Estimating the relationship between environmental exposures and acute exacerbations of COPD and exacerbation-like respiratory events

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Abstract

Background:

Chronic obstructive pulmonary disease (COPD) is a common lung condition characterized by chronic breathlessness. Patients with COPD can develop sudden attacks known as acute exacerbations. These exacerbation episodes represent the most common cause of hospital admission in Canada. While infections are conventionally thought of as a leading cause of these episodes, non-infectious causes such as short-term increases in air pollution concentrations and extreme weather may play a clinically important role.

Objectives:

To estimate the relationship between short-term exposures to air pollution and acute respiratory events ("exacerbation-like events") using single-pollutant and multi-pollutant models in individuals with mild-moderate COPD from a population-based sample, during the Warm and Cool Seasons.

Methods:

Between July 1, 2012 and December 31, 2019, "exacerbation-like events" ("Symptom-Based": ≥1 of increased dyspnea/sputum volume/purulence for ≥48hrs; "Event-Based": 'Symptom-Based' plus requiring either antibiotics/corticosteroids or healthcare use) were collected prospectively from participants diagnosed with COPD by spirometry in 9 Canadian cities within the Canadian Cohort Obstructive Lung Disease (CanCOLD). Daily air pollution estimates of nitrogen dioxide (NO_2), fine particulate matter ($PM_{2.5}$), and ozone (O_3) as well as daily mean temperature (Temp.) and relative humidity (RH) were obtained from national databases of fixed monitoring stations in each city. A case-crossover design was used to compare the 24-hour outdoor air pollutant concentrations of the hazard period ('Day 0' of the event) with those of 3-4 matching control periods using a time-stratified sampling approach. Hazard and control period lags (Days '-1' to '-6') were also compared. Events recalled within 4 months were included in the analysis. Given the seasonal Canadian climate, all data were dichotomized into 'Warm' (May-Oct.) and 'Cool' (Nov.-April) Seasons. Odds ratios (ORs) and their 95% confidence intervals [95% CI] were estimated. Generalized estimating equations (GEE) based on binary

distribution with logit link and repeated statement were used to account for within-subject correlations of repeated measures. Primary analysis involved fitting single-pollutant models, unadjusted (un.) and adjusted (adj.) for both Temp. and RH. Secondary analyses (all adjusted for Temp. and RH) involved fitting two-pollutant models, as well as separate analyses by i) sex and ii) airflow obstruction severity. In sensitivity analyses, all primary analyses were repeated using all events regardless of the recall period. The results included within the present abstract are presented per interquartile range (IQR) increase and are limited to the primary analysis.

Results:

Analyses were performed on 449 eligible CanCOLD COPD participants by study end, with 1,400 symptom-based and 841 event-based exacerbation-like events. Overall mean (and IQR) air pollutant estimates during Warm and Cool Seasons were, respectively: NO_2: 9.51 (7.3), 13.9 (10.27) ppb; $PM_{2.5}$: 6.78 (4.47), 7.01 (4.85) $\mu g/m^3$; and O_3: 20.08 (11.77), 19.64 (14.33) ppb. Positive associations ($P<0.05$) in the Cool Season between $PM_{2.5}$ with symptom-based events on Lag -1 (un. 1.07 [1.01, 1.13], adj. 1.09 [1.02, 1.16]) were observed, and in the Warm Season between NO_2 and symptom-based events on Lag -3 (adj. 1.08 [1.00, 1.17]). A negative association ($P<0.05$) was observed between O_3 and symptom-based events on Lag -3 of the Warm Season (adj. 0.81 [0.66, 0.99]).

Conclusion:

Exposure to ambient pollutants $PM_{2.5}$ (during the Cool Season) and NO_2 (during the Warm Season) was associated with an increased odds of exacerbation-like events, particularly in the 72 hours prior to the event. These findings challenge the conventional understanding of the precipitants for acute respiratory events in patients with COPD.

Résumé

Contexte

La maladie pulmonaire obstructive chronique (MPOC) est une affection pulmonaire courante caractérisée par un essoufflement chronique. Ces patients peuvent développer des crises soudaines appelées exacerbations aiguës, la cause la plus fréquente d'admission à l'hôpital au Canada. Bien que les infections soient traditionnellement considérées comme la principale cause de ces épisodes, des causes non infectieuses telles que l'augmentation relative de la concentration de la pollution atmosphérique et les conditions météorologiques pourraient jouer un rôle cliniquement important.

Objectifs

Estimer la relation entre les expositions à court terme à la pollution de l'air et les « événements de type exacerbation » en utilisant des modèles à polluant(s) unique et multiples chez les personnes atteintes de MPOC légère-modérée à partir d'un échantillon de population, durant les saisons chaudes et froides.

Méthodes

Entre le 1er juillet 2012 et le 31 décembre 2019, les « *exacerbation-like events* » (ELE – *Basé sur symptômes (ELE-s)*: ≥1 de dyspnée/volume de l'expectoration/purulence pendant ≥48h ; *Basé sur événements (ELE-e)*: *Basé sur symptômes* plus nécessitant soit des antibiotiques/corticostéroïdes, soit un recours aux soins) ont été collectés de manière prospective chez les participants diagnostiqués avec une MPOC par spirométrie dans 9 villes canadiennes au sein de l'étude *Canadian Cohort Obstructive Lung Disease* (CanCOLD). Les estimations de pollution quotidienne de dioxyde d'azote (NO_2), de particules fines ($PM_{2,5}$) et d'ozone (O_3) ainsi que la température moyenne quotidienne (Temp.) et l'humidité relative (HR) ont été obtenues. Un plan d'échantillonnage croisé a été utilisé pour comparer les concentrations de polluants sur 24 heures de la période de risque (jour 0 de l'événement) avec celles de 3-4 périodes de contrôle correspondantes en utilisant une approche stratifiée dans le temps. Les décalages des périodes de risque et de contrôle (jours -1 à -6) ont également été comparés. Les ELE rappelés depuis ≤4 mois ont été inclus. Toutes les données ont été dichotomisées en saisons « chaudes » (mai-

octobre) et « froides » (novembre-avril). Les rapports de cotes et leurs intervalles de confiance à 95% [IC95%] ont été estimés au moyen d'une équation d'estimation généralisée basée sur une distribution binaire avec lien logit et déclaration répétée, en tenant compte des corrélations intra-sujet des mesures répétées. L'analyse primaire a consisté à ajuster des modèles à un seul polluant, non ajustés (non.) et ajustés (aj.) pour Temp. et HR. Les analyses secondaires (toutes ajustées pour Temp. et HR) ont impliqué l'ajustement de modèles à deux polluants, ainsi que des analyses séparées par i) le sexe et ii) la gravité de maladie. Dans les analyses de sensibilité, les analyses primaires ont été répétées en utilisant tous les ELE. Les résultats inclus dans cet ouvrage sont limités à l'analyse primaire.

Résultats

Les analyses ont été effectuées sur 449 participants CanCOLD MPOC à la fin de l'étude, avec 1400 ELE-s et 841 ELE-e. Les estimations globales moyennes (et IQR) des polluants de l'air pendant les saisons chaudes et froides étaient, respectivement : NO_2 : 9,51(7,3), 13,9(10,27)ppb ; $PM_{2,5}$: 6,78(4,47), 7,01(4,85)µg/m3 ; et O_3 : 20,08(11,77), 19,64(14,33)ppb. Des associations positives sont rapportés ($P<0,05$) dans la saison froide entre $PM_{2,5}$ et les ELE-s sur le jour -1 (non. 1,07 [1,01, 1,13], aj. 1,09 [1,02, 1,16]), et dans la saison chaude entre le NO_2 et les ELE-s sur le jour -3 (aj. 1,08 [1,00, 1,17]). Une association négative ($P<0,05$) a été observée entre O_3 et les ELE-s dans la saison chaude le jour -3 (aj. 0,81 [0,66, 0,99]).

Conclusion

L'exposition aux polluants NO_2 (saison froide) et $PM_{2,5}$ (saison chaude) a été associée à une probabilité accrue d'ELE dans les 72 heures avant l'événement. Ces résultats remettent en question la compréhension conventionnelle des précipitants des événements respiratoires aigus dans la MPOC.

Contribution of Authors

I, Dr. Bryan Ross, MSc candidate in Epidemiology and Respirologist, led and was involved in all parts of the thesis project under the supervision of Dr. Jean Bourbeau. Specifically, this encompasses all aspects including the literature review, the study design, the development and refinement of the objectives and of the statistical approach, the application towards grant competitions for the acquisition of funding support for the project, the coordination of data access requests and acquisitions from all databases used, the performance of statistical analyses and the interpretation of the results, the presentation of study findings at institutional-level, provincial-level, and international-level venues, and the writing of all text included in this thesis.

Dr. Dany Doiron, Research Associate (Respiratory Epidemiology and Clinical Research Unit of the McGill University Health Centre), Data Linkage Lead and Special Projects Manager (CANUE; Canadian Urban Environmental Health Research Consortium), and expert in environmental epidemiology and respiratory health, provided significant guidance in developing and refining the objectives and statistical approach, in providing insight on the interpretation of study results within the context of the literature, and reviewed this thesis.

Pei Zhi Li, Data Analyst, performed extensive data cleaning/preparation of raw data upon initial receipt from databases, aided in the statistical analysis plan, performed more advanced statistical analyses included, and reviewed this thesis.

Dr. Andrea Benedetti, Biostatistician and Associate Professor at McGill University, is an MSc Thesis panel committee member. She provided significant guidance on statistical theory and application and on appropriate study methodology, and reviewed this thesis.

Dr. Jean Bourbeau, Respirologist and Professor at McGill University, is the Principal Investigator and Supervisor of this MSc thesis. He is also the Lead Investigator of the Canadian Cohort Obstructive Lung Disease (CanCOLD), the cohort from which participants were recruited for this thesis project. He provided supervision and guidance on all aspects of the thesis project, and reviewed this thesis.

