sin, 2012).

The introduction of cytokines into the circulatory system is thought to induce atherosclerosis (Crisan et al., 2019). Studies that have tried to determine the role of markers in such theoretical models have not found consistent and promising results (Crisan et al., 2019). According to a 2018 systematic review, fibrinogen, interleukin-6 and total bilirubin are high-yield predictors of mortality related to COPD (Goncalves,

Guimaraes, Van Zeller, Menezes, Moita & Simao, 2018). However, Troponin 1 has been found to be a predictor of future CVD related death and events in COPD patients (Adamson et al., 2018).

## Chapter 3: Study Rationale, Hypothesis and Study Objectives

The study hypothesis is that there is a relationship between ambient air pollution concentration and CVD, and that COPD and the severity of airflow obstruction amplify this relationship in an aging population.

This MSc thesis project will have the following specific research objectives:

(1) To assess the relationship of ambient air pollution (more specifically fine particulate matter, PM2.5) and ischemic heart disease, in an aging population;

(2) To assess whether COPD exposure and severity of airflow obstruction modulates the relationship of ambient air pollution and ischemic heart disease, in an aging population.

This new knowledge would be of importance considering that COPD has recently been described as the pulmonary component of systematic endothelial disease whereby a range of 'inflammageing' processes simultaneously affect other organs, such as CVD (Fabbri, 2016; Rabe, 2017). Furthermore, new convincing evidence could lead to a more targeted approach for the management of CVD in people with COPD.

## Chapter 4: Manuscript

**Title:** Ambient air pollution and cardiovascular diseases: Is the relationship amplified by chronic obstructive pulmonary disease in an aging population?

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**Running title:** Air pollution, cardiovascular disease and COPD in an ageing population study

**Abstract:**

**Introduction** Cardiovascular disease (CVD) is the second leading cause of death globally. It has been linked with exposure to ambient air pollution, and presence of Chronic Obstructive Pulmonary Disease (COPD). The combined effect of air pollution and COPD on CVD, and in particular, ischemic heart disease, has not been evaluated.

**Methods** The Canadian Longitudinal Study on Aging (CLSA) database was used to assess the relationship between air pollution and CVD, and the combined effect of air pollution and COPD on CVD, in particular, ischemic heart disease in this cross-sectional study. Multiple logistic regression and interaction models were conducted, adjusted for sociodemographic variables such as age, sex, highest education level attained, total household income, ethnicity, as well as, BMI, diet (frequency of fruits and vegetables eaten), smoking status, in addition to the main independent and dependent variables, $NO_2$ concentration, $PM_{2.5}$ concentrations, $O_3$ concentrations, and ischemic heart disease diagnosis.

**Results** Statistically significant associations were demonstrated between air pollution and ischemic heart disease: 6%, 3% and 4% increase in the odds of ischemic heart disease per 1 point increase of the exposure, $PM_{2.5}$, $NO_2$, and $O_3$ ($p<0.001$), respectively. There was, however, no statistically significant combined effect of air pollution and COPD, and severity of airflow obstruction, on ischemic heart disease.

**Conclusion** The positive relationship between ischemic heart disease and ambient air pollution exposure is in line with previous evidence in the literature. The hypothesized interaction between COPD and air pollution on ischemic heart disease prevalence was not supported. Longitudinal studies with a larger number of COPD subjects are needed before we can be more confident of our conclusion.

## Introduction

Globally, the burden of Cardiovascular Diseases (CVD) is immense and rapidly growing. There is also a growing body of information surrounding the relationship between air pollution and CVD. In particular, among the various air pollution components, $PM_{2.5}$ is thought to be one of the major contributors to CVD morbidity and mortality (Watkins et al., 2013; Rajagopalan, Al-Kindi & Brook, 2018). In 2015 alone, approximately 4.2 million deaths, a the majority of which were CVD related, could be attributed to $PM_{2.5}$ air pollution exposure (Cohen et al., 2017).

There are several proposed pathways by which air pollution is said to be linked to CVD, including an inflammatory response resulting in cytokine production, suggested to be liked with the induction of atherosclerosis and thrombosis (Brook et al., 2010; Chin et al., 2015; Cosselman, Navas-Acien & Kaufman, 2015; Franklin, Brook & Pope, 2015). Another proposed pathway is linked with sensory receptors located in the lung and the activation of the sympathetic pathway (Brook et al., 2010; Chin et al., 2015; Cosselman, Navas-Acien & Kaufman, 2015; Franklin, Brook & Pope, 2015). An alternative pathway suggests the potential translocation of PM particles into the circulatory system and subsequent inflammation as the mechanism linking air pollution and CVD (Brook et al., 2010; Chin et al., 2015; Cosselman, Navas-Acien & Kaufman, 2015; Franklin, Brook & Pope, 2015).

Developing data strongly suggests that there is an association between CVD and chronic respiratory illnesses, and in particular, Chronic Obstructive Pulmonary Disease (COPD) (Nishiyama et al., 2010; Man, Van Eeden & Sin, 2012). Emerging knowledge reveal that this association is independent of other common confounders, including age and cigarette smoke

(Finkelstein, Cha & Scharf, 2009; Agusti et al., 2012; Onishi, 2017; GOLD, 2017). Furthermore, lung function impairment has been identified as an independent risk factor for CVD (Friedman, Klatsky & Siegelaub, 1976; Sin & Man, 2005; Sin, Wu & Man, 2005; Onishi, 2017).

Of recent time, it has been found that the prevalence of COPD is linked to increased PM concentrations (Doiron et al., 2019). Our understanding of the biological mechanisms that link COPD and various forms of CVD has improved significantly over the past decade. But despite broad acceptance of the prognostic significance of CVDs in COPD, there remains widespread under-recognition and under-treatment of comorbid CVD in this population. Given the link between air pollution and CVD, as well as the relationship between ambient air pollution and COPD, addressing whether CVD morbidity, in relation to ambient air pollution, is independent or amplified by COPD is a gap in our current body of knowledge (Di, Dai, Wang, et al., 2017; Di, Wang, Zanobetti, et al., 2017).

One of the objectives of the current study was to assess whether COPD and airflow obstruction severity modulates the relationship of ambient air pollution and ischemic heart disease, in an aging population. We first assessed, that in an aging population, ambient air pollution contributes to the occurrence of ischemic heart disease (IHD), and then assessed evaluated whether this effect was modified when air pollution is considered in combination with COPD. It was hypothesized that there is a relationship between ambient air pollution concentration and CVD, and that COPD and the severity of airflow obstruction amplify this risk in an aging population.

**Methods**

A cross-sectional study design was conducted, that made use of a population-based study, the Canadian Longitudinal Study on Aging (CLSA) database, to achieve the study objectives.

**Study Population**

The CLSA is a cohort study collecting data on 51,388 individuals (ages 45-85) across Canada (clsa elcv, 2020; Raina et al., 2009). Spirometry data is collected from 11 sites across Canada (clsa elcv, 2020; Raina et al., 2009). Research Ethics Board approval for data from all 11 sites has been obtained. Individuals included in the database are fluent English and/or French speakers (clsa elcv, 2020; Raina et al., 2009).

The CLSA has currently completed two waves of data collection (clsa elcv, 2020; Raina et al., 2009). The first wave of data collection was used in this study. The data collection for this wave of data was completed between 2011 and 2015 (clsa elcv, 2020; Raina et al., 2009). Data has been collected using telephone interviews, at-home interviews, and visits to data collection sites (once every three years) for physical assessments (e.g. spirometer test, etc.) (clsa elcv, 2020; Raina et al., 2009).

Of the 51,388 individuals in the CLSA, this study has focused on 30,097 participants, as only these participants have completed the in-home interviews and on-site assessments (clsa elcv, 2020). The remaining 21,241 participants completed the telephone interview only, and as such, did not have spirometry to confirm the diagnosis of COPD. The CLSA is well-suited for this study as the database's inclusion criteria is individuals in Canada over the age of 45 and COPD clinically presents itself mostly in individuals over the age of 40 (clsa elcv, 2020; Raina et al., 2009; GOLD, 2017). The inclusion criteria for this particular study were individuals with data

available on: (1) spirometry including forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) (2) IHD diagnosis (3) fine particulate matter air pollution concentration and (4) other confounding variables, including age, sex, highest education level attained, total household income, BMI, ethnicity, diet (frequency of fruits and vegetables eaten per day), length of primary highway within 200m of postal code, and smoking status, with a complete case analyses approach. The exclusion criterion was any participant missing one of the aforementioned variables. Individuals with missing variables were excluded from the study.

**Definitions of Independent and Dependent Variables: COPD, CVD, and Air Pollution**

**COPD definitions**

**COPD is defined** using the Tiffeneau-Pinelli fixed ratio index (FEV1/FVC). The Lower Limit of Normal (LLN) is another definition of COPD, in addition to the fixed post-bronchodilator ratio of 0.70 in which individuals with a spirometry FEV1/FVC<0.70, were considered to have COPD (Pellegrino et al., 2005; Hansen, Sun & Wasserman, 2007; GOLD 2017). For the LLN COPD definition, a Tiffeneau-Pinelli index lower than the fifth percentile of the patients age-matched, healthy reference group was considered a COPD diagnosis (Pellegrino et al., 2005; Hansen, Sun & Wasserman, 2007). In particular, LLN was determined using the equation of National Health and Nutrition Examination Survey (NHANES) III data set (Hankinson, Odencrantz & Fedan, 1999; Smith, 2018).

In this study, $FEV_1$ was used in the interaction model for the secondary objective. Furthermore, both LLN was utilized to consider the effect of COPD on the relationship between air pollution and cardiovascular disease; in particular, individuals were subdivided in subsets of COPD severity

by GOLD 1 or 2+ in supplementary analysis. Fixed ratio FEV1/FVC<0.70 for COPD was used as an alternative definition for COPD.

**CVD definitions**

**CVD subjects was defined** using the self-reported ischemic heart disease variable. CVD subjects included anyone who responded yes to the following question: " Has a doctor ever told you that you have heart disease?". Additional definitions for heart disease were used in sensitivity analyses, including participants' responses to self-reported myocardial infarction (MI): "Has a doctor ever told you that you have had a heart attack or myocardial infarction?".

**Air Pollution**

To assess the relationship between ambient air pollution exposure and ischemic heart disease, we used annual average concentrations of fine particulate matter (PM2.5), ozone (O3), and nitrogen dioxide (NO2) provided by the Canadian Urban Environmental Health Research (CANUE) consortium and linked to the residential postal codes of CLSA participants (Brook et al., 2018). $NO_2$ concentrations (parts per billion, ppb) were estimated using a national land use regression (LUR) model for the year 2006 and adjusted for subsequent years using monitoring station data. $NO_2$ (ppb) LUR was formulated using satellite $NO_2$ estimates, road lengths, industrial land, and tools indicated in the work by Hystad et al., 2011. $O_3$ estimations (ppb) were made using the Canadian Hemispherical Regional Ozone and NOx System and Global Environmental Multi-scale Modelling Air Quality and Chemistry Model (Environment and Climate Change Canada). This allowed for the incorporation of estimations from 2002-2015. $PM_{2.5}$ concentrations (ug/mL) were derived from satellite data (Aerosol Optical Depth estimate using the NASA MODIS

instrument) from all across North America from 2000-2012. This data was adjusted for regional bias using a statistical model, a geographic regression, incorporating ground-based observations. Fine particulate matter air concentration of 10ug/$m^3$, on an annual basis, was considered to be below WHO air quality guidelines (Ambient (Outdoor) Air Quality and Health, World Health Organization).

**Statistical Analysis**

Frequencies and percentages or mean and standard deviations were used to describe participant characteristics and health outcome and exposures. Covariates included age, sex, highest education level attained, total household income, BMI, ethnicity, diet (frequency of fruits and vegetables eaten), smoking status, in addition to the main exposure and outcome variables, $NO_2$ concentration, $PM_{2.5}$ concentrations, $O_3$ concentrations, and IHD diagnosis. In this study, due to the lack of post-bronchodilator (post-BD) sub-cohort, sensitivity analysis excluding participants with asthma, was used in order to mitigate limitations produced by the lack of post-BD in the COPD definition. The SPSS Statistics Software (Version 23.0) and SAS software were used for analysis.

**For the primary objective, we first ascertained the relationship of ambient air pollution (more specifically, fine particulate matter, PM2.5) and ischemic heart disease, in this aging population.** Multiple logistic regression models using ischemic heart disease as the outcome and air pollution metrics (e.g. $O_3$, $PM_{2.5}$ and $NO_2$ concentrations) as the main exposures were conducted to calculate the predictability of exposures on ischemic heart disease. The regression coefficients were used to generate odds ratios (OR with 95% confidence intervals), adjusting for

age, sex, smoking, and other important covariates. Separate models were run for each main exposure variable, in interquartile quartiles and per unit increases.

**To achieve the secondary objective, which was to assess whether COPD exposure and severity of airflow obstruction modulates the relationship of ambient air pollution and ischemic heart disease, in an aging population,** interaction terms between COPD status ($FEV_1$) and ambient air pollution estimates were included in our models. As described above, separate adjusted logistic regressions were used to estimate the modification effect of COPD, and in particular, airflow obstruction, on the association between each pollutant and CVD. COPD and airflow obstruction was considered using the continuous variable $FEV_1$, as well as using the lower limit normal (LLN) and fixed ratio. To examine COPD effect modification, we included interaction terms between the continuous variable, $FEV_1$ and each air pollutant metric in the main model. In additional tables, analysis was stratified by COPD status (non-COPD, GOLD-1, GOLD-2+) for both LLN and fixed ratio definitions.

For the primary objective, associations between air pollution and CVD was expressed per interquartile range increase in pollutant concentrations and as per point increase. For the secondary objective, only the former was conducted to be able to determine the interaction between per IQR increase the air pollution metric and per 100mL FEV in each model. Sensitivity analysis included additional heart disease questions relating to MI in addition to self-reported ischemic heart disease, excluding for asthma.

**Sample size calculation**

Primary Objective. To estimate the association between CVD and PM2.5

Proc POWER in SAS was used to compute the statistical power. Based on the available recruited subjects n=18,320, if 9.6% of subjects will develop CVD in this population, we can provide 85% power to detect a OR of smaller than 0.935 and greater than 1.07, a mean and standard deviation for PM2.5 of 5.32 and 1.22 respectively, with two sides and an alpha error of 0.05 (Please see Figure 2 below).

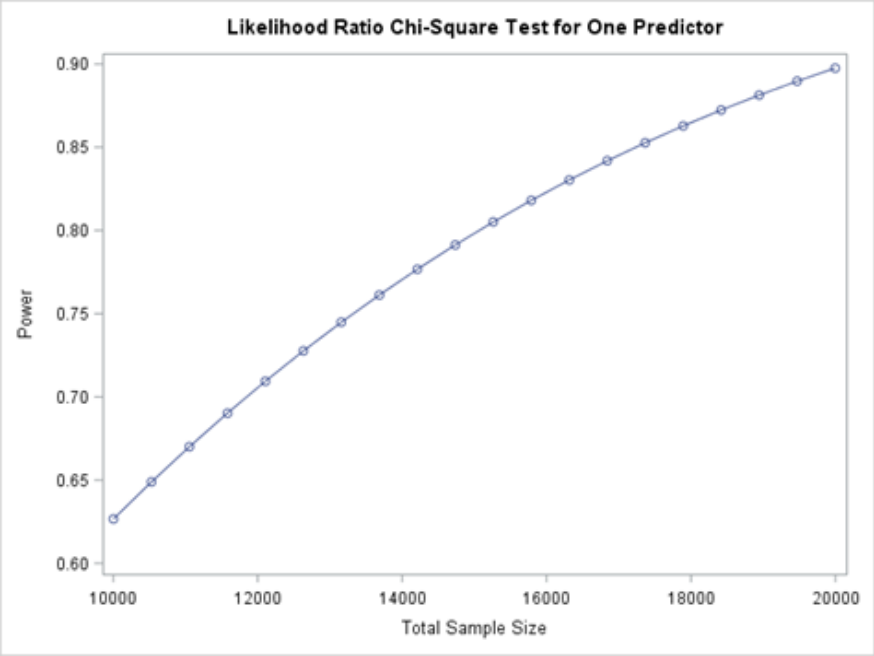


Figure 2. Sample size calculation test for the primary objective considering the association between ischemic heart disease and the primary air pollution metric, $PM_{2.5}$.

**Results**

*Study Population and Characteristics*

From the original sample of 30,097 participants, 18,118 participants were included in the analytical sample after excluding those with missing data for self-reported heart disease

diagnosis, COPD diagnosis (i.e. spirometry), $PM_{2.5}$ air pollution concentration, and co-variables of importance(Figure 3).

Table 1 presents the differences between the original and analytical sample populations in age, BMI, smoking status, and cases of cardiovascular diseases. Participants in the original sample were slightly older, with a higher BMI and more likely to be an ever smoker than the analytical sample. In particular, the mean study population age was 61.9 ± 10.0, with a mean BMI of 27.9 ± 5.3. There are 48.2% male participants, and 96.1% Caucasian study participants (other ethnicities include North East Asian, African American, South East Asian, and Other/Mixed). The majority of participants (35.3%) were in the '$50,000 or more, but less than $100,000' total household income category, with the least number of participants (4.3%) in the 'Less than $20,000' category. Most participants were either never or former smokers (49.4% and 42.6%, respectively), with only 8% participants being current smokers. There was a very small population of COPD participants in the study sample, with only 11.5% participants with fixed ratio COPD and 4.9% participants with LLN COPD. There were more cases of cardiovascular diseases and related comorbidities, such as ischemic heart disease, MI and asthma in the original population as compared to the analytical sample. A total of 1769 (9.8%) of participants in the study sample reported having ischemic heart disease.

Air pollution metrics considered include, $PM_{2.5}$, $NO_2$, and $O_3$, of which the mean (± SD) and median (minimum-maximum) concentrations are: 6.5 (± 1.8) & 6.6 (1.8-12), 9.3 (± 3.2) & 9.16 (0.75-16.86), and 23.7 (± 3.4) & 32.1 (17.02-31.81), respectively. The $PM_{2.5}$, $NO_2$, and $O_3$ IQR are 2.8, 4.27, and 4.78, respectively.

*COPD versus Non-COPD participants*

As presented in Table 2, participants with COPD defined by the LLN had a lower percentage of post-secondary education attainment and lower total household income in comparison with the non-COPD group. Both groups did however have similar ethnicity, with slightly more South East Asian participants in the COPD LLN group than in the non-COPD group. The non-COPD group had more never smokers and higher $FEV_1$ and FEV/FVC, along with higher air pollution concentrations, in relation to the COPD LLN group. Asthma, MI and COPD, including phlegm production in the mornings, most mornings, and most days, were all more prevalent in the COPD group as compared to the non-COPD group.