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I deeply value and appreciate my friends for being so supportive of my ambitions and for being a constant and genuine outlet to relax, have fun and recharge. Finally, as I near the end of such a long academic journey I am indebted to my partner Lilia and to my family. Lilia has been so incredibly supportive of me in my many pursuits inside and outside of the academic realm, and I am so excited to embark on this new life in Montreal with her. To my family, I happened upon the *Acknowledgments* section from my first MSc Thesis degree at McGill back from 2010. I said

it best then - and since it is as true now as it was over a decade ago, I choose to end with these same words now: *My siblings are the most caring and supportive brothers and sisters I could ever hope for. It is always a special treat when we get the chance to come together and spend time with one another. My mother and father are grounding pillars in my life. They are without a doubt the foundation of everything I have achieved. They are the most selfless, compassionate people I have ever known and to them I dedicate this thesis.*

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List of Abbreviations and Acronyms

AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
CanCOLD	Canadian cohort obstructive lung disease
CI (95% CI)	Confidence interval (95% Confidence interval)
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
ED	Emergency department
ELE	Exacerbation-like event
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GEE	Generalized estimating equations
GOLD	Global initiative for chronic obstructive lung disease
HAD	Health administrative database
ICD	International classification of disease
IQR	Interquartile range
m^3	Meter cubed (cubic meter)
µg	Microgram
µm	Micrometer
NAPS	National air pollution surveillance program
NO_2	Nitrogen dioxide
NHANES	National health and nutrition examination survey
O_3	Ozone
OR	Odds ratio
PM	Particulate matter
$PM_{2.5}$	Fine particulate matter
PM_{10}	Particulate matter smaller than 10µm in aerodynamic diameter
Ppb	Parts per billion
RH	Relative humidity
SD	Standard deviation
SO_2	Sulfur dioxide
WHO	World health organization

Chapter 1: Introduction and Organization of Thesis

Chronic obstructive pulmonary disease (COPD) is one of the commonest adult respiratory diseases and afflicts millions of individuals around the world. The *Global Initiative for Chronic Obstructive Lung Disease* (GOLD) defines COPD as "*a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development*"[1]. Much like how the cause of COPD has been traditionally thought to be due to cigarette smoking, the cause of sudden attacks of COPD – acute exacerbations of COPD (AECOPD) – have been traditionally thought to be due to viral or bacterial infection. However, much like how non-cigarette causes of COPD are increasingly being discovered, non-infectious causes such as air pollution and weather are increasingly being recognized as potential etiological triggers of acute respiratory events in patients living with COPD.

The present thesis focuses on the relationship between short-term exposures to air pollutants (specifically, to nitrogen dioxide (NO_2), fine particulate matter ($PM_{2.5}$) and ozone (O_3)) and acute respiratory events in a Canadian cohort of individuals with COPD (which has been confirmed by spirometry) from a population-based sample. Mean temperature and relative humidity was also adjusted for, and the effect of demographic variables including sex and severity of disease were also investigated.

Following this introductory Chapter, in Chapter 2 the epidemiology, risk factors, clinical definition and pathophysiology of COPD is reviewed. This is followed by a review of acute exacerbations of COPD and of exacerbation-like events (ELEs), including the history and nuances in nomenclature from the published literature which has led to their contemporary definitions and their use as relevant study outcomes. Acute exacerbations of COPD have been defined by a change in symptoms alone (such as in the 'Anthonisen' definition) or by a change in symptoms which also requires treatment in order to qualify (such as in the *Global Initiative for Chronic Obstructive Lung Disease* (GOLD) definition). From these definitions and from important reports in the literature led to the development of the 'symptom-based' and 'event-based' patient-reported outcome used in the *Canadian Cohort Obstructive Lung Disease (CanCOLD)*: the 'exacerbation-like event'. Attention is then focused on air pollution including

mechanisms of action on the human respiratory system and a summary of the existing literature on the association between transient elevations in air pollution and acute respiratory events in patients with COPD.

Chapter 3 provides the details of all methodological aspects of the present study. Chapter 4 provides all results from the thesis project, including the results of single-pollutant and two-pollutant models and the effect of demographic variables. Chapter 5 contains the interpretation and contextualization of all study findings, including a summary of the strengths and limitations of the study and an overall conclusion regarding the novel contributions of this study towards the existing field of knowledge. All references for the thesis are provided in Chapter 6, and all supplemental tables and figures are contained in the Appendix.

Chapter 2: Literature Review

Epidemiology of Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a very common and serious chronic condition[2]. It is the third-leading cause of global morbidity[3] and has become the third-leading cause of death worldwide[4-6]. The in-patient care for patients with COPD represents the highest rate of hospital admissions and rehospitalization in Canadian adults among major chronic illnesses[7, 8]. COPD has an estimated global prevalence of 10.1% to 13.1%[6, 9], and an estimated prevalence of 16.2% in Canada in 2021[3]. With population aging, COPD prevalence has increased by 44.2 percent from 1990 to 2015 in Canada[10]. The economic burden associated with moderate and severe exacerbations in Canada has been estimated at between $646 million to $736 million per year[11].

Notably, no study to date has followed the full natural history of COPD through its entire course. Existing longitudinal studies conducted over 20 or more years have indicated that there are a variety of patterns of decline in lung function (as measured by the forced expiratory volume in 1 second, FEV_1) which include not only accelerated lung function decline but also a gradual decline even from the time of early adulthood[12]. Given that COPD is a global disease, there is a great heterogeneity in the risk factors for its development and progression. The factors that predispose to the development of COPD can be broadly divided into inhalational exposure factors and host risk factors.

Cigarette smoking over many years has historically been attributed as the principal cause of COPD, however other risk factors including occupational exposures and even concomitant asthma can contribute to fixed airflow obstruction[3]. Furthermore, non-cigarette noxious inhaled stimuli are increasingly being recognized as contributing to the development of COPD. This is highlighted by the observation that many patients with COPD are never-smokers[13]. Canadian data has demonstrated that the prevalence of COPD was 6.4% in never smokers and 15.2% in ever-smokers, with “never smokers” accounting for 27% of all COPD subjects[14]. A similar prevalence of COPD in never smokers has been reported internationally[15] – for example, in the 14-country Burden of Obstructive Lung Disease (BOLD) study[16]. There is increasing evidence to support the role of non-cigarette exposures, such as ambient air pollution over many years, in contributing to the pathogenesis and eventual development of COPD. Long-term exposure to

outdoor air pollution has been linked to lower lung function and COPD prevalence in adults[17], as well as slower lung function growth in children and adolescents[18, 19].

Inhalational Risk Factors in the Development of Chronic Obstructive Pulmonary Disease

The most widely studied association amongst all the inhalational risk factors in the development of COPD is cigarette smoking. Participants of the Framingham Offspring cohort who were non-smokers at baseline were observed over a median 23-year follow-up period, and baseline respiratory symptoms, subsequent cumulative cigarette smoking exposure, and lung function testing by spirometry were collected[20]. Smoking was strongly associated with lung function decline in both male and female participants. Notably, the effect of cigarette smoking was heterogeneous. Specifically, the subgroup of subsequent smokers who reported respiratory symptoms at baseline appeared to be more susceptible to the effects of cigarette smoke exposure than to those subsequent smokers without baseline respiratory symptoms. This individual-level susceptibility to cigarette smoking may also help explain why COPD does not necessarily occur in all smokers in their lifetime.

Other forms of tobacco smoke, including cigar smoking, pipe smoking and water pipe smoking[21, 22], marijuana smoking[23], as well as second-hand cigarette smoke exposure[24], have also been identified as risk factors in the development of COPD. The use of electronic cigarettes (e-cigarettes), referred to also as ‘vaping’, is a relatively newer source of chronic inhalational exposure which will require mid-term and long-term observational studies to confirm its association with the development of COPD, though it has already been associated with the development of acute lung injury which has been termed ‘vaping-associated lung injury’[25, 26].

Occupational exposures are another important category of inhalational exposure which can lead to the development of COPD. In developed nations, specific occupations which may predispose to the development of COPD may include gardeners/park keepers, warehouse workers, sculptors/painters, and plastics processors/moulders[27]. Industries including manufacturing (rubber, plastics, leather, mill products and food products) and construction, transportation and trucking are also associated with an increased odds of developing COPD in developed nations[28]. In low- and middle-income countries, there is an even higher occupational risk to unregulated or uncontrolled exposures. High exposures to pesticides, crop and dung burnings, coal and

byproducts of indoor (cooking) and to outdoor biomass fuels are important occupational risk factors in the development of COPD in these settings[29, 30]. In both developing[31] and developed[32] nations, and in a sense indirectly related to occupational status, low socioeconomic status is also consistently associated with the development of COPD through mechanisms which remain to be fully explored.

Host Risk Factors in the Development of Chronic Obstructive Pulmonary Disease

Host-specific factors in the development of COPD can be divided into three broad categories: genetic factors, respiratory system predisposing factors (including early life lung development and co-morbid respiratory conditions), and demographic factors (including age, ethnicity, and sex).

The most direct example for a genetic predisposition to the development of COPD comes from a condition called alpha-1 antitrypsin deficiency. Alpha-1 antitrypsin deficiency is an autosomal co-dominant condition caused by mutations in the serine proteinase inhibitor (SERPINA) 1 gene. This condition mainly affects Caucasians of European heritage and it predisposes to the development of emphysema of the lung as well as to abnormalities in the liver, skin, and blood vessels. It is a rare condition with a higher prevalence in Northern European populations, where it affects roughly 0.12% of patients living with COPD[33]. The normal composition of lung parenchyma includes elastin, and elastin can be broken down by an enzyme called protease. Protease is normally inhibited by alpha-1 antitrypsin and thus alpha-1 antitrypsin is a protease inhibitor. A deficiency in alpha-1 antitrypsin therefore leads to unregulated breakdown of lung tissue and to the development of emphysema[34]. While patients with COPD tend to develop disease later in life, patients with alpha-1 antitrypsin deficiency tend to develop emphysema in the third decade of life. Canadian guidelines recommend screening all patients who have been diagnosed with COPD before the age of 65, or with a smoking history of less than 20 pack-years of cumulative exposure, for this condition[35].

Regarding respiratory system predisposing factors, any process which affects normal lung development, growth, maturation, or function can be a risk factor for the subsequent development of COPD. There is a positive association between weight at birth and pulmonary function (as measured by the forced expiratory volume in 1 second),[36] and there is even an

association between lower birthweight and death from chronic obstructive lung diseases[37]. Recurrent infections in early childhood and even into adulthood can alter the normal anatomic structure and physiologic function of the airways and of the lung tissue involved, which can also predispose to the subsequent development of chronic airflow obstruction[12]. In this sense, any cause of recurrent lung infection, including a history of tuberculosis infection, a history of acute or chronic infection of the lung with bacteria such as Pseudomonas, and co-morbid diseases of immunodeficiency such as human immunodeficiency virus (HIV) infection can all predispose to the development and worsening of COPD[38-40].

The demographic risk factors for the development of COPD vary widely around the world, and demographic patterns of disease have also varied considerably over time. Regarding age distributions in disease, even in normal individuals without COPD, pulmonary function (using the forced expiratory volume in 1 second) improves from childhood into early adulthood, peaks around age 20, and then gradually declines thereafter over the typical lifespan[41]. Given that COPD is a disease associated with exposure to noxious inhaled stimuli over many years, advanced age (a reflection of cumulative years of exposure) can be considered a risk factor for COPD. One exception to this, and as noted above, is the early onset of emphysema in patients with alpha-1 antitrypsin deficiency. In general, advanced age is associated with worse lung function, lower exercise tolerance, and higher prevalence of supplemental oxygen use in patients with COPD[42].