*Primary Analysis: Relationship between Ischemic Heart Disease and Air Pollution*

Table 4 shows the relationship between air pollution metrics (i.e. $PM_{2.5}$, $NO_2$, and $O_3$) and ischemic heart disease. There was a 6%, 3% and 4% increase in the odds of ischemic heart disease with the per point increase of exposure of $PM_{2.5}$, $NO_2$, and $O_3$. An increase of the odds of 24%, 25% and 35% for the second, third, and fourth $PM_{2.5}$ quartiles; 39%, 42 and 32% for $NO_2$ quartiles; and 55%, 41% and 41% for $O_3$ quartiles. Additionally, there was a 24%, 11% and 4% increase in the odds of ischemic heart disease with the per IQR increase of exposure of $PM_{2.5}$, $NO_2$, and $O_3$, respectively.

*Secondary Analysis*

Table 5 shows the OR between each air pollution metric, including $PM_{2.5}$, $NO_2$, and $O_3$ (per interquartile range, IQR), as well as $FEV_1$ mL, with ischemic heart disease. The p-interaction value for each air pollution and ischemic heart disease OR with $FEV_1$ and ischemic heart disease was not significant.

Table 6 and 7 shows COPD defined by categories of non-COPD, COPD GOLD1, and COPD GOLD2+, using the LLN and fixed ratio, respectively, while excluding those who had reported a physician diagnosis of asthma. This analysis, which is conducted by considering COPD as a categorical variable rather than as a continuous variable, finds similar results, such that there is no effect modification seen by COPD on the relationship between air pollution and ischemic heart disease. Furthermore, on consideration of COPD, with the added exclusion criteria of participants without reported asthma, the same results are found, wherein, there was no effect on the relationship between air pollution and ischemic heart disease by COPD.

Additional analysis was completed using Myocardial Infarction (MI) in place of ischemic heart disease as the cardiovascular disease outcome (Tables 8 and 9). However, as with ischemic heart disease with the different air pollution metrics, $PM_{2.5}$, $NO_2$, and $O_3$, COPD has no effect modification on this relationship between MI and air pollution.

**Discussion**

The primary finding of the study confirmed that there is indeed a relationship between air pollution, including $PM_{2.5}$, $NO_2$, and $O_3$, and ischemic heart disease. However, in relation to the second objective, the study was not able to demonstrate a joint effect of COPD and air pollution

on ischemic heart disease. Non-significant results were found in both an interaction model using COPD as a continuous variable and when COPD was considered categorically (i.e. non-COPD, COPD1, COPD2+ for LLN and fixed ratio definitions). In additional analyses, considering an alternative cardiovascular disease definition of myocardial infarction (MI) in place of ischemic heart disease, the same trend was found, wherein, there was no effect modification by COPD on the relation between air pollution and MI.

The primary finding, that there is in fact a relationship between air pollution, including $PM_{2.5}$, $NO_2$, and $O_3$, and ischemic heart disease, is consistent with existing literature. There is homogenous evidence indicating a strong relation between PM and cardiovascular diseases and related comorbidities, including ischemic heart disease, atherosclerosis, and stroke (Brook *et al.,* 2010; Shah *et al.,* 2015; Newby *et al.,* 2015; Liu *et al.,* 2019; Kaufman *et al.,* 2016; Rajagopalan *et al.,* 2018; Yusuf *et al.,* 2020). Other air pollution metrics, in addition to PM, including ozone and nitrogen dioxide, have also been shown to be closely related with cardiovascular disease in both cross-sectional and longitudinal studies (Di, Dai, Wang, et al., 2017; Di, Wang, Zanobetti, et al., 2017; Paoin et al., 2021; Grande, Ljungman, Eneroth, Bellander, & Rizzuto, 2020). The pathophysiology underlying the relationship between air pollution and cardiovascular diseases, including ischemic heart disease, is not completely understood, and this study finding supports the need to further explore this relationship.

Based on the evidence linking air pollution and ischemic heart disease but also air pollution and COPD (Brook *et al.,* 2010; Shah *et al.,* 2015; Newby *et al.,* 2015; Liu *et al.,* 2019; Kaufman *et al.,* 2016; Rajagopalan *et al.,* 2018; Yusuf *et al.,* 2020; Schraufnagel *et al.,* 2019), there was good

rationale to hypothesize that the relationship of air pollution and CVD would be amplified in group of individuals having COPD. The results of the current study suggest that the exposure effect was homogeneous and COPD was not a characteristic that had an effect modification on the relationship of air pollution and CVD. Literature is lacking, wherein, no studies have previously considered the combined effect of air pollution and COPD on ischemic heart disease.

This study has various strengths, such as a large sample size of 18,118 participants. The sample was representative of an elderly Canadian population with data sites across the country. Another strength is that air pollution was measured robustly within the Canadian Urban Environmental Health Research Consortium dataset which was linked to the Canadian Longitudinal Study on Aging. A limitation for this study is that although the authors attempted to include all cofounders in analyses, it is possible that there are additional cofounders that were not included. Moreover, selection bias may influence the database, such that, volunteering to be included in the study may exclude certain individuals in the Canadian population, such as COPD subjects, resulting in underrepresentation of certain groups. For example, a study completed using a similar database, the Canadian Cohort of Obstructive Lung Disease (CanCOLD), had 1,936 of 6,551 participants with COPD (~30%), whereas, this study had only 1300 of 18,118 (7%) (Bourbeau & Wan Tan, 2019). Although the CanCOLD databases' basis for sample selection was selectively for COPD subjects, the prevalence of COPD patients in the CLSA is lower than expected with 13.8% of all Canadians (in the 10 provinces) over the age of 35 having COPD (Bourbeau et al., 2014; Leung et al., 2021; Statistics Canada, 2021). Classification and recall bias are also potential limitations. The cardiovascular disease variable is a self-reported variable, "Has a doctor ever told you that you have heart disease," not specifying in particular for ischemic heart disease, but rather, heart

disease generally – i.e. classification bias is a limitation. As a self-reported variable is utilized, recall bias is also introduced. Furthermore, as this study is cross-sectional, causal inferences cannot be made. Future longitudinal studies are encouraged to help mitigate this limitation. Additional limitations are that the COPD variable was not established using the clinical post-bronchodilator definition and that that there was a significantly smaller group of COPD participants as compared to non-COPD participants (794 LLN COPD GOLD2+ versus 17,324 non-COPD). The small sample of COPD participants (1227 COPD GOLD2+ fixed ratio and 794 COPD GOLD2+ LLN) as compared to an overall population of 18,118, may have hindered the findings. It would be beneficial to reconsider this association with a larger sample size of COPD participants to non-COPD participants, as well as in a longitudinal study design.

In conclusion, the study findings confirm that there is indeed a relationship between air pollution and ischemic heart disease in a Canadian adult aged population. However, no effect modification by COPD on this relationship between air pollution and ischemic heart disease was demonstrated. Future studies should further assess whether there is an effect modification of COPD on the relationship between air pollution and ischemic heart disease within a longitudinal study design and with a greater sample size of COPD participants including the whole spectrum of disease severity.

## TABLES & FIGURES

**Table 1.** Study participants' characteristics compared to those of the original CLSA population

| **Characteristics** | **Total Original Population (n=29914)** | | **Study Population (n=18118)** | |
|---|---|---|---|---|
| | **N** | **Mean ± SD or n(%)** | **Mean ± SD or n(%)** | **P value** |
| *Sociodemographic Variables* | | | | |
| Age, in year | 29914 | 62.9 ± 10.2 | 61.9 ± 10.0 | <0.001* |
| Sex, male gender, n (%) | 29914 | 14683 (49.1) | 8736 (48.2) | 0.065 |
| Height, cm | 22704 | 168.2 ± 9.7 | 168.4 ± 9.7 | 0.096 |
| BMI | 29779 | 28.1 ± 5.4 | 27.9 ± 5.3 | 0.006* |
| Education, no post-secondary education, n (%) | 29864 | 4451 (14.9) | 2413 (13.3) | <0.001* |
| Total household income, n (%) | | | | |
| Less than $20,000 | 27985 | 1547 (5.5) | 778 (4.3) | <0.001* |
| $20,000 or more, but less than $50,000 | 27985 | 6302 (22.5) | 3718 (20.5) | <0.001* |
| $50,000 or more, but less than $100,000 | 27985 | 9852 (35.2) | 6395 (35.3) | 0.84 |
| $100,000 or more, but less than $150,000 | 27985 | 5498 (19.6) | 3779 (20.9) | 0.002* |
| $150,000 or more | 27985 | 4786 (17.1) | 3448 (19.0) | <0.001* |
| Race, n (%) | | | | |
| Caucasian | 28543 | 27426 (96.1) | 17411 (96.1) | 0.952 |
| African American | 28543 | 203 (0.7) | 120 (0.7) | 0.535 |
| North East Asian | 28543 | 258 (0.9) | 170 (0.9) | 0.704 |
| South East Asian | 28543 | 368 (1.3) | 230 (1.3) | 0.853 |
| Other/mixed | 28543 | 288 (1.0) | 187 (1.0) | 0.808 |
| Diet, n (%) | | | | |
| < 2 sources/day | 29483 | 11357 (38.5) | 6755 (37.3) | 0.476 |
| ≥ 2 & < 3 sources/day | 29483 | 7910 (26.8) | 4915 (27.1) | 0.802 |
| ≥ 3 & < 4 sources/day | 29483 | 4830 (16.4) | 2984 (16.5) | 0.103 |
| ≥ 4 & < 6 sources/day | 29483 | 4232 (14.4) | 2699 (14.9) | 0.097 |
| ≥ 6 sources/day | 29483 | 1154 (3.9) | 765 (4.2) | |
| *Smoking, spirometry, COPD and respiratory symptoms* | | | | |
| Smoking status, n (%) | | | | <0.001* |
| Never | 29913 | 14154 (47.3) | 8954 (49.4) | 0.017* |

| | | | | |
|---|---|---|---|---|
| Former | 29913 | 13065 (43.7) | 7711 (42.6) | <0.001* |
| Current | 29913 | 2694 (9.0) | 1453 (8.0) | 0.007* |
| $FEV_{1,}$ L | 21211 | 2.7 ± 0.8 | 2.7 ± 0.8 | 0.021* |
| $FEV_1$, % predicted | 21201 | 94.7 ± 16.9 | 94.8 ± 17.0 | 0.32 |
| FEV1/FVC | 21204 | 0.8 ± 0.1 | 0.8 ± 0.1 | 0.204 |
| COPD-fixed, n (%) | | | | |
| Non-COPD | 21204 | 18710 (88.2) | 16033 (88.5) | 0.434 |
| Over 80% | 21204 | 1066 (5.0) | 891 (4.9) | 0.618 |
| Over 50%, but under 80% | 21204 | 1279 (6.0) | 1077 (5.9) | 0.715 |
| Over 30%, but under 50% | 21204 | 134 (0.6) | 106 (0.6) | 0.552 |
| Under 30% | 21204 | 14 (0.1) | 11 (0.1) | 0.835 |
| COPD-LLN, n (%) | | | | |
| Non-COPD | 21194 | 20129 (95.0) | 17229 (95.1) | 0.591 |
| Over 80% | 21194 | 271 (1.3) | 226 (1.2) | 0.782 |
| Over 50%, but under 80% | 21194 | 665 (3.1) | 563 (3.1) | 0.863 |
| Over 30%, but under 50% | 21194 | 115 (0.5) | 89 (0.5) | 0.48 |
| Under 30% | 21194 | 14 (0.1) | 11 (0.1) | 0.834 |
| Cough up phlegm in the morning | 29893 | 2047 (6.8) | 1034 (5.7) | <0.001* |
| Cough phlegm most mornings | 29888 | 1366 (4.6) | 704 (3.9) | <0.001* |
| Bring up phlegm most days | 29887 | 1624 (5.4) | 824 (4.6) | <0.001* |
| *Medical Conditions (comorbidities)* | | | | |
| Ischemic heart disease, n (%) | 29914 | 3503 (11.7) | 1769 (9.8) | <0.001* |
| Asthma | 29836 | 3966 (13.3) | 2321 (12.8) | <0.001* |
| Angina | 29812 | 1310 (4.4) | 663 (3.7) | <0.001* |
| MI | 29832 | 1446 (4.8) | 719 (4.0) | <0.001* |
| Angina or MI | 29782 | 2262 (7.6) | 1139 (6.3) | <0.001* |
| *Air Pollution Exposure* | | | | |
| PM2.5 | 29019 | 6.6 ± 1.8 | 6.5 ± 1.8 | 0.059 |
| NO2 | 25443 | 9.3 ± 3.1 | 9.3 ± 3.2 | 0.207 |
| SO2 | 23395 | 1.2 ± 0.8 | 1.2 ± 0.8 | 0.166 |
| O3 | 28730 | 23.8 ± 3.4 | 23.7 ± 3.4 | 0.054 |
| length of primary highway 200m | 29914 | 68.1 ± 75.2 | 67.2 ± 73.4 | 0.962 |

**Table 2.** Characteristics of population (LLN COPD status)

| | Completed cases (including spirometry test) (n=18118) | | | |
|---|---|---|---|---|
| | **Total (n=18118)** | **LLN** | | |
| | | **COPD (n=889)** | **Non-COPD (n=17229)** | **P value** |
| *Sociodemographic Variables* | | | | |
| Age, in year | 61.9 ± 10.0 | 62.5 ± 10.4 | 61.9 ± 9.9 | 0.075 |
| Sex, male gender, n (%) | 8736 (48.2) | 418 (47.0) | 8318 (48.3) | 0.463 |
| Height, cm | 168.4 ± 9.7 | 168.3 ± 10.0 | 168.4 ± 9.7 | 0.696 |
| BMI | 27.9 ± 5.3 | 26.7 ± 5.1 | 28.0 ± 5.3 | <0.001* |
| Education, no post-secondary education, n (%) | 2413 (13.3) | 143 (16.1) | 2270 (13.2) | 0.013* |
| Total household income, n (%) | | | | |
| Less than $20,000 | 778 (4.3) | 62 (7.0) | 716 (4.2) | <0.001* |
| $20,000 or more, but less than $50,000 | 3718 (20.5) | 244 (27.4) | 3474 (20.2) | <0.001* |
| $50,000 or more, but less than $100,000 | 6395 (35.3) | 306 (34.4) | 6089 (35.3) | 0.575 |
| $100,000 or more, but less than $150,000 | 3779 (20.9) | 147 (16.5) | 3632 (21.1) | 0.001* |
| $150,000 or more | 3448 (19.0) | 130 (14.6) | 3318 (19.3) | <0.001* |
| Race, n (%) | | | | |
| Caucasian | 17411 (96.1) | 845 (95.1) | 16566 (96.2) | 0.098 |
| African American | 120 (0.7) | 8 (0.9) | 112 (0.7) | 0.371 |
| North East Asian | 170 (0.9) | 9 (1.0) | 161 (0.9) | 0.814 |
| South East Asian | 230 (1.3) | 21 (2.4) | 209 (1.2) | 0.003* |
| Other/mixed | 187 (1.0) | 6 (0.7) | 181 (1.1) | 0.28 |
| Diet, n (%) | | | | |
| < 2 sources/day | 6755 (37.3) | 358 (40.3) | 6397 (37.1) | 0.059 |
| ≥ 2 & < 3 sources/day | 4915 (27.1) | 233 (26.2) | 4682 (27.2) | 0.528 |
| ≥ 3 & < 4 sources/day | 2984 (16.5) | 142 (16.0) | 2842 (16.5) | 0.682 |
| ≥ 4 & < 6 sources/day | 2699 (14.9) | 119 (13.4) | 2580 (15.0) | 0.194 |
| ≥ 6 sources/day | 765 (4.2) | 37 (4.2) | 728 (4.2) | 0.927 |
| *Smoking, COPD and Air Pollution Exposure* | | | | |
| Smoking status, n (%) | | | | |
| Never | 8954 (49.4) | 260 (29.2) | 8694 (50.5) | <0.001* |
| Former | 7711 (42.6) | 422 (47.5) | 7289 (42.3) | 0.002* |
| Current | 1453 (8.0) | 207 (23.3) | 1246 (7.2) | <0.001* |
| $FEV_{1,}$ L | 2.7 ± 0.8 | 2.0 ± 0.7 | 2.8 ± 0.8 | <0.001* |

| | | | | |
|---|---|---|---|---|
| $FEV_1$, % predicted | 94.8 ± 17.0 | 69.1 ± 15.9 | 96.2 ± 16.0 | <0.001* |
| FEV1/FVC | 0.8 ± 0.1 | 0.6 ± 0.1 | 0.8 ± 0.0 | <0.001* |
| COPD-fixed, n (%) | | | | |
| Non-COPD | 16033 (88.5) | 4 (0.4) | 16029 (93.0) | - |
| Over 80% | 891 (4.9) | 222 (25.0) | 669 (3.9) | - |
| Over 50%, but under 80% | 1077 (5.9) | 563 (63.3) | 514 (3.0) | - |
| Over 30%, but under 50% | 106 (0.6) | 89 (10.0) | 17 (0.1) | - |
| Under 30% | 11 (0.1) | 11 (1.2) | 0 (0.0) | - |
| COPD-LLN, n (%) | | | | |
| Non-COPD | 17229 (95.1) | 0 (0.0) | 17229 (100.0) | - |
| Over 80% | 226 (1.2) | 226 (25.4) | 0 (0.0) | - |
| Over 50%, but under 80% | 563 (3.1) | 563 (63.3) | 0 (0.0) | - |
| Over 30%, but under 50% | 89 (0.5) | 89 (10.0) | 0 (0.0) | - |
| Under 30% | 11 (0.1) | 11 (1.2) | 0 (0.0) | - |
| PM2.5 | 6.5 ± 1.8 | 6.6 ± 1.8 | 6.5 ± 1.8 | 0.056 |
| NO2 | 9.3 ± 3.2 | 9.2 ± 2.9 | 9.3 ± 3.2 | 0.371 |
| SO2 | 1.2 ± 0.8 | 1.2 ± 0.7 | 1.2 ± 0.8 | 0.01* |
| O3 | 23.7 ± 3.4 | 23.3 ± 3.4 | 23.7 ± 3.4 | <0.001* |
| length of primary highway 200m | 67.2 ± 73.4 | 62.3 ± 61.4 | 67.4 ± 73.9 | 0.937 |
| *Medical Conditions* | | | | |
| Ischemic heart disease, n (%) | 1769 (9.8) | 92 (10.3) | 1677 (9.7) | 0.547 |
| Asthma | 2321 (12.8) | 289 (32.7) | 2032 (11.8) | <0.001* |
| Angina | 663 (3.7) | 41 (4.6) | 622 (3.6) | 0.119 |
| MI | 719 (4.0) | 53 (6.0) | 666 (3.9) | 0.002* |
| Angina or MI | 1139 (6.3) | 76 (8.6) | 1063 (6.2) | 0.004* |
| Cough up phlegm in the morning | 1034 (5.7) | 126 (32.7) | 908 (5.3) | <0.001* |
| Cough phlegm most mornings | 704 (3.9) | 91 (14.2) | 613 (3.6) | <0.001* |
| Bring up phlegm most days | 824 (4.6) | 106 (11.9) | 718 (4.2) | <0.001* |

Table 2 displays the characteristics of the participants in the sample population (n = 18,118). Participant characteristics for sociodeomographic variables, such as age, sex, BMI, education, income, race, exposure variables, such as COPD, air pollution (e.g. PM2.5, NO2, SO2, and O3) and medical condition variables, such as angina, MI, ischemic heart disease and phlegm production, are included in Table 2.
Participants are also sub-categorized according to COPD status defined by the lower limit of normal (LLN), determined by the participants healthy age, sex, ethnicity and height matched reference group.