Regarding ethnic and racial distribution of disease, all races and ethnicities are at risk for the development of COPD. There are important racial and ethnic disparities that are evident in both developing and developed nations. For example, black non-smokers have a higher prevalence of COPD than white non-smokers, and for a given cumulative smoking exposure, black populations tend to exhibit more severe disease. These findings may relate to disproportionate occupational and community exposures to non-cigarette noxious stimuli, to societal barriers of equity, or even to possible biological ethnicity-specific differences in nicotine metabolism[43, 44].

Regarding sex differences in the distribution of COPD, in a multinational household survey of 106,876 households, the majority of countries outside of the Unites States demonstrated a slightly higher prevalence in men than in women, while in the United States there was a slightly higher prevalence in women than in men. There has been a notably increasing prevalence of COPD in women over the last several decades, which is largely thought to reflect the changing

(increased) pattern of cigarette smoking during that period in women[45]. Traditionally, men were thought to exhibit more severe forms of disease, and even higher mortality rates than women when matched by disease severity[46], and men may have a higher burden of emphysema than women[47]. However, more recent data has demonstrated disproportionate severity of disease in women in a variety of domains. Smoking women have a reduced internal diameter of their airways compared with smoking men, women have more severe dyspnea and airflow limitation at younger ages compared with men, women with mild COPD report more severe dyspnea scores than men with mild disease, and women may actually have a disproportionately higher burden of emphysema when compared to men after adjusting for smoking exposure history[42, 48]. Biologically, differences between women and men in regards to immune system T-cell expression patterns, metabolism of inhaled cigarette particles, chemicals and metabolites, and pro-inflammatory cytokine responses have been reported[44].

There are notable interactions between the demographic variables of age, ethnicity, and sex. As a general example of the intersection between sex and age, severe forms of early-onset COPD have been described to disproportionately affect young women[49]. As an example of the intersection between sex, age, ethnicity, socioeconomic status and cultural norms, biomass fuel exposure is an important risk factor for COPD particularly in younger women from rural and urban low and middle income countries due to its use as a cooking source in this setting[50].

Clinical Definition of Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (or the interchangeable term, COPD) encompasses a variety of separate causes and conditions, each of which lead to airflow obstruction that is not fully reversible[6]. Airflow obstruction is detected by testing lung function using post-bronchodilator spirometry. The forced vital capacity (FVC – the maximum volume of air during a full, forced exhalation maneuver following a full inhalation) of an individual is compared with their forced expiratory volume in 1 second (FEV_1 – the expiratory volume in the first second of a forced vital capacity maneuver)[51]. A low forced expiratory volume in 1 second to forced vital capacity ratio (an FEV_1/FVC ratio of less than 0.7, or a ratio less than their predicted lower limit of normal (LLN) value) which is not reversible supports a diagnosis of COPD, and the magnitude of impairment in the forced expiratory volume in 1 second indicates the spirometric 'severity' of airflow obstruction[1, 52, 53]. The pathologic hallmarks of COPD are chronic bronchitis and emphysema. Patients with COPD experience symptoms of dyspnea, chronic cough, daily

sputum production, wheeze, and exercise limitation.

Pathophysiology of Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is a complex heterogeneous disease, resulting from interactions between an individual's genotype, phenotype, behaviours and environment[12]. Though COPD is defined by lung function testing and is classically thought of as a respiratory disease, it is a multi-system inflammatory disorder. For example, the prevalence of co-morbid cardiac, metabolic and other disorders in patients with COPD is substantially higher than is observed in the general population[15]. Pathologically, noxious inhaled gases and particles inhaled into the respiratory system can cause damage to the lungs. Abnormal and overwhelmed host responses to continued exposure to these toxic gases and particles is what eventually leads to the manifestations of disease.

The innate immune system of the healthy lung provides the first line of protection at the site of the lower respiratory tract, and includes tight junctions across neighbouring epithelial cells (to maintain a barrier from entry along the inner lining of the airway wall), a muco-ciliary 'escalator' which helps clear inhaled debris from more deep and distal airways towards the more central and upper airways, and macrophages residing in the lungs at the level of the small bronchi (bronchioles) and on alveolar surfaces which engulf and clear particles and debris[54]. In the presence of local tissue damage, pro-inflammatory cytokines and chemokines are recruited, and these aid in the further recruitment and coordination of polymorphonuclear leukocytes to the site of damage. T lymphocytes, monocytes and basophils can also be recruited. The lymphocyte response in patients with COPD appears to be predominated by T helper type 1 over T helper type 2 cell types. While a predominantly neutrophilic inflammation is typically observed, increases in eosinophils (which may be T helper type 2 cell-mediated) can also be observed[55]. There is increasing evidence that when the level of peripheral blood eosinophil counts in patients living with COPD are elevated, they are at an increased risk of experiencing acute exacerbations[56]. Histological changes that develop in the presence of ongoing toxic inhalation includes the deposition and persistent infiltration of these immune cells into the increasingly damaged lung tissue. The subsequent adaptive immune system (T-cell and B-cell based) responses appear to be in proportion to the severity of disease[57]. Irreversible remodeling of the walls of the small airways is the final eventual result[58].

The histological pattern of emphysema was first described in 1957 by Leopold and Gough[59]. The

infiltration of the bronchiolar walls was noted in that study to extend more distally, to the level of terminal bronchioles and towards the alveoli, and to a lesser extent in the surrounding ('peribronchiolar') lung tissue including the surrounding connective tissue and parenchyma. The terminal bronchiole and the alveoli reside in the centre of the anatomic pulmonary lobule. It is for this reason that a 'centrilobular' pattern of destruction characteristic of emphysema is observed in radiological imaging of patients with COPD. Notably, the small airway abnormalities largely precedes the emphysematous changes in the natural history of disease and include inflammation, fibrosis and mucous plugging[60].

Inflammation and narrowing of the peripheral airways from the development of chronic bronchitis leads to a narrowing of the internal diameter of the airway, thereby increasing airway resistance and increasing the work of breathing. Likewise, emphysema and parenchymal lung destruction leads to reduced tethering support of the distal airways to keep them open, leading to earlier narrowing and closure of these airways during exhalation and therefore also increased airway resistance and an increased work of breathing. Emphysematous destruction of the alveoli and of the alveolar-capillary interfaces, the sites of gas exchange (i.e. the sites of transfer of oxygen and of carbon dioxide between the respiratory and circulatory systems) leads to significant gas exchange abnormalities. Normal lungs require both ventilation of gas and perfusion of blood at the level of the alveolar-capillary unit in order to be able to oxygenate the circulating capillary blood, and in order to remove and expel carbon dioxide byproducts of cellular metabolism from the bloodstream. When regions of the lung are ventilated but do not participate in exchange with the circulatory system because of this destruction of the alveolar-capillary interface (characteristic of emphysema), it is referred to physiologically as 'deadspace' ventilation. More deadspace ventilation from a physiological standpoint has the consequence that, for every respiratory cycle of inspiration and expiration, only a proportion of the inhaled gas will actually participate in meaningful gas exchange of oxygen and carbon dioxide[61]. Thus, a higher burden of emphysema translates to a greater ventilation-perfusion mismatch and greater deadspace ventilation, which ultimately leads to lungs which are less functional in their critical role of gas exchange within the body when compared with normal lungs[62].

The gradual development of small airways disease over prolonged periods of exposure to noxious inhaled stimuli is often not detected over many years and is often referred to clinically as the 'silent zone'[63, 64]. This is because of the large physiological pulmonary 'reserve' which

allows a substantial buffering period prior to the development of actual symptoms. A sizeable proportion of the small airways need to become affected prior to the manifestation of symptoms and prior to the clinical detection of airflow obstruction when using spirometry. This unfortunate reality means that, by the time the individual has become symptomatic or has presented for evaluation or diagnosis of COPD, there has already been widespread and largely non-reversible damage to the small airways and even to the parenchymal tissue of the lungs at the histological level.

The natural history of COPD entails a progressive decline in lung function over time. Patients living with COPD are more prone to the development of shortness of breath with exertion (exertional dyspnea) as well as to experiencing sudden lung attacks (acute exacerbations of COPD) when compared to normal individuals with normal lung function. This lower threshold of tolerance is due to a variety of pathophysiological mechanisms which include airflow limitation, gas trapping, gas exchange abnormalities, and mechanical constraints[65, 66]. Patients with COPD have expiratory airflow limitation as documented by their reduced forced expiratory volume in 1 second in relation to their forced vital capacity. This airflow limitation translates to an inability to fully empty the lungs during exhalation, prior to the next inhalation. This is attributed in part to the increased airway resistance (from chronic bronchitis and from emphysema, as described above) and in part by the loss of elastic recoil of the lung due to the emphysematous destruction of the lung parenchyma. With any trigger which may promote inflammation, bronchoconstriction, or mucous production, patients with COPD are at risk of experiencing even worsening airway narrowing, even worsening airway resistance, and a further inability to deflate the lung during exhalation in the acute setting.

Acute Exacerbations of Chronic Obstructive Pulmonary Disease

A limitation that endures even to the present era is the fact that there remains no consistent clinical definition for an acute exacerbation of COPD. Fletcher and Peto conducted a prospective cohort study[67] on smoking and non-smoking London workers in 1977, in which they were one of the earliest to describe acute ‘chest episodes’ in individuals with COPD. They concluded at the time that there was no relationship between lung function decline and chest infections. However, more recent studies (in particular, the East London Cohort) suggest that the frequency of exacerbations does indeed contribute to long-term decline in lung function in patients with moderate to severe COPD[68].

Clinical research into which therapies may best treat these acute respiratory attacks then led to a need to define what exactly an acute exacerbation of COPD *was* in the scientific literature. The most enduring clinical definition stems from the landmark randomized clinical trial conducted by Anthonisen *et al.*, who in 1987 defined an exacerbation as *'increased dyspnea, sputum production, and sputum purulence'* in testing the role of antibiotic therapy in treating acute exacerbations of COPD[69]. In that trial, exacerbations were sub-categorized into *'Type I'* (all three of increased dyspnea/sputum production/sputum purulence), *'Type II'* (two of these three symptoms present) and *'Type III'* (one of these symptoms present, plus at least one of: upper respiratory infection, fever, wheezing, cough, or increased respiratory rate or heart rate). Patients with Type I and Type II exacerbations were shown to benefit from antibiotic therapy. This operational definition has become commonly adopted in clinical practice due to its ease of use and high relevance to patient management.

Variations of this same definition continue to be used in recent landmark clinical trials which used acute exacerbations of COPD as the study outcome. For example, the landmark 2016 *Effect of Indacaterol Glycopyronium vs. Fluticasone Salmeterol on COPD Exacerbations (FLAME)* Trial[70] defined an acute exacerbation of COPD as a worsening of 2 major symptoms (dyspnea, sputum volume, sputum purulence) for 2 or more consecutive days. The landmark 2018 *Informing the Pathway of COPD Treatment (IMPACT)* Trial[71] defined an acute exacerbation of COPD in exactly the same way, with a separate/additional definition of worsening of any 1 major symptom plus any of sore throat/cold/fever/cough/wheeze for 2 or more consecutive days. Finally, the landmark 2020 *Efficacy and Safety of Triple Therapy in Obstructive Lung Disease (ETHOS)* Trial[72] defined an acute exacerbation of COPD as a change for 2 or more days of at least 1 major symptom (dyspnea, sputum volume, sputum color) and at least 1 minor symptom (cough/wheeze/sore throat/cold symptoms/fever).