**Table 3.** Characteristics of population (fixed COPD status)

| | Completed cases (including spirometry test) (n=18118) | | | |
|---|---|---|---|---|
| | **Total (n=18118)** | **Fixed ratio** | | |
| | | **COPD (n=2085)** | **Non-COPD (n=16033)** | **P value** |
| *Sociodemographic Variables* | | | | |
| Age, in year | 61.9 ± 10.0 | 66.6 ± 10.4 | 61.3 ± 9.7 | <0.001* |
| Sex, male gender, n (%) | 8736 (48.2) | 1117 (53.6) | 7619 (47.5) | <0.001* |
| Height, cm | 168.4 ± 9.7 | 169.1 ± 9.9 | 168.3 ± 9.7 | <0.001* |
| BMI | 27.9 ± 5.3 | 27.0 ± 5.1 | 28.0 ± 5.3 | <0.001* |
| Education, no post-secondary education, n (%) | 2413 (13.3) | 346 (16.6) | 2067 (12.9) | <0.001* |
| Total household income, n (%) | | | | |
| Less than $20,000 | 778 (4.3) | 132 (6.3) | 646 (4.0) | <0.001* |
| $20,000 or more, but less than $50,000 | 3718 (20.5) | 604 (29.0) | 3114 (19.4) | <0.001* |
| $50,000 or more, but less than $100,000 | 6395 (35.3) | 743 (35.6) | 5652 (35.3) | 0.731 |
| $100,000 or more, but less than $150,000 | 3779 (20.9) | 343 (16.5) | 3436 (21.4) | <0.001* |
| $150,000 or more | 3448 (19.0) | 263 (12.6) | 3185 (19.9) | <0.001* |
| Race, n (%) | | | | |
| Caucasian | 17411 (96.1) | 2019 (96.8) | 15392 (96.0) | 0.065 |
| African American | 120 (0.7) | 14 (0.7) | 106 (0.7) | 0.956 |
| North East Asian | 170 (0.9) | 12 (0.6) | 158 (1.0) | 0.068 |
| South East Asian | 230 (1.3) | 24 (1.2) | 206 (1.3) | 0.608 |
| Other/mixed | 187 (1.0) | 16 (0.8) | 171 (1.1) | 0.204 |
| Diet, n (%) | | | | |
| < 2 sources/day | 6755 (37.3) | 825 (39.6) | 5930 (37.0) | 0.022* |
| ≥ 2 & < 3 sources/day | 4915 (27.1) | 561 (26.9) | 4354 (27.2) | 0.809 |
| ≥ 3 & < 4 sources/day | 2984 (16.5) | 343 (16.5) | 2641 (16.5) | 0.98 |
| ≥ 4 & < 6 sources/day | 2699 (14.9) | 274 (13.1) | 2425 (15.1) | 0.017* |
| ≥ 6 sources/day | 765 (4.2) | 82 (3.9) | 683 (4.3) | 0.485 |
| *Smoking, COPD and Air Pollution Exposure* | | | | |
| Smoking status, n (%) | | | | |
| Never | 8954 (49.4) | 703 (33.7) | 8251 (51.5) | <0.001* |
| Former | 7711 (42.6) | 1044 (50.1) | 6667 (41.6) | <0.001* |
| Current | 1453 (8.0) | 338 (16.2) | 1115 (7.0) | <0.001* |
| $FEV_{1,}$ L | 2.7 ± 0.8 | 2.2 ± 0.7 | 2.8 ± 0.7 | <0.001* |

| | | | | |
|---|---|---|---|---|
| $FEV_1$, % predicted | 94.8 ± 17.0 | 76.5 ± 16.4 | 97.2 ± 15.6 | <0.001* |
| FEV1/FVC | 0.8 ± 0.1 | 0.6 ± 0.1 | 0.8 ± 0.0 | <0.001* |
| COPD-fixed, n (%) | | | | |
| Non-COPD | 16033 (88.5) | 0 (0.0) | 16033 (100.0) | - |
| Over 80% | 891 (4.9) | 891 (42.7) | 0 (0.0) | - |
| Over 50%, but under 80% | 1077 (5.9) | 1077 (51.7) | 0 (0.0) | - |
| Over 30%, but under 50% | 106 (0.6) | 106 (5.1) | 0 (0.0) | - |
| Under 30% | 11 (0.1) | 11 (0.5) | 0 (0.0) | - |
| COPD-LLN, n (%) | | | | |
| Non-COPD | 17229 (95.1) | 1200 (57.6) | 16029 (100.0) | - |
| Over 80% | 226 (1.2) | 222 (10.6) | 4 (0.0) | - |
| Over 50%, but under 80% | 563 (3.1) | 563 (27.0) | 0 (0.0) | - |
| Over 30%, but under 50% | 89 (0.5) | 89 (4.3) | 0 (0.0) | - |
| Under 30% | 11 (0.1) | 11 (0.5) | 0 (0.0) | - |
| PM2.5 | 6.5 ± 1.8 | 6.6 ± 1.8 | 6.5 ± 1.8 | 0.096 |
| NO2 | 9.3 ± 3.2 | 9.2 ± 3.0 | 9.3 ± 3.2 | 0.06 |
| SO2 | 1.2 ± 0.8 | 1.1 ± 0.7 | 1.2 ± 0.8 | 0.232 |
| O3 | 23.7 ± 3.4 | 23.3 ± 3.4 | 23.8 ± 3.4 | <0.001* |
| length of primary highway 200m | 67.2 ± 73.4 | 63.2 ± 65.7 | 67.7 ± 74.3 | 0.076 |
| *Medical Conditions* | | | | |
| Ischemic heart disease, n (%) | 1769 (9.8) | 297 (14.2) | 1472 (9.2) | <0.001* |
| Asthma | 2321 (12.8) | 535 (25.8) | 1786 (11.2) | <0.001* |
| Angina | 663 (3.7) | 130 (6.3) | 533 (3.3) | <0.001* |
| MI | 719 (4.0) | 125 (6.0) | 594 (3.7) | <0.001* |
| Angina or MI | 1139 (6.3) | 207 (10.0) | 932 (5.8) | <0.001* |
| Cough up phlegm in the morning | 1034 (5.7) | 240 (11.5) | 794 (5.0) | <0.001* |
| Cough phlegm most mornings | 704 (3.9) | 170 (8.2) | 534 (3.3) | <0.001* |
| Bring up phlegm most days | 824 (4.6) | 200 (9.6) | 624 (3.9) | <0.001* |

Table 3 displays the characteristics of the participants in the sample population (n = 18,118).

Participant characteristics for socio-demographic variables, such as age, sex, BMI, education, income, race, exposure variables, such as COPD, air pollution (e.g. PM2.5, NO2, SO2, and O3) and medical condition variables, such as angina, MI, ischemic heart disease and phlegm production, are included in Table 3.

Participants are also sub-categorized according to COPD status defined by the fixed ratio (FEV/FVC<0.70).

**Table 4.** Multiple analysis of the association between ischemic heart disease and air pollution metrics

| | Completed cases (n=18118) | |
|---|---|---|
| **Air Pollution Metrics** | **aOR (95% CI)** | **P value** |
| PM2.5 — per increase of 1 point | 1.06 (1.03-1.09) | <0.001* |
| PM2.5 — per increase of IQR (2.80) | 1.18 (1.08-1.28) | <0.001* |
| PM2.5 quartile | | |
| 1st quartile | REF | |
| 2nd quartile | 1.24 (1.06-1.44) | 0.006* |
| 3rd quartile | 1.25 (1.07-1.45) | 0.004* |
| 4th quartile | 1.35 (1.16-1.57) | <0.001* |
| NO2 — per increase of 1 point | 1.03 (1.01-1.05) | <0.001* |
| NO2 — per increase of IQR (4.21) | 1.14 (1.06-1.23) | 0.004* |
| NO2 quartile | | |
| 1st quartile | REF | |
| 2nd quartile | 1.39 (1.18-1.63) | <0.001* |
| 3rd quartile | 1.42 (1.21-1.67) | <0.001* |
| 4th quartile | 1.32 (1.12-1.56) | 0.001* |
| O3 — per increase of 1 point | 1.04 (1.02-1.05) | <0.001* |
| O3 — per increase of IQR (4.78) | 1.18 (1.10-1.27) | <0.001* |
| O3 quartile | | |
| 1st quartile | REF | |
| 2nd quartile | 1.55 (1.33-1.81) | <0.001* |
| 3rd quartile | 1.41 (1.21-1.65) | <0.001* |
| 4th quartile | 1.41 (1.20-1.65) | <0.001* |

Table 4 displays the association between ischemic heart disease and various air pollution metrics, including PM2.5 (fine particulate matter), NO2 (nitrogen dioxide), and O3 (ozone).