An acute exacerbation of COPD (AECOPD) is a clinically significant acute event or episode that represents a major contributor to the overall burden of the chronic disease of COPD by way of worsening of lung function, impairment in quality of life, the need for frequent urgent care visits or hospitalizations, and the costs of care[73, 74]. A pro-inflammatory and abrupt bronchospasm, mucosal edema and copious sputum production observed during acute exacerbations of COPD further increases airway resistance and further increases the pulmonary mechanical work required to breathe above and beyond the chronic baseline condition, which lead to worsening

expiratory flow limitation and dynamic hyperinflation[75]. As the disease progresses over time, the severity and frequency of these acute exacerbations of COPD are a clear prognostic factor for mortality in these patients[76]. In Canada, the treatment of the acute exacerbation episodes account for 60% of the total cost of the care of this patient population[77]. Much like the many different long-term causes of chronic airflow obstruction (described above) which themselves eventually lead to COPD, there are similarly a large number of ***acute*** causes of acute exacerbation episodes which have not yet been completely studied. While acute exacerbations of COPD have traditionally been thought to be triggered by infection (bacteria and viruses), it is possible that more 'unconventional' causes such as transient increases in ambient air pollution may precipitate exacerbations[78]. This uncertainty regarding the etiologies for acute exacerbations of COPD is reflected in its contemporary definition, which defines the event by the way in which it is treated (rather than by its cause or mechanism). The *Global Initiative for Chronic Obstructive Lung Disease* (GOLD) 2021 and 2022 international guides continue to define an acute exacerbation of COPD as 'an acute worsening of respiratory symptoms which results in additional therapy'; a 'mild' exacerbation requires short-acting bronchodilators, a 'moderate' exacerbation requires treatment with at least antibiotics or oral corticosteroids, and a 'severe' exacerbation requires a hospitalization or emergency department visit[1, 52]. The Canadian Thoracic Society (CTS) defines an acute exacerbation of COPD and its severity similarly[53].

The typical frequency of acute exacerbations experienced per year by patients with COPD is dependent largely on the operational definition used, as well as on the severity of disease of the patient population under study. Exacerbation rates from large observational cohorts such as the *Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE)* study and the *Canadian Cohort Obstructive Lung Disease (CanCOLD)* study are available in the existing literature. Exacerbation data from ECLIPSE published by Hurst *et al.*[79], a large clinical cohort of patients with moderate to very severe COPD, was derived using a functional exacerbation case definition which was based on the decision of the treating physician or study personnel to prescribe antibiotics or systemic corticosteroids. Exacerbation events were reported overall as well as separately by those requiring hospitalization, oral corticosteroids only, antibiotics only, and oral corticosteroids and antibiotics. Exacerbation data from CanCOLD published by Labonté *et al.*[80], a population-based cohort of mild to moderate COPD, was derived using the operational definition of an "exacerbation-like event" (ELE - *please see the following*

subsections below for details) and sub-categorized into 'symptom-based' or 'event-based' events. While Hurst *et al.* reported an overall annual rate of exacerbations in 2,138 patients in the first 12 months of the study as 1.21 events per patient per year, Labonté *et al.* reported an overall annual rate of exacerbation-like events in 505 patients with COPD confirmed by spirometry as 0.39 events per patient over one year. This observed discrepancy is likely explained by the difference in the severity of disease between the two cohorts: while participant data from the ECLIPSE study was comprised of a convenience sample in the clinical setting of patients with moderate (n=945), severe (n=900) and very severe (n=293) COPD (and no participants with mild COPD), participant data from the CanCOLD study was conversely comprised of a population sample of participants with mild (n=279) and mainly moderate (n=226) COPD. However, annual exacerbation rates observed between the physician-diagnosed mainly 'moderate' COPD subgroup from CanCOLD (0.71 events per patient per year) were comparable with the 'moderate' COPD subgroup from ECLIPSE (0.85 events per patient per year). These estimates would appear to reflect the typical annual rate of acute exacerbations of COPD and of exacerbation-like events that may be anticipated from participants within large observational cohorts.

Detection, Quantification and Measurement of Acute Exacerbations of COPD

The operational definition used for an acute exacerbation of COPD, the methods used to measure these events, and the criteria used to grade the severity of events each have different strengths and limitations that are important to review[81]. Two broad categories of methods used to measure acute exacerbations of COPD are *healthcare resource use* methods and *patient-reported* methods[82].

While the 'Anthonisen' definition of an acute exacerbation of COPD only relies on symptoms and does not necessarily require the need for healthcare use or treatment, other definitions such as the *Global Initiative for Chronic Obstructive Lung Disease* (GOLD) definition require for additional therapy to be prescribed/taken in response to a sustained worsening in patient status in order to qualify. In between these two groups of definitions are also definitions which simply acknowledge that treatment *may* be warranted. For example, an influential working group on the definition and classification of acute exacerbations of COPD published in 2003 defined an acute

exacerbation as *"a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations that is acute in onset and may warrant additional treatment in a patient with underlying COPD".* When using definitions for acute exacerbations of COPD in studies such as the GOLD definition or other similar operational definitions which require treatment to qualify, the use of healthcare administrative database (HAD) records to detect acute exacerbations of COPD and categorize their severity is convenient and has been widely used in the majority of previous published trials.

There are many steps involved in the utilization of healthcare resources in response to an acute exacerbation of COPD. The patient must be able to recognize a change in their own symptoms in order to seek appropriate medical attention; then the patient must report these symptom changes to a clinician; and then the clinician must feel that the prescription of treatments such as antibiotics, systemic corticosteroids or both are warranted prior to providing the prescription. The individual COPD patient 'experience' and the individual-level perception of breathlessness and of exacerbation symptoms is remarkably heterogeneous between patients[83, 84], as is the high variability between physicians in the clinical decision-making process of whether to prescribe or withhold treatment for acute exacerbations of COPD[85, 86]. These patient- and physician-related variations may have a sizeable impact on whether acute exacerbations of COPDs are managed as an inpatient or as an outpatient, whether they are ever ultimately treated at all, and therefore whether or not they would be detected using healthcare resource use methods. This could be particularly true for milder events which may still be clinically meaningful[81, 82]. In addition to these variabilities are the realities of having COPD disease status correctly labeled in certain clinical settings[81]. For example, it has been reported that patients who present to the primary care clinic or Emergency Department with a cough and shortness of breath are commonly prematurely labeled as having 'COPD' for that visit in their chart without ever having actually performed proper diagnostic testing with spirometry, despite the fact that a variety of non-COPD respiratory diseases (such as asthma and bronchiectasis) as well as non-respiratory conditions (such as congestive heart failure and venous thromboembolism) can manifest with similar clinical presenting symptoms[87, 88]. Within the subgroup of patients who are in fact properly labeled as having COPD, accurately labeling a particular visit or hospitalization as specifically being due to an acute exacerbation of COPD (an 'acute exacerbation of COPD' visit) can also be challenging. A majority of patients with COPD also have co-morbid chronic cardiovascular

disease[89] and other diseases which may have overlapping symptoms and can also prompt the need for acute healthcare use.

Though employing healthcare resource use methods to detect and quantify acute exacerbations of COPD has been previously widely used, these important considerations have led to a growing movement towards ascertaining acute exacerbation events using patient-reported outcomes (PROs)[81] which are anticipated to play an increasing role in future studies[82]. The support for patient-reported outcomes has become particularly well-established following the release of the Food and Drug Administration (FDA) report (first released in 2009 and most recently updated in 2019)[90], which defines PROs as "any report of the status of a patient's health condition that comes directly from the patient". Patient-reported outcomes can be particularly strong at detecting changes in symptom burden for patients at the individual level and at identifying acute events, properties which support their suitability to the task of detecting and quantifying acute exacerbations of COPD. A variety of distinct patient-reported methods and tools have been developed including daily diary cards and electronic diary tools, questionnaires, and other standardized tools/tests. These patient-reported outcomes can be collected in a prospective manner in studies on acute exacerbations of COPD.

Prior to the widespread availability of technology and of electronic platforms in clinical trials, participant daily diaries first originated in the form of daily symptom diary cards. Data from the East London cohort demonstrated that patients can reliably recall the number of exacerbations experienced during the previous year, and that the estimates are comparable to the values ascertained from daily diary cards that collect information on changes in symptoms[91]. Thus, when 'Anthonisen' (or similar) definitions of an acute exacerbation of COPD are used which rely on symptom change, diary cards can be effectively used to collect this outcome[92, 93]. This has been well-documented within those East London cohort studies which used both daily symptom cards as well as physiological testing (such as daily peak expiratory flow rate testing) to detect, characterize and grade the severity of acute respiratory events[68, 73, 91, 94, 95]. Importantly, these patient-reported instruments can identify otherwise 'unreported' acute exacerbations of COPD[96]. Using such methods may therefore provide more 'real-world' annual frequency estimates for acute exacerbations of COPD in clinical trials as well as a more comprehensive representation of the patient experience. The subsequent incorporation of technology to the paper-based patient symptom diary has led to the creation of 'electronic' symptom diary tools

such as the ‘e-Diary’ which can additionally remind and prompt patients to complete electronic symptom scores[82]. While COPD health status measures such as the standardized 8-item COPD Assessment Test (CAT) and the standardized 20-item Chronic Respiratory Disease Questionnaire (CRQ) do effectively measure health status and health-related quality of life, these have not been validated in the acute setting for the detection of acute exacerbations of COPD[82]. The development of the *Exacerbations of Chronic Obstructive Pulmonary Disease* (EXACT) tool in compliance with the FDA patient-reported outcome guide has provided an additional important patient-reported exacerbation data collection method in acute exacerbation trials. The EXACT tool can detect symptom-based exacerbations (i.e. an acute exacerbation of COPD that is defined by a change in symptoms rather than whether treatment was provided or not), and therefore events that may have been traditionally unreported in clinical trials have the potential to be captured and quantified using this tool. For example, when participants from the *Aclidinium to Treat Airway Obstruction in COPD Patients* (ATTAIN) study[97] completed the EXACT tool prospectively, it was demonstrated that the otherwise unreported (symptom-based) acute exacerbations of COPD had similar health consequences as the reported or ‘detected’ acute exacerbations in that study[98]. The ATTAIN trial study drug was also noted to reduce both ‘EXACT-reported’ and ‘EXACT-unreported’ acute exacerbations of COPD, lending further credibility to these unreported symptom-based acute exacerbations of COPD as important but possibly overlooked endpoints in previous large-scale clinical trials.

Exacerbation-Like Events

In the setting of persistent debate as to the most appropriate definition to be using for an acute exacerbation of COPD as it relates to clinically important outcomes, Bourbeau *et al.* assessed the clinical impact of acute exacerbation events, defined as a change in any of the cardinal respiratory symptoms (dyspnea, or increased sputum volume, or increased sputum purulence) lasting more than 24 hours, in a multicentre single-arm study of 421 participants with COPD over a period of 6 months[99]. A clinically significant deterioration in the St. George’s Respiratory questionnaire (SGRQ), a principal tool in assessing changes in health and quality of life in the COPD patient population, were observed in 71% of the 176 participants that reported an acute exacerbation of COPD when using this more sensitive definition. From the same research group, Langsetmo *et al.* then reported that in these same participants, over two thirds of the respiratory events that actually met criteria for an exacerbation (this time using a definition of at least one of

the cardinal respiratory symptoms for more than 48 hours) went unreported to the study team[96]. Subsequent to this, Xu *et al.*[100] applied the same definition used in the study by Langsetmo *et al.* in a different prospective cohort of 491 patients with moderate, severe, and very severe COPD in China. It was once again demonstrated that this symptom-based outcome (obtained by monthly telephone visits) detected both those events that were brought to medical attention ('reported': n=410) as well as an even greater number of events never ultimately brought to medical attention ('unreported': n=466) over a 12-month follow-up period[100]. The change in the St. George's Respiratory questionnaire (SGRQ) score was found to be similar between 'reported' events and 'unreported' events. Moreover, the magnitude of change in the SGRQ score following exacerbation events was significantly worse within those patients who experienced more than one unreported event over the 12-month follow-up period. Collectively, these studies would indicate that even when acute exacerbations of COPD are defined less severely (i.e. a change in a single respiratory cardinal symptom, even when not requiring step-up therapy), they are still clinically important events and go commonly underreported by patients with COPD.

The utility of this less 'severe' definition for an acute exacerbation of COPD, termed as an "exacerbation-like event" (ELE), has subsequently been established in the literature as a meaningful, clinically important and potentially more sensitive outcome in COPD and even in non-COPD populations. The exacerbation-like event has been used as the *Canadian Cohort Obstructive Lung Disease (CanCOLD)* study outcome in a variety of published studies[14, 80, 101, 102] and is subdivided into 'symptom-based' exacerbation-like events (defined by an increase in dyspnea, or sputum volume, or sputum purulence lasting 48 hours or more) which is more similar to traditional 'Anthonisen'-type definitions, and 'event-based' exacerbation-like events (defined as meeting criteria for a 'symptom-based exacerbation-like event' plus requiring either antibiotic or corticosteroid treatment or requiring unscheduled doctor or emergency room visit or hospitalization) which is more similar to *Global Initiative for Chronic Obstructive Lung Disease* (GOLD)-type definitions. Within the CanCOLD cohort, Labonté *et al.*[80] sought to determine the burden of healthcare use in participants with a diagnosis of COPD confirmed by spirometry but remaining clinically undiagnosed by a physician. Symptom-based and event-based exacerbation-like events were collected prospectively every 3 months by telephone interview. The study found that although undiagnosed participants with COPD experience fewer exacerbation-like events than those participants with COPD who are also diagnosed as having COPD by a physician,

when undiagnosed participants do experience exacerbation-like events they use a similar amount of health services as those with physician-diagnosed COPD. This study supported the feasibility and value of collecting exacerbation-like event data with periodic telephone interviews in a prospective and longitudinal manner, and also further supported the utility of the exacerbation-like event as a relevant study outcome.

Air Pollution, Climate Change and Acute Respiratory Events

The World Health Organization identifies climate change as one of the greatest health threats of the 21st century[103]. The consequences of climate change are particularly relevant for the large and vulnerable COPD patient population. Air pollution (for example, wildfire smoke exposure) and weather events (for example, particularly cold days during the cooler months/seasons and particularly hot days during the warmer months/seasons) brought about by climate change have the potential to aggravate existing respiratory diseases[104].

Patients with COPD may be particularly susceptible to relative acute increases in air pollutant concentrations as well as to relative/seasonal extremes in weather, as these may provoke acute respiratory events including acute exacerbations of COPD and exacerbation-like events. This may be the case even in the Canadian setting for the following reasons.

Firstly, compared with most of the world's population and particularly compared with low- and middle-income nations, Canada has relatively lower levels of ***annual*** average ambient air pollution[105]. For example, the 2020 State of Global Air report groups Canada among the 10 countries with the lowest population-weighted annual average $PM_{2.5}$ exposures in the world[106]. However, supra-linear relationships for fine particulate matter ($PM_{2.5}$), ozone (O_3), and redox-weighted average of nitrogen dioxide (NO_2) and O_3 (Ox) with the *incidence* of COPD were recently described in a Canadian provincial-level population-based retrospective study[107], where the degree of change in associations was the steepest at low concentrations. The risk of mortality from cardiovascular events attributed to $PM_{2.5}$ in patients with COPD in California were also recently shown to have supra-linear relationships such that the hazard ratios for mortality per $10\mu g/m^3$ of $PM_{2.5}$ were highest at lower concentrations[108]. The authors concluded that the current accepted annual regulatory levels do not sufficiently protect individuals with COPD from adverse outcomes.

Secondly, despite relatively lower annual averages on the global stage, the Canadian population is still susceptible to acute increases in ambient air pollution. For example, the vast majority of

the Canadian population live in large urban centres and these settings are more susceptible to relative spikes in ambient air pollution. Air pollution from forest fires also continue to cause acute increases in pollutant concentrations which are sizeable in magnitude. An estimated 2.25 hectares of forest burn annually in Canada; the annual Canadian health impact costs of these forest fires are estimated at $410 million - $1.8 billion (acute) and between $4.3 - $19 billion (chronic); and it was estimated that 17.1% of all population-weighted $PM_{2.5}$ exposure comes from forest fire events[109, 110]. With current climate projections, wildfire seasons are expected to become longer and more severe. 'Extreme fire' weather could increase by as much as 200-300% in Eastern Canada, and by 50% in Western Canada, over the next century[111].

Particularly because of these projections, a better understanding of the relationship between acute exacerbations of COPD and acute air pollution episodes is warranted. As it relates to triggering acute exacerbations of COPD and "exacerbation-like events", it is possible that important respiratory health benefits may be achieved through the reduction of pollutant concentrations even at the generally lower concentrations seen in developed nations[112]. It will be important to start studying these relationships within vulnerable populations, such as those living with chronic respiratory disease, across the whole spectrum of disease severity.

Mechanisms of Air Pollution and Weather in Triggering Acute Respiratory Events

Several different types of air pollutants exist, each with unique sources, composition, and acute effects on the human respiratory system. The principal ambient air pollutants include particulate matter (including fine particulate matter, $PM_{2.5}$), ozone (O_3), and nitrogen dioxide (NO_2)[113]. NO_2 is produced mainly by vehicles through incomplete combustion of nitrogen-containing chemicals, and ground-level O_3 is formed in the presence of sunlight following a chemical reaction of oxides of nitrogen. Though air pollutants affect virtually every organ system in the body[113, 114], particle size is the most important determinant of the location of deposition along the respiratory tract. While particles greater than 5μm are more likely to deposit in the proximal (upper) airways, particles less than 5μm are more likely to deposit in the distal airways (bronchioles) and alveoli[115]. Fine particulate matter, particles smaller than 2.5μm in aerodynamic diameter, can either be formed directly from a variety of primary sources (including motor vehicles, biomass burning and industrial facilities) or can also be formed as complex mixtures of

secondary natural and non-natural sources (road dust, construction, agriculture)[116]. The large heterogeneity of composition of $PM_{2.5}$, not only geographically but also in the same geographical region over time[117, 118], adds to the complexity in identifying the exact molecules and mechanisms of action on human respiratory health. Moreover, there is a surprising global interconnectedness of ambient particles, which once produced can cross provincial/state and national borders and are influenced by wind and weather patterns[116].

The effects of air pollutants on the respiratory system have long been studied. $PM_{2.5}$, NO_2 and O_3 have irritant effects which can acutely provoke bronchial hyperreactivity, cough, and sputum production[114]. The principal mechanisms of action of acute harm following inhalation include injury from free radical peroxidation; dysregulation of intracellular calcium levels; and direct injury via inflammatory cytokine signaling, modification of expression patterns of alveolar macrophages, recruitment of neutrophils and eosinophils, and cumulative local tissue damage at the site of deposition along the respiratory system[119].

It has been put forth that in both healthy and in COPD patient populations, a principal mechanism of action of air pollutants on acute respiratory function occurs at the level of the respiratory epithelium lining the airways[120]. For example, NO_2, $PM_{2.5}$ and O_3 have each been demonstrated to stimulate the release of interleukin-8, a pro-inflammatory 'chemokine' which attracts neutrophils, by respiratory epithelial cells[121-123]. It is notable that *serum* levels of interleukin-8 levels have also been reported to be elevated during acute exacerbations of COPD[124, 125]. This provides biological plausibility to the effects of these air pollutants on increasing the inflammation of the airway wall and promoting bronchospasm, thereby reducing airway diameter, increasing the work of breathing, and potentially being recognized clinically as a sudden acute respiratory episode. Mechanistic studies which are specific to only the COPD patient population remain scarce in the literature, though the potential impact of acute episodes of air pollution on acute exacerbations of COPD has previously been reported in large epidemiological studies in patients with COPD living in Asia, Europe, and in North and South America[126-130]. A recent mechanistic study in Beijing, China performed individual lung function testing and bloodwork on a COPD cohort every 3 months for 1 year[131]. Bloodwork for 20 common serum cytokines were collected at three visits, and hourly municipal air pollutant concentrations from several fixed-site monitoring stations were also collected and averaged to provide daily estimates of short-term air pollutant exposures. Models were adjusted for daily