Analysis is conducted while adjusting for age, sex, BMI, education level attained, total household income, ethnicity, diet, and smoking status.

Participants are considered using both per point increase of air pollution and quartiles.

**Table 5.** Multiple analysis of the association between ischemic heart disease and air pollution metrics: Interaction between air pollution and FEV1

| | aOR (95% CI) | P value |
|---|---|---|
| **Model 1** | | |
| PM2.5 — per increase of IQR | 1.13 (0.83-1.54) | 0.44 |
| FEV1 — per 100 ML increase | 0.94 (0.91-0.97) | <0.001* |
| Interaction P-value | | 0.826 |
| **Model 2** | | |
| NO2 — per increase of IQRt | 1.34 (1.02-1.75) | 0.037* |
| FEV1 — per 100 ML increase | 0.96 (0.93-0.98) | <0.001* |
| Interaction P-value | | 0.257 |
| **Model 3** | | |
| O3 — per increase of IQR | 1.23 (0.95-1.60) | 0.121 |
| FEV1 — per 100 ML increase | 0.95 (0.90-1.00) | 0.046* |
| Interaction P-value | | 0.73 |

Table 5 displays the interaction between the various air pollution metrics, including PM2.5 (fine particulate matter), NO2 (nitrogen dioxide), and O3 (ozone), and FEV1 (forced expiratory volume), in respect to ischemic heart disease.

Analysis is conducted while adjusting for age, sex, BMI, education level attained, total household income, ethnicity, diet, and smoking status.

Air pollution is considered per increase of IQR (interquartile range).

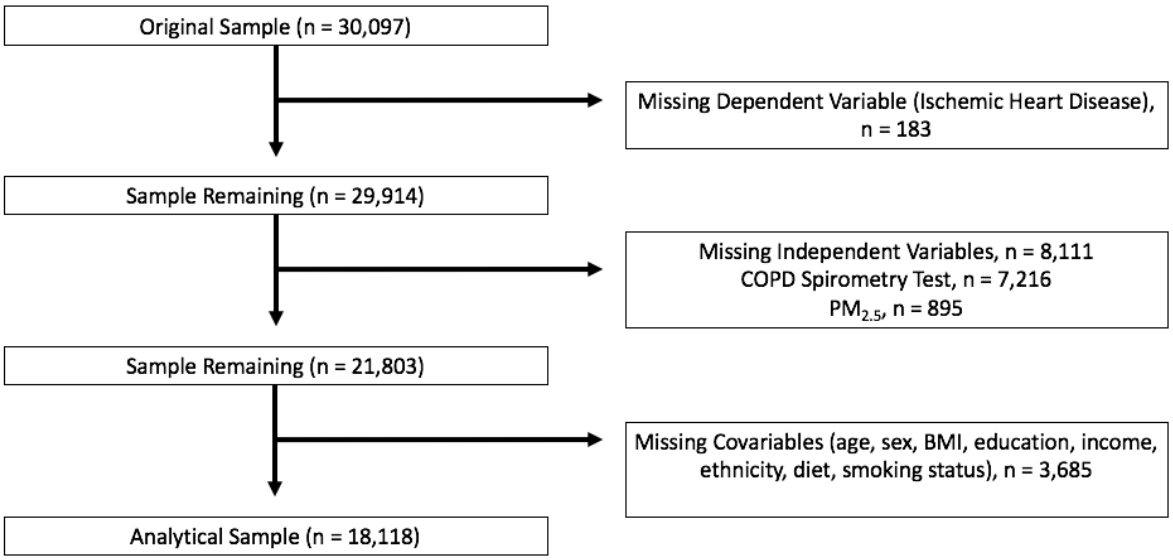


**Figure 3. Study flow diagram.** A flowchart representation of the population and the participants that meet the eligibility criteria, including the dependent (self-reported heart disease), independent ($PM_{2.5}$ air pollution and spirometry tests) and covariables. Covariables include age, sex, highest education level attained, total household income, BMI, ethnicity, diet (frequency of fruits and vegetables eaten per day), length of primary highway within 200m of postal code, and smoking status.

**Sensitivity Analysis Tables and Figures:**

**Table 6.** Multiple analysis of the association between ischemic heart disease and air pollution metrics stratified by COPD status (LLN), excluding asthma

| Variables | Total | | non-COPD-LLN | | COPD-LLN | | Interaction P-value | COPD-GOLD1 | | COPD-GOLD2+ | | Interaction P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | aOR (95% CI) | P value | aOR (95% CI) | P value | aOR (95% CI) | P value | | aOR (95% CI) | P value | aOR (95 % CI) | P value | |
| PM2.5 — per increase of IQR | 1.16 (1.06-1.28) | <0.001* | 1.15 (1.05-1.26) | 0.003* | 1.37 (0.87-2.15) | 0.178 | 0.556 | 1.31 (0.31-5.59) | 0.717 | 1.30 (0.80 - 2.12) | 0.288 | 0.775 |
| NO2 — per increase of IQR | 1.14 (1.05-1.23) | 0.001* | 1.12 (1.04-1.22) | 0.005* | 1.64 (1.02-2.64) | 0.042* | 0.218 | 1.67 (0.31-8.96) | 0.551 | 1.71 (1.00 - 2.92) | 0.052 | 0.437 |
| O3 — per increase of IQR | 1.19 (1.10-1.29) | <0.001* | 1.19 (1.10-1.30) | <0.001* | 1.33 (0.88-2.00) | 0.173 | 0.766 | 2.67 (0.57-12.41) | 0.211 | 1.35 (0.86 - 2.10) | 0.183 | 0.945 |

Table 6 displays the effect modification of COPD (LLN) on the relationship between ischemic heart disease and air pollution, in particular PM2.5 (fine particulate matter), NO2 (nitrogen dioxide), and O3 (ozone), and FEV1 (forced expiratory volume).

Analysis is conducted while adjusting for age, sex, BMI, education level attained, total household income, ethnicity, diet, and smoking status.

Air pollution is considered per increase of IQR (interquartile range). COPD (chronic obstructive pulmonary disease) is considered using the definition of LLN (lower limit of normal).

**Table 7.** Multiple analysis of the association between ischemic heart disease and air pollution metrics stratified by COPD status (fixed), excluding asthma

| Variables | non-COPD-fixed | | COPD-fixed | | Interaction P-value | COPD-GOLD1 | | COPD-GOLD2+ | | Interaction P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| | aOR (95% CI) | P value | aOR (95% CI) | P value | | aOR (95% CI) | P value | aOR (95% CI) | P value | |
| PM2.5 — per increase of IQR | 1.17 (1.06-1.29) | 0.001* | 1.09 (0.85-1.39) | 0.493 | 0.519 | 1.24 (0.84-1.83) | 0.281 | 0.98 (0.71-1.35) | 0.897 | 0.382 |
| NO2 — per increase of IQR | 1.12 (1.03-1.22) | 0.011* | 1.28 (1.01-1.61) | 0.039* | 0.458 | 1.18 (0.82-1.68) | 0.375 | 1.36 (0.99-1.85) | 0.055 | 0.582 |
| O3 — per increase of IQR | 1.19 (1.09-1.30) | <0.001 * | 1.29 (1.05-1.60) | 0.018* | 0.695 | 1.29 (0.92-1.80) | 0.141 | 1.27 (0.96-1.68) | 0.094 | 0.739 |

Table 7 displays the effect modification of COPD (fixed) on the relationship between ischemic heart disease and air pollution, in particular PM2.5 (fine particulate matter), NO2 (nitrogen dioxide), and O3 (ozone), and FEV1 (forced expiratory volume).

Analysis is conducted while adjusting for age, sex, BMI, education level attained, total household income, ethnicity, diet, and smoking status.

Air pollution is considered per increase of IQR (interquartile range). COPD (chronic obstructive pulmonary disease) is considered using the definition of fixed ratio.

**Table 8.** Multiple analysis of the association between MI and air pollution metrics stratified by COPD status

| Variables | Total | | non-COPD-fixed | | COPD-GOLD1 | | COPD-GOLD2 | | COPD-GOLD3+ | | Interaction P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | aOR (95% CI) | P value | aOR (95% CI) | P value | aOR (95% CI) | P value | aOR (95% CI) | P value | aOR (95% CI) | P value | |
| PM2.5 — per increase of IQR | 1.15 (1.02-1.31) | 0.025* | 1.17 (1.02-1.34) | 0.024* | 1.43 (0.83-2.44) | 0.194 | 0.74 (0.48-1.14) | 0.174 | 1.71 (0.69-4.22) | 0.245 | 0.161 |
| NO2 — per increase of IQR | 1.11 (0.99-1.24) | 0.068 | 1.10 (0.98-1.24) | 0.114 | 0.87 (0.53-1.42) | 0.575 | 1.15 (0.77-1.74) | 0.496 | 1.91 (0.81-4.48) | 0.138 | 0.409 |
| O3 — per increase of IQR | 1.11 (0.99-1.24) | 0.071 | 1.08 (0.96-1.22) | 0.199 | 1.16 (0.73-1.85) | 0.533 | 1.23 (0.84-1.79) | 0.294 | 2.17 (0.97-4.85) | 0.058 | 0.724 |