temperature and humidity. Single-day and multi-day lag models demonstrated that short-term exposure to $PM_{2.5}$, SO_2 and CO (but not NO_2, PM_{10} and O_3) were associated with a reduction in forced vital capacity but not in the forced expiratory volume in 1 second. While increasing air pollutant concentration exposure was associated with *decreased* circulating levels of the cytokines released by T helper type 2 cells (eoxatin, interleukin-4 and interleukin-13), they were associated with *increased* circulating levels of those pro-inflammatory cytokines released by T helper type 1 cells (interleukin-2, interleukin-12, interferon gamma, monocyte displacing protein 1 and soluble cluster of differentiation 40 ligand) and T helper 17 cells (interleukin 17A). In another recent study, the neutrophil responses to diesel exhaust exposure (assessed by bloodwork and bronchoalveolar lavage collection) in non-smokers, ex-smokers and mild-moderate COPD participants were investigated using a controlled human-exposure crossover design, and an exaggerated neutrophil activation response was observed in the COPD participants[132]. Cumulatively, the data support that disease-specific systemic pro-inflammatory and abnormal immune responses such as T cell subset (Th1 and Th2) imbalances and increased neutrophilic responses in patients with COPD may disproportionately predispose them to be more susceptible to the same acute effects of air pollution exposure that are described in the general population. The effects of weather conditions including mean temperature and mean relative humidity as general stressors on the human body are also well-established. Pertaining to specific respiratory system effects, cold weather can cause bronchoconstriction and can impair muco-ciliary clearance, while hot weather can lead to stress and inflammation[133]. Humidification of the respiratory tract is important to maintain normal function, and therefore changes in ambient relative humidity (low humidity in particular) may affect respiratory function. Acute exacerbations of COPD have been associated with temperature and season, independent of air pollution, with higher risks in colder seasons[134, 135]. Conversely, particularly hot weather during the summer months has been estimated in epidemiological studies to be associated with an increase the risk of death attributable to COPD by up to 25%[136]. Some studies have shown that low humidity can increase the risk of acute exacerbations of COPD, while higher humidity levels may be protective[117, 137]. Similar to the effects of air pollution, the mechanisms of action of extreme temperature and humidity conditions on the normal respiratory system are in general felt to be the same mechanisms in patients with COPD. The lower threshold for bronchoconstriction in hot weather is likely to explain the greater susceptibility in patients with COPD than in the

general population[133]. Regarding cold weather in patients with COPD, daily lung function and symptom data from 76 patients with COPD within the East London cohort collected over 1 year demonstrated a significant decline in both forced expiratory volume in 1 second (by 45 millilitres) and forced vital capacity (by 74 millilitres) during the coolest week of the study when compared to the warmest week, supporting a rationale for cold weather-related morbidity even in COPD populations living in temperate climates[138]. Cold weather may cause bronchoconstriction disproportionately in patients with COPD via cutaneous reflex activation (for example, exposure to the face to cold air)[139].

The respective effects of weather conditions and air pollution may become increasingly interconnected, since climate change not only affects extreme weather patterns but is also expected to further increase the concentrations of particulate matter and ground-level ozone in the years to come[103].

Prior Time Series Studies

Due to the limitations of animal studies, and to the obvious ethical limitations of intentional pollution exposure to human participants, most of the studies published to date which estimate the association between acute increases in air pollution and acute exacerbations of COPD have been epidemiological studies. The large majority of these prior studies, which have greatly contributed to the field, were performed using ecological and time series study designs. The time series design is commonly used in the field of environmental epidemiology and is a useful design in estimating short-term associations (for example, day-to-day variations between an exposure and outcome of interest) when exposure and outcome data are available in regular intervals over time[140]. When sub-seasonal, seasonal, and long-term trends do exist, these can act as confounders and interfere with the short-term associations being estimated and therefore must be controlled for in the modeling of time series studies. Because the outcome of time series studies represent event ‘counts’ of a population, and because the level of inference is often made at the population level in these studies (i.e. not at the level of the individual), time series studies tend to use hospital administrative database (HAD) and international classification of disease (ICD) data to classify both disease as well as outcome. Delays (lags) in the association between the exposure and outcome under study can be effectively investigated in time series studies. Study settings with lower levels of acute air pollutant concentrations, as well as COPD patient populations with less severe forms of disease (mild-moderate COPD), tend to be under-represented in the existing

literature. A majority of these prior studies have been conducted in developing nations, which have annual and acute air pollutant concentrations that are on average well above those of developed nations. The largest systematic review and meta-analysis to date was published by Li *et al.*[129] in 2016. Due to the well-established lag effect of some air pollutants in precipitating exacerbations, studies which estimated the association between exposure and outcome with a duration of up to 7 days (i.e. 6 'lag' days) were included in that meta-analysis. NO_2, $PM_{2.5}$ and O_3 were studied, as well as particulate matter smaller than 10μm in aerodynamic diameter (PM_{10}), carbon monoxide (CO) and sulfur dioxide (SO_2). Short-term exposure to each of the air pollutants (in single-pollutant models) was associated with a significant increase in the odds of acute exacerbations of COPD, of which the associations were strongest at lag 0 (for gaseous pollutants) and lag -3 (particulate pollutants).

Several time series studies conducted in the Canadian setting over the last two decades have been instrumental in further supporting an association between transient air pollutant exposure and acute respiratory events even in this relatively lower-pollutant setting. Chen *et al.* conducted a time series study in Vancouver, Canada on the effect of particulate matter ('thoracic' PM_{10}; 'coarse' $PM_{10-2.5}$; and 'fine' $PM_{2.5}$) and the coefficient of haze on hospitalizations for acute exacerbation of COPD, as defined using international classification of diseases codes, in patients aged 65 years and older with COPD[141]. Seasonal and sub-seasonal trends were adjusted for using general linear models with parametric natural cubic splines, while weather (temperature and relative humidity) and gaseous pollutant (CO, SO_2, NO_2 and O_3) estimates were collected for adjustment. Lags of 0 to 7 days were studied. Despite relatively low pollutant concentrations, in single-pollutant models adjusted for weather conditions, each of the particulate matter types and coefficient of haze were positively associated with 'COPD hospitalizations' with lags of 0-2 days prior to the event. Following adjustment for NO_2 in two-pollutant models each of these associations no longer reached statistical significance. In a similar follow-up study by the same group on the same Vancouver elderly population with COPD over a similar time period, the association between the gaseous pollutants (NO_2, SO_2 and O_3) on COPD hospitalization events were investigated and only NO_2 was found to have a positive association with COPD hospitalization events in single pollutant models[142]. This association was no longer statistically significant following adjustment for PM_{10}.

Subsequently, Stieb *et al.* conducted a multi-site time series trial based in 7 Canadian cities to

estimate the association between air pollutants (CO, NO_2, O_3, SO_2, $PM_{2.5}$ and PM_{10}) and a variety of cardiac and respiratory clinical outcomes in adults and children[143]. Data from fixed site monitors from the *National Air Pollution System* (NAPS) database was used to estimate city-wide average air pollutant exposure, and Environment Canada archives were used to collect weather (temperature and relative humidity) data which were inserted into the quasi-Poisson models along with seasonal air pollutant cycles, day of the week and holidays to adjust for these. Furthermore, given the extremes in weather observed in the Canadian climate, data during the Warm season (April to September) and the Cool season (October to March) were analyzed separately in subgroup analysis. Lags of 0-2 days were assessed. Disease classification and outcome events were ascertained using emergency department discharge diagnosis international classification of diseases codes. There was a pattern of association between ozone and 'COPD visits' particularly on lag day 2, however few statistically significant associations were observed between ozone (or any of the air pollutants) and most of the acute respiratory outcomes. No consistent associations were observed between air pollutant concentration and either respiratory or cardiac visits during the Cool season.

More recently, To *et al.* assessed the effects of air pollutant concentration (NO_2, $PM_{2.5}$ and O_3) and of the Air Quality Health Index (a composite measure of these three principal air pollutants) on health service use for adults and children with 11 chronic disease conditions in Ontario, Canada over an 8-year period. Air pollutant exposure was estimated using fixed-site monitoring stations, and international classification of disease codes were used to classify chronic disease as well as primary care, emergency department visit and hospitalization event outcomes. Temperature, age group (10-year groupings), sex, residence region, socioeconomic status, day of the week, season and year were added as covariates for adjustment into the Poisson regression models. Lags of 0 to 2 days were studied. On Lag Day 0, there was a positive association between both Air Quality Health Index score as well as short-term increases in NO_2 concentration for all 'COPD visit' types. Conversely, short-term increases in O_3 concentration were *negatively* associated with all COPD visit types. Short-term increases in $PM_{2.5}$ concentration was positively associated with emergency department visits but was *negatively* associated with outpatient visits and hospitalizations.

Prior Case-Crossover Studies

The case-crossover design has several unique properties which allow for the same association

(for example, the association between transient air pollutant exposure and acute respiratory events in patients with COPD) to be estimated as in time series studies but by using a different analytical approach. The results of these two separate well-established study designs creates the opportunity for the same association to be investigated from two different but complementary perspectives. Therefore, the interpretation and comparison of results across these different trial designs stands to strengthen the body of knowledge on this association.

The case-crossover design was first introduced by Maclure *et al.* in 1991[144] as a method to estimate the effect of transient exposures on acute outcomes. In the case-crossover design, every participant included has experienced the outcome of interest, and importantly, each participant acts as their own control[145]. This analytical approach allows for the inherent controlling for individual-level confounders that do not vary with time. The level of inference is based on a comparison of *exposure* distribution (i.e. the *level of exposure* preceding the outcome of interest, in comparison with the *level of exposure* preceding control periods).

The case-crossover design is established in the field of air pollution epidemiology as a useful method to estimate the association between transient air pollution changes and acute respiratory events[146]. Despite this, few case-crossover studies estimating the association between transient increases in air pollution on acute exacerbations in patients with COPD exist in the literature. Even fewer studies have been performed in North America, and in a well-characterized cohort of participants with COPD which has been confirmed by spirometry.

Lin *et al.*[147] conducted a case-crossover study on 277 elderly patients with COPD in Taiwan to determine the effect of NO_2, $PM_{2.5}$, O_3, PM_{10}, SO_2 and CO and hospitalizations for acute exacerbation of COPD. All data was stratified into "warming up" (April-September) and "cooling down" (October-March) seasons in order to properly assess the effect of seasonal extremes (i.e. the effect of hot weather during the "warm" months of the year, and the effect of cold weather during the "cool" months of the year). Models were also adjusted for weather parameters (mean temperature, relative humidity, and ambient pressure). While NO_2, CO, O_3 and PM_{10} were positively associated with hospitalizations for acute exacerbation of COPD, season-dependent temperature (hot temperatures in the warm season and cold temperatures in cool season) was also positively associated with hospitalizations for acute exacerbation of COPD.

In the North American setting, Devries *et al.*[117] conducted a case-crossover multi-city study in Massachusetts on 168 patients with COPD confirmed by spirometry and followed in a COPD

clinic with specialized COPD nurses. NO_2, $PM_{2.5}$, and SO_2 concentrations were estimated as an area-level average of 3 fixed-station monitors of the 3 neighbouring cities. Given the relatively lower North American air pollution setting of the study, the more sensitive outcome of early outpatient acute exacerbations of COPD (detected by serial COPD nurse telephone visits) was used. This decision to collect *outpatient* acute exacerbation of COPD data was similarly performed in the 2011 East London study by Peacock *et al.*[148] on 94 participants with spirometry-confirmed COPD, in which the outcome of outpatient acute exacerbations of COPD was collected using participant-completed diary cards over a median follow-up period of 518 days. Generalized estimating equations (GEE) methods were used to account for variation within and between individuals. Short-term NO_2 and PM_{10} exposure in particular were observed to worsen lung function and dyspnea. Devries *et al.* adjusted models for temperature, relative humidity, and self-reported influenza status, however relative humidity was not included in final modeling. Single-pollutant models revealed that NO_2 and SO_2 were positively associated with acute exacerbations of COPD s, while surprisingly a *negative* association was found between $PM_{2.5}$ and acute exacerbations of COPD.