**Table 9.** Multiple analysis of the association between MI and air pollution metrics stratified by COPD status (excluding asthma)

| Variables | Total | | **non-COPD-fixed** | | **COPD-GOLD1** | | **COPD-GOLD2** | | **COPD-GOLD3+** | | **Interaction P-value** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | aOR (95% CI) | **P value** | **aOR (95% CI)** | **P value** | **aOR (95% CI)** | **P value** | **aOR (95% CI)** | **P value** | **aOR (95% CI)** | **P value** | |
| PM2.5 — per increase of IQR | 1.16 (1.02-1.32) | 0.025* | 1.17 (1.02-1.34) | 0.024* | 1.43 (0.83-2.44) | 0.194 | 0.74 (0.48-1.14) | 0.174 | 1.71 (0.69-4.22) | 0.245 | 0.161 |
| NO2 — per increase of IQR | 1.08 (0.96-1.22) | 0.068 | 1.10 (0.98-1.24) | 0.114 | 0.87 (0.53-1.42) | 0.575 | 1.15 (0.77-1.74) | 0.496 | 1.91 (0.81-4.48) | 0.138 | 0.409 |
| O3 — per increase of IQR | 1.12 (1.00-1.26) | 0.058 | 1.12 (0.98-1.27) | 0.093 | 1.27 (0.78-2.07) | 0.341 | 1.13 (0.75-1.71) | 0.561 | 1.45 (0.57-3.68) | 0.437 | 0.948 |

**Supplementary Tables and Figures:**

**Table 10.** Multiple analysis of the association between ischemic heart disease and air pollution metrics stratified by COPD status (LLN)

| Variables | non-COPD-LLN | | COPD-LLN | | Interaction P-value | COPD-GOLD1 | | COPD-GOLD2+ | | Interaction P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| | aOR (95% CI) | P value | aOR (95% CI) | P value | | aOR (95% CI) | P value | aOR (95% CI) | P value | |
| PM2.5 — per increase of IQR | 1.18 (1.08-1.28) | <0.001* | 1.13 (0.77-1.65) | 0.541 | 0.675 | 0.99 (0.32-3.10) | 0.988 | 1.13 (0.75-1.70) | 0.556 | 0.903 |
| NO2 — per increase of IQR | 1.13 (1.05-1.22) | 0.002* | 1.34 (0.92-1.95) | 0.126 | 0.51 | 0.61 (0.21-1.77) | 0.359 | 1.51 (1.00-2.30) | 0.052 | 0.139 |
| O3 — per increase of IQR | 1.18 (1.09-1.27) | <0.001* | 1.35 (0.97-1.89) | 0.076 | 0.519 | 1.55 (0.49-4.87) | 0.455 | 1.38 (0.97-1.98) | 0.077 | 0.758 |

**Table 11.** Multiple analysis of the association between ischemic heart disease and air pollution metrics stratified by COPD status (fixed ratio)

| **Variables** | **non-COPD-fixed** | | **COPD-fixed** | | **Interaction P-value** | **COPD-GOLD1** | | **COPD-GOLD2+** | | **Interaction P-value** |
|---|---|---|---|---|---|---|---|---|---|---|
| | **aOR (95% CI)** | **P value** | **aOR (95% CI)** | **P value** | | **aOR (95% CI)** | **P value** | **aOR (95% CI)** | **P value** | |
| PM2.5 — per increase of IQR | 1.19 (1.08-1.30) | <0.001* | 1.13 (0.77-1.65) | 0.541 | 0.675 | 0.99 (0.32-3.10) | 0.988 | 1.13 (0.75-1.70) | 0.556 | 0.903 |
| NO2 — per increase of IQR | 1.12 (1.04-1.22) | 0.002* | 1.34 (0.92-1.95) | 0.126 | 0.51 | 0.61 (0.21-1.77) | 0.359 | 1.51 (1.00-2.30) | 0.052 | 0.139 |
| O3 — per increase of IQR | 1.17 (1.08-1.27) | <0.001* | 1.29 (1.07-1.56) | 0.007* | 0.462 | 1.24 (0.91-1.69) | 0.175 | 1.28 (1.00-1.62) | 0.046* | 0.78 |

**Table 12.** Air Pollution Metrics

| **Variables** | **Mean ± SD** | **Median** | **Minimum** | **Maximum** | **IQR** |
|---|---|---|---|---|---|
| PM2.5 (ug/mL) | 6.5 ± 1.8 | 6.60 | 1.80 | 12.00 | 2.80 |
| NO2 (ppb) | 9.3 ± 3.2 | 9.16 | 0.75 | 16.86 | 4.27 |
| O3 (ppb) | 23.7 ± 3.4 | 23.10 | 17.02 | 31.81 | 4.78 |

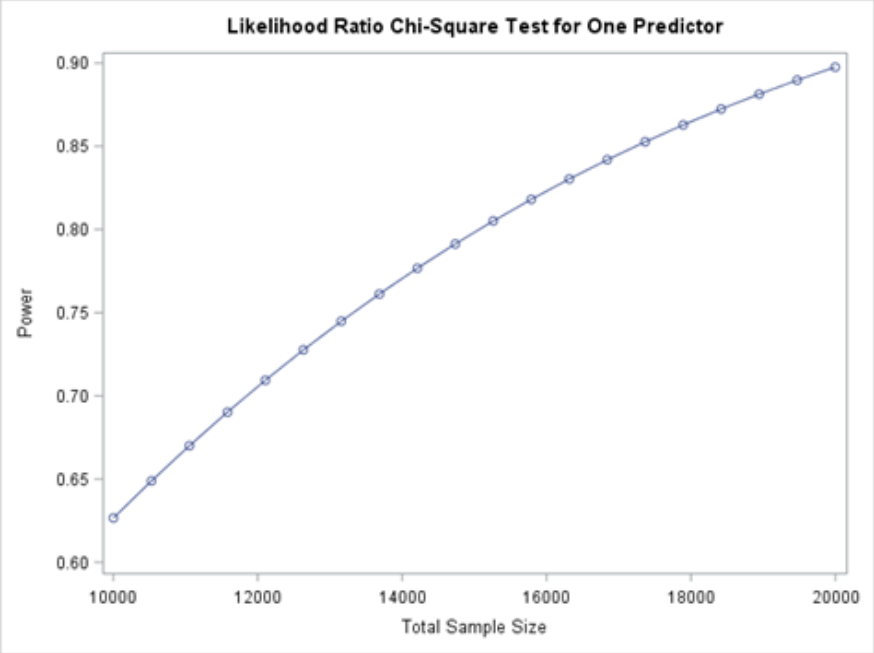


**Figure 2**. Sample size calculation test for the primary objective considering the association between ischemic heart disease and the primary air pollution metric, $PM_{2.5}$.

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# Chapter 5: General Discussion

Our study examines the relationship between air pollution and ischemic heart disease as well as the effect modification by chronic obstruction pulmonary disease. It has been found that there is indeed a relationship between air pollution and ischemic heart disease, and the relationship was increased with exposure to higher concentrations of $PM_{2.5}$, $NO_2$, and $O_3$. However, no effect modification could be demonstrated in individuals having COPD and no interaction according to the severity of airflow obstruction.

The study's first research objective was to assess the relationship of ambient air pollution, and more specifically fine particulate matter, $PM_{2.5}$, and ischemic heart disease, in an aging population. Overall, the study population was diverse with data sites from across Canada and an average age of 61.9, effectively including the geriatric population in Canada. It was found that, within this representative sample of the older adult Canadian demographic, ambient air pollution is indeed associated with ischemic heart disease. This is in concurrence with the current literature, in that, there is strong evidence indicating a relationship between air pollution and cardiovascular diseases and comorbidities (Brook *et al.,* 2010; Shah *et al.,* 2015; Newby *et al.,* 2015; Liu *et al.,* 2019; Kaufman *et al.,* 2016; Rajagopalan *et al.,* 2018; Yusuf *et al.,* 2020). It has been suggested that the short- and long-term effects of $PM_{2.5}$ exposures can range from risk of mortality due to cardiovascular-related reasons to a shorter life expectancy and cardiovascular mortality (Brook *et al.,* 2010). A modifiable risk factor, reduced $PM_{2.5}$ has been found to have an impact on cardiovascular outcomes in as short as some years' time (Brook *et al.,* 2010). In fact, elevations of $PM_{2.5}$ have been indicated to increase risk of acute cardiovascular events by 1% to

3% in few days' time (Rajagopalan *et al.,* 2018). Previously, a study has found that a 10 ug/$cm^3$ increase in $PM_{2.5}$ increased CVD events by 76% and coronary heart disease by 43% (Di, Dai, Wang, et al., 2017; Di, Wang, Zanobetti, et al., 2017). In our study, ischemic heart disease was associated closely with higher concentrations of $PM_{2.5}$, followed by ozone and nitrogen dioxide. Several models that hypothesize the underlying pathways that may explain this association include, induced oxidative stress, atherothrombosis, endothelial dysfunction, and systemic inflammation (Miller*,* 2020). Fine particulate matter has been associated with pathways of progressive atherosclerosis, inducing oxidative stress, inflammation, and other harmful effects on vasculature and platelets (Miller*,* 2020). It is prudent that the assessment of the association between air pollution and ischemic heart disease be further investigated, as, in this study, there was a limitation due to a potential classification and recall bias. As the definition for ischemic heart disease was "Has a doctor ever told you that you have heart disease," the assessment of cardiovascular disease was generally for all heart disease (including ischemic heart disease) rather than solely heart disease that is ischemic in nature.