Szyszkowicz *et al.*[149] conducted a 9-city case-crossover study in Ontario, Canada in which *National Air Pollution Surveillance* (NAPS) fixed-site stations were used to estimate $PM_{2.5}$, NO_2, O_3 and SO_2 concentrations, and their relationship with 183,542 events were estimated using lags of 0 to 8 days. All data were stratified by sex. International classification of disease codes were used to identify patients with COPD (under the code "COPD and bronchiectasis") and to identify emergency department visits for acute respiratory conditions as a correlate of acute exacerbations of COPD. Fixed-effects modeling (i.e. treating repeated visits by the same participant as separate/individual observations, thereby risking a violation of the assumption of independent observations) was used. Sex-specific positive associations between air pollutants and emergency department acute respiratory visits (in males: NO_2 on lags 3-6, $PM_{2.5}$ on lags 1-8, and SO_2 on lags 4-8; in females: O_3 on lags 2-4; SO_2 on lags 3-6) were observed.

Potential limitations of these prior case-crossover studies include not having individual-level demographic and disease-specific data derived from well-characterized cohorts[149]; using international classification of disease codes and health administrative records to define disease category[149] and outcome[147, 149]; restricting the study population to a sub-national (municipal or sub-provincial/sub-state) level[117, 147, 149]; and not controlling for potential confounding by

specific day of the week or by sub-seasonal trends[117, 147]. The main results from these case-crossover studies are also conflicting. For example, acute increases in the ambient concentration of the principal air pollutant $PM_{2.5}$ was found to be associated with an *increased odds* of exacerbations[149], with *no change in the odds* of exacerbations[147], and even with a *reduced odds* of exacerbations[117] across these case-crossover studies. Lastly, none of these studies focused on participant populations with mild to moderate COPD. Therefore, important unaddressed gaps remain in this field of research.

Rationale

Despite the relatively lower annual average concentrations of air pollution in Canada compared with many developing nations, acute relative increases in air pollutants (brought about by wildfires or in densely populated urban areas) are not uncommon in the Canadian setting and are expected to increase as a result of climate change. Moreover, acute exacerbations of COPD often go under-reported, and are clinically significant even when less severe definitions are used. Given the enormous burden of COPD and of the burden of acute respiratory events experienced by these patients and by the healthcare system alike, it remains very relevant and important to investigate the association between even subtle increases in air pollutant concentrations and acute respiratory events in the Canadian setting and in other nations with similar air quality using a robust study design and methodology. The impetus for such research is further supported by the sobering projections of increased wildfire frequency and extreme weather events in the years to come. To conduct such a study effectively, it would be important to use a sufficiently sensitive outcome. The majority of prior studies investigating this association have used hospital administrative database data and international classification of disease codes to document acute exacerbation events. Moreover, prior such studies in the Canadian setting have been limited to one province or to one geographical region and have largely focused on severe COPD rather than on the sizeable population living with less severe forms of disease. In this regard, what is needed to properly estimate this association is a study with i) well-characterized participants, with extensive demographic information and with disease status confirmed by spirometry; ii) a well-characterized cohort sampled from many cities and provinces across the general Canadian population; iii) a sensitive[80, 96, 99, 100] method of measuring clinically relevant acute respiratory events (outcomes) in the mild-to-moderate COPD patient population (capable of detecting both symptom-based and event-based acute events); and iv) a study design that can effectively

address important confounders.

Objectives and Hypotheses

The **general objective** of the study is to evaluate the effects of acute "short-term" air pollution and weather exposures on exacerbation-like events in a population cohort of individuals with predominantly mild and moderate COPD.

The **specific objectives** are to estimate the relationship between short-term exposures to nitrogen dioxide (NO_2), fine particulate matter ($PM_{2.5}$) and ozone (O_3) and exacerbation-like events, using single-pollutant and multi-pollutant models, in individuals with COPD confirmed by spirometry from a population-based sample during the Warm and Cool Seasons of the year as well as to investigate for any differences in these associations which are based on sex and based on the severity of disease.

The **main hypothesis of the study** is that in the Canadian setting, short-term increases in each of the ambient air pollutants (nitrogen dioxide, fine particulate matter, and ozone) will be associated with an increase in the odds of both symptom-based and event-based exacerbation-like events in a mild-moderate COPD cohort during both Warm and Cool Seasons of the year, and that these associations will persist following adjustment for weather covariates and across multi-pollutant models. The secondary hypotheses of the study are that important differences in the associations under investigation will be observed based on sex and based on disease severity.

Chapter 3: Methodology

Study Design

A case-crossover design[144, 146] was used to compare the 24-hour average concentration of each air pollutant ($PM_{2.5}$, NO_2, and O_3) on the day of an "exacerbation like event" (defined as the hazard period) with the 24-hour average concentrations sampled from three or four separate reference time periods (defined as the control periods). Exposure lags ranging from 0 to 6 days prior to the onset of a self-reported exacerbation-like event were used as hazard periods. This lag timeframe was chosen as it is the most commonly reported timeframe in the literature[129, 149, 150], and is specifically recommended in the largest systematic review and meta-analysis performed to date (so as not to miss important delayed air pollutant effects)[129]. Time-stratified referent selection[151-154], a method that has been shown to reduce overlap bias and confounding by time-trend[154, 155], was used. Control periods on the same day of the week and in the same month and year as the hazard period were selected. Thus, depending on the date on which the hazard period fell within a given month, the control periods could precede the hazard period, follow the hazard period, or could both precede and follow the hazard period. Furthermore, depending on the date of the hazard period, the sampling of either 3 control periods or 4 control periods per hazard period was possible. This methodology was selected such that the hazard period is controlled for confounding by annual trends, seasonal trends, sub-seasonal trends and day-of-the-week trends by design[145, 154].

Participants

Data from the longitudinal Canadian Cohort Obstructive Lung Disease (CanCOLD) study[156] was used in the present study. In total, 1,561 participants were enrolled into CanCOLD. CanCOLD is a Canadian cohort of adult participants from 9 Canadian cities (Vancouver, Calgary, Saskatoon, Toronto, Kingston, Ottawa, Montreal, Quebec City, and Halifax) across 6 different provinces. There is a wide spectrum of disease within CanCOLD participants which ranges from healthy subjects (never-smokers without COPD), at-risk subjects (smokers without COPD), and COPD confirmed by spirometry. The majority of participants within CanCOLD with a confirmed diagnosis of COPD at enrolment (diagnosed when the ratio of the forced expiratory volume in 1 second over the forced vital capacity of less than the lower limit of normal is reached, using the *National Health and Nutrition Examination Survey* (NHANES) criteria[157]) had either 'mild'

(*Global Initiative for Chronic Obstructive Lung Disease* 'GOLD' grade 1: forced expiratory volume in 1 second of greater than or equal to 80% of predicted) or 'moderate' (GOLD grade 2: forced expiratory volume in 1 second greater than 50% of predicted but less than 80% of predicted) disease, with far fewer participants with 'severe' (GOLD grade 3: forced expiratory volume in 1 second greater than 30% of predicted but less than or equal to 50% of predicted) and no participants with 'very severe' (GOLD grade 4: forced expiratory volume in 1 second less than or equal to 30% of predicted) disease.

Only participants in CanCOLD with COPD diagnosed by spirometry were included. Those CanCOLD COPD participants who experienced at least 1 exacerbation-like event (with a recall period of ≤4 months) between July 2012 and December 2019 were included in the analysis.

The study protocols were approved by ethical review boards at all participating sites as well as by the Research Institute of the McGill University Health Centre (RI-MUHC, principal site) and formal request for collaboration and data sharing with CanCOLD was submitted and approved. Detailed demographic information for all participants, including spirometry data, were retrieved from the CanCOLD database.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria[156, 158] for this study are as follows:

Inclusion Criteria:

- Men and women (aged ≥40 years, non-institutionalized).
- Diagnosed with COPD by spirometry (post-bronchodilator ratio of the forced expiratory volume in 1 second over the forced vital capacity that is less than the lower limit of normal using the *National Health and Nutrition Examination Survey* criteria[157]).
- Permanent residence in one of 9 study sites in Canada (Vancouver, Calgary, Saskatoon, Toronto, Kingston, Ottawa, Montreal, Quebec City, and Halifax).

Exclusion criteria:

- *Participants:*
    - Inability to provide informed consent.
    - No evidence of fixed airflow obstruction on spirometry.
- *Exacerbation-like events:*
    - Recall period of greater than 4 months from the time of the exacerbation-like

event.

- Date of event prior to July 1, 2012 or after December 31, 2019.

Outcome Measurement: Exacerbation-Like Events

From July 2012, self-reported "exacerbation-like events"[102] were prospectively collected along with their respective date of onset for all participants (both with and without COPD) in CanCOLD through telephone interviews using a standardized questionnaire conducted every 3 months (see Appendix **Figure A1**). All CanCOLD participants were instructed to prospectively record the date of onset of each exacerbation-like event as they occurred. Participants could then refer to these records at the time of each interview when providing information over the telephone, in the interest of providing the most accurate possible date of onset for each event. The standardized questionnaire was developed to minimize recall bias, was based on previously published work of measuring acute exacerbations of COPD using questionnaires in large cohorts[99, 100, 159, 160], and was expanded to collect additional information that pertains to the present study. The questionnaire was also specifically modeled to capture milder acute respiratory events which may not necessarily prompt emergency department or acute care visits but may still affect quality of life[96] and/or impact on health[80].

The outcome of interest, an "exacerbation-like event", is sub-divided into 'symptom-based' (defined as an increase in dyspnea, sputum volume or sputum purulence lasting 48 hours or more), and 'event-based' (defined as an increase in dyspnea, sputum volume or sputum purulence lasting 48 hours or more *as well as* requiring either antibiotic or corticosteroid treatment, or requiring unscheduled doctor visit, emergency room visit or hospitalization)[80]. Both symptom-based and event-based exacerbation-like events were recorded by the questionnaire. Though exacerbation-like event data continued to be collected within CanCOLD in 2020 and 2021, at the time of completion of the present study *National Air Pollution Surveillance* program air pollutant concentrations were only available up until December 2019. Therefore, data from July 1, 2012 to December 31, 2019 inclusive was used in the present case-crossover study embedded within CanCOLD.