The second research objective, aimed to assess whether COPD exposure and severity of airflow obstruction modulates the relationship of ambient air pollution and ischemic heart disease, in an aging population. We could not demonstrate that there was amplification or effect modification by COPD and airflow obstruction severity on the relationship between air pollution and ischemic heart disease. As a result, we did not reject the null hypothesis, that there is no effect modification by COPD and severity on this relationship. Given the known relationship between both air pollution and COPD, as well as air pollution and cardiovascular diseases (e.g. ischemic heart disease), there was a strong rationale for the hypothesis of an amplification of the

association of air pollution and ischemic heart disease in people having COPD. Our study didn't reach statistical significance, i.e., the study had a low probability rejecting the null hypothesis, given that the null hypothesis was assumed to be true. However, as mentioned in the discussion of the manuscript, the lack of statistical significance could be because the study was underpowered (lower prevalence of COPD individuals in the CLSA than expected) and/or that the lack of effect reflects the characteristics of the population recruited in the CLSA. There is a lack of studies, currently, that have assessed the relationship, exploring COPD as an effect modifier and potential amplifier for the relationship between air pollution and ischemic heart disease.

The finding of a relationship between air pollution and cardiovascular disease, in particular, ischemic heart disease, aligns with previous evidence, and signifies the importance of addressing this pervasive risk factor and health outcome, respectively. Moreover, it further emphasizes the need to explore COPD as it can potentially influence this relationship in future studies that address the current study's limitations. The burden of air pollution, cardiovascular and respiratory disease is immense, as the 4$^{th}$ risk factor for all-cause mortality, 2$^{nd}$ and 4$^{th}$ leading causes of death, respectively (Brauer *et al.,* 2021; Statistics Canada: Heart Disease in Canada, 2017; GOLD, 2017). A recent systemic analysis, by Murray *et al.,* finds that nearly a tenth of all mortality in 2019 is accredited to air pollution (2020). Furthermore, it has been suggested by literature that there is a link between air pollution and respiratory disease, wherein, several cross-sectional studies have explored the relationship between forced expiratory volume/forced vital capacity and hospitalization due to COPD (Nuvolone D, et al., 2011; Pujades-Rodriguez M, et al., 2009; Pujades-Rodriguez M, et al., 2009). The impact of respiratory disease, such as COPD,

in and of itself, is of great concern, with nearly 174 million affected globally in 2015 alone, and more cases if the spirometry definition is considered (Systematic analysis for the Global Burden of Disease Study 2015; Adeloye et al., 2015). Furthermore, there is a vast amount of evidence supporting the relationship between COPD and cardiovascular disease, such that the prevalence of cardiovascular disease in patients with COPD is nearly 30-70% (Mullerova, Agusti, Erqou & Mapel, 2013). Due to this overwhelming evidence, further studies need to be done including individuals with the whole spectrum of disease severity, most likely those with more severe COPD. Between these burdensome diseases (i.e. COPD and ischemic heart disease) and risk factor (i.e. air pollution), it becomes essential that the interrelatedness of these diseases and related risk factor be explored to better understand clinical risk, outcomes, and potential management procedures for the same.

In conclusion, this study, which aimed to ascertain the relationship between air pollution, i.e. $PM_{2.5}$, $NO_2$ and $O_3$, and cardiovascular disease, i.e. ischemic heart disease, but also further explore the effect of COPD on this relationship, finds that there is indeed a relationship between air pollution and ischemic heart disease, but no effect modification by COPD on this relationship. Future steps should include assessing the effect modification of COPD on the relationship between air pollution, namely $PM_{2.5}$, $NO_2$ and $O_3$, and cardiovascular disease, such as ischemic heart disease, with a larger sub-group of COPD patients within the database, and making sure there is representativeness of subjects with more advanced disease. Furthermore, a longitudinal study should be considered for greater ability to make inferences from study findings. If it is indeed found that COPD amplifies the relationship between air pollution and ischemic heart disease or this to a selected group of COPD patients, this can be impactful on

mitigating risks, risk management, and clinical outcomes in targeting specific patients for personalized risk management.

## TABLE

**Table 13.** Air Pollution Components and Sources (data retrieved from: World Health Organization https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health)

| Component of Air Pollution | Description and Health Affect | Principle Source(s) | Recommended Guideline (Threshold level below which it is safe) |
|---|---|---|---|
| Particulate Matter (PM) | It is said to be the most impactful component of air pollution and is often used as a surrogate for air pollution. Particulates less than 10 microns in size can insert themselves in the lungs. Whereas, particulates less than 2.5 microns, which are more dangerous, can penetrate the lung tissue and enter the blood system. | The primary source is indoor pollution (i.e. domestic combustion sources such as cooking using biomass fuels) for particulate matter (less than 10 microns). | $PM_{2.5}$ (average): 24-hour = 25 $ug/m^3$ annual = $10ug/m^3$<br><br>$PM_{10}$ (average): 24-hour = $50ug/m^3$ annual = $20ug/m^3$ |
| Ozone ($O_3$) | This does not refer to the ozone layer in the atmosphere, but rather a photochemical smog. It can cause a decline in lung function and contribute to respiratory illness. | The primary source is pollutants (e.g. $NO_2$) and volatile organic compounds from vehicle and industry related emission sources that react with sunlight. | 8-hour = 100 $ug/m^3$ |
| Nitrogen dioxide ($NO_2$) | $NO_2$ is a toxic gas and is the source for nitrate aerosols. In turn, nitrate aerosols are a part of $PM_{2.5}$ and when in contact with UV rays, a part of ozone too. In concentrations over $200ug/m^3$ they can cause serious lung inflammation. The majority of studies that focus on the health effects of $NO_2$ have been focused on children. | The primary source of $NO_2$ are processes of combustion such as engines, heating and power generation. | 1-hour = $200ug/m^3$ annual = $40ug/m^3$ |
| Sulfur dioxide ($SO_2$) | $SO_2$ is a colourless gas that can have an impact on lung function. Respiratory inflammation can increase likelihood of lung infections. It has been found that there is a higher mortality rate and hospital admission rate for cardiac reasons on days with | The main source of $SO_2$ is the burning of fossil fuels (which contain $SO_2$) (i.e. for vehicles, home heating, power generation). | 10-minute = 500 $ug/m^3$ 24-hour = |

| | | | |
|---|---|---|---|
| | higher $SO_2$ related pollution concentrations. | | |

## FIGURE

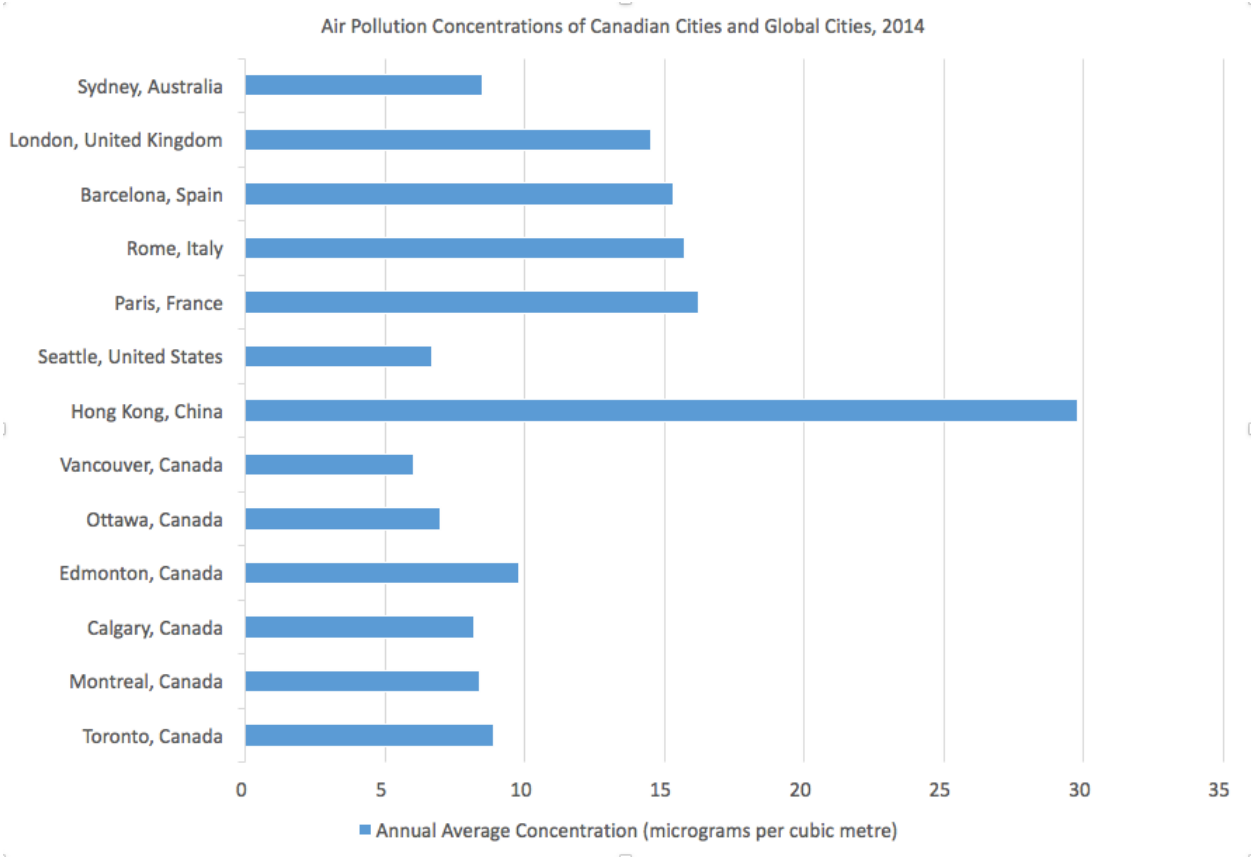


**Figure 1.** Air Pollution Concentrations of Canadian Cities and Global Cities, 2014 (data retrieved from: https://www.canada.ca/en/environment-climate-change/services/environmental-indicators/international-comparison-urban-air-quality.html)

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