Because of the importance of accurate recall of event date for each reported exacerbation-like event (which in turn dictates the date of the hazard period as well as the date of the three or four corresponding control periods, for each of Days '0' to '-6'), the interval between the date of the self-reported exacerbation-like event and the date of the follow-up telephone call to collect this

information from the participant was limited to 4 months or less. All events with a recall period of greater than 4 months were excluded from analysis, and by extension any participant with COPD without at least one exacerbation-like event between July 1, 2012 and December 31, 2019 which had a recall period of 4 months or less were excluded. Over the course of the study period, CanCOLD participants completed three in-site visits (one 'baseline' and two subsequent follow-up visits) at which spirometry was collected. All participants who did not meet criteria for fixed airflow obstruction on spirometry at baseline, but who subsequently demonstrated fixed airflow obstruction on a subsequent spirometry test at a CanCOLD follow-up visit, were also assessed for eligibility. If these particular participants also experienced at least 1 symptom-based or event-based exacerbation-like event with a recall period of ≤4 months which occurred subsequent to the time of their diagnosis and prior to December 31, 2019, these participants and events were also included in the primary and secondary analyses of the study.

Estimation of Exposure: Air Pollution

The *National Air Pollution Surveillance* (NAPS) program database was used to estimate daily air pollution exposure concentration in the present study. As a collaboration of federal, provincial, and local governments, the *National Air Pollution Surveillance* program is the principal reference for standardized ambient air quality data in populated regions of Canada. Continuous data are collected at several fixed-location gas and particulate monitors. These fixed-location monitoring stations are located in municipalities across Canada. Continuous data measured at each station are subsequently made publicly available as hourly estimates. The first annual *National Air Pollution Surveillance* program summary was published in 1972. Over the subsequent decades, the number of participating provinces and territories, the number of monitoring stations in the different municipalities, and the methods used to measure air quality have evolved. Presently, there are 286 monitoring stations in 203 communities from every province and territory. Hourly records of fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) between July 2012 and December 2019 were collected from the *National Air Pollution Surveillance* program database for this study.

To estimate participants' air pollutant exposures, the 6-digit residential postal codes of CanCOLD participants were obtained to identify the air pollution concentrations from the most appropriate monitoring stations in each study city. Because the number of fixed-location monitoring stations vary by city size, a pragmatic approach was pursued whereby all monitoring

stations within each CanCOLD site city boundaries were included. For example, 1 monitoring station was used for Saskatoon, whereas 7 monitoring stations were used for Toronto. In each city, hourly measurements from the selected monitoring stations were then aggregated into 24-hour averages to provide a single daily area-level concentration estimate for each city. Inverse-distance weighting was not performed. This area-level estimation approach is in keeping with the published literature on case-crossover trial protocols in North America[117, 118, 149, 161].

Delays in the effects of air pollutants on precipitating acute respiratory events by a magnitude of days have been repeatedly demonstrated in the literature[129], in a manner that varies by both the type of air pollutant and on the type of respiratory disease under study[162]. Assessing lags from 0 to 6 days prior (i.e. total of 7 days) is the most commonly reported schedule[129]. The association of each distinct lag day (for example, the 24-hour average air pollutant concentration on the same day of the exacerbation-like event; on the day prior to the exacerbation-like event; on two days prior to the exacerbation-like event; etc.) was estimated for each lag day from Day 0 to Day -6 in order to determine the most influential lag period for each air pollutant in potentially precipitating exacerbation-like events.

Estimation of Weather Covariates

Mean temperature and mean relative humidity were obtained for each study city as continuous variables from the Applied Climatology Services/Meteorological Service of Canada (Environment and Climate Change Canada, Government of Canada). Open-access files of weather data, in hourly (mean relative humidity) and daily (mean temperature) averaged format, were obtained. Lag days (Days 0 to -6) of mean daily temperature and mean daily relative humidity (to match daily air pollution and exacerbation-like event data, for each day and in each city) were derived.

Statistical Analysis

Outcomes (symptom-based and event-based exacerbation-like events), exposures (NO_2, $PM_{2.5}$, and O_3 concentrations), and covariates (mean temperature and mean relative humidity) were all linked by date and city for all recorded events of each participant. This yielded matched data for the hazard period of Day ‘0’ (and the three or four corresponding control periods for Day ‘0’), as well as matched data for each individual hazard period between Lag Days ‘1’ to ‘-6’ inclusive (and the three or four control periods corresponding to each of these 6 lag days)[154].

Given the seasonal extremes in the Canadian climate, where an acute respiratory event may be precipitated by relatively hotter temperatures (in the warmer months of the year) and by relatively colder temperatures (in the cooler months of the year), all data were dichotomized into 'Warm' (May-October) and 'Cool' (November-April) Seasons and analyzed separately (as described previously)[147, 149, 161] to establish directionality when interpreting the magnitude of the effect of temperature (see Appendix **Figure A2**).

Results are presented for both symptom-based exacerbation-like events and event-based exacerbation-like events (given the way that they are defined, event-based exacerbation-like events are a subset of symptom-based exacerbation-like events).

Models were fit to matched hazard (x1) and control (x3-4) periods using a generalized estimating equation (GEE). GEE methodology was used in order to account for the 'clustering' of events, since a single participant in the study could contribute more than one exacerbation event between July 2012 and December 2019 to the overall analysis. Without employing a GEE methodology these within-participant event clusters would risk violating the assumption of 'independent observations'[148, 163]. Odds ratios (ORs) and their 95% confidence intervals [95% CI] were estimated using the PROC GENMOD in SAS version 9.4 (SAS Institute Inc. Cary, North Carolina, U.S), based on binary distribution, with logit link and repeated statement, accounting for the within-subject correlations of repeated measures. Because general estimating equations were used in the analyses, the *'Quasi-likelihood under the Independence model Criterion'* (QIC), rather than the Akaike's Information Criterion (AIC), was used in the selection of the most appropriate correlation structure to employ[164]. Two commonly used correlation structures in this setting are the '*Exchangeable*' structure, which suggests the same correlation between any two within-subject responses, and the '*Unstructured*' structure, which suggests an unknown correlation between responses[165, 166]. All univariable models in the primary analysis were performed using the *Exchangeable* structure and were then repeated using the *Unstructured* structure to obtain the QIC of each model. The final choice of the correlation structure was guided by which correlation structure consistently demonstrated the lowest QIC[166]. When compared within each Season, air pollutant, and lag period, QIC values were smaller in the *Exchangeable* symptom-based exacerbation-like event models when compared with the *Unstructured* symptom-based exacerbation-like event models, and QIC values were similar between *Exchangeable* and *Unstructured* event-based exacerbation-like event models (see

Tables A1 and **A2**). These comparisons led to the decision to employ the *Exchangeable* correlation structure for all models in all primary, secondary and sensitivity analyses.
The 'robust' (also referred to as 'empirical' or 'sandwich') estimation was used to yield robust standard error estimates in the generalized estimating equation analyses. An important strength of 'robust' standard error estimates in the GEE method is that it is robust to misspecification of the correlation structure[167].
All model results are presented as odds ratios (ORs) per increase in interquartile range (IQR) for each air pollutant.

Primary Analysis

In the ***primary analysis*** single-pollutant models[168] (NO_2, $PM_{2.5}$, and O_3, respectively) were fitted, first as univariable (unadjusted) models. Since daily mean temperature and daily mean relative humidity are both ***time-varying exposures*** as it relates to the case-crossover design,[145] and because the adjustment for both temperature and relative humidity has been a widely accepted approach in both time series and case-crossover studies alike, both of these variables were also adjusted for in separate multivariable single-pollutant regression models as part of the primary analysis.

Secondary Analysis

Two-pollutant models were estimated in the secondary analysis. Only those two-pollutant models with a correlation of less than 0.5 in magnitude between pollutants were included. Furthermore, the effect of i) sex and ii) COPD severity (by spirometry, using the *Global Initiative for Chronic Obstructive Lung Disease* 'GOLD' grade) were also assessed, by performing separate analyses in i) males and females (sex subgroups) and in ii) GOLD '1' and GOLD '2+' disease categories (COPD severity subgroups). In all secondary analyses, models were adjusted for both mean temperature and for mean relative humidity.

Sensitivity Analyses

Sensitivity analyses involved repeating all primary analyses (unadjusted and adjusted models for each air pollutant) using all exacerbation-like events (i.e. without excluding exacerbation-like events based on recall period).

Chapter 4: Results

Study Population

The flowchart of CanCOLD participants included in the present study at baseline and by the end of the study is outlined in **Figure 1**. Of 1,561 CanCOLD participants at baseline, 719 participants had a diagnosis of COPD confirmed by spirometry. Of these participants, 389 reported at least 1 exacerbation-like event through prospective telephone interview between July 1, 2012 and December 31, 2019 with a recall period of 4 months or less. Amongst the participants without COPD who were excluded at baseline, between July 1, 2012 and December 31, 2019, sixty of those participants subsequently demonstrated fixed airflow obstruction on a follow-up spirometry test and experienced at least 1 eligible exacerbation-like event which both followed their new diagnosis of COPD and occurred prior to the end of the study period. The demographic characteristics of the CanCOLD participants with COPD included in the study at baseline, in comparison with those CanCOLD participants who had reported at least 1 exacerbation-like event but did not have COPD confirmed by spirometry (and therefore were not included into the study at baseline), are presented in **Table 1**. In the 389 included participants with COPD at baseline, there is a roughly equivalent gender representation. Slightly more than half of participants included in the study had mild (*Global Initiative for Chronic Obstructive Lung Disease* 'GOLD' stage 1) COPD by spirometric criteria [1, 52].

The demographic characteristics of those participants who were initially excluded and were then subsequently included into the study following diagnosis of COPD over the duration of the study period are also presented in **Table 1.** As part of the collection of demographic data and spirometric data in the CanCOLD cohort on a longitudinal basis, all CanCOLD participants attended three study visits. Visit 1 took place between November 2009 to August 2015; Visit 2 took place between June 2011 and November 2015; and Visit 3 took place between January 2013 to August 2019. The median follow-up period between study Visits 1 and 3 was approximately 37 months. Thus, as it relates to the present study, all baseline spirometric and characteristic data presented in **Table 1** are from Visit 1 in eligible participants with COPD. The spirometric and demographic data presented for the subgroup of participants who were not eligible at baseline but who subsequently became eligible over the study period were retrieved from the most recent study visit which preceded their first eligible exacerbation-like event (Visits 2 and 3). Notably,

the demographic characteristics between participants with COPD at baseline and those COPD participants included over the study period following subsequent diagnosis are very similar.
A total of 1,400 symptom-based exacerbation-like events and a total of 841 event-based exacerbation-like events were included in the primary and secondary analyses. The number of eligible exacerbation-like events experienced by study participants between July 1, 2012 and December 31, 2019 is presented in **Figure A3**. Most participants experienced 5 or less symptom-based or event-based exacerbation-like events during the study period. Both histograms reveal a rightward skew, with one participant that experienced 27 symptom-based exacerbation-like events and one participant that experienced 21 event-based exacerbation-like events over the roughly 7.5-year study period.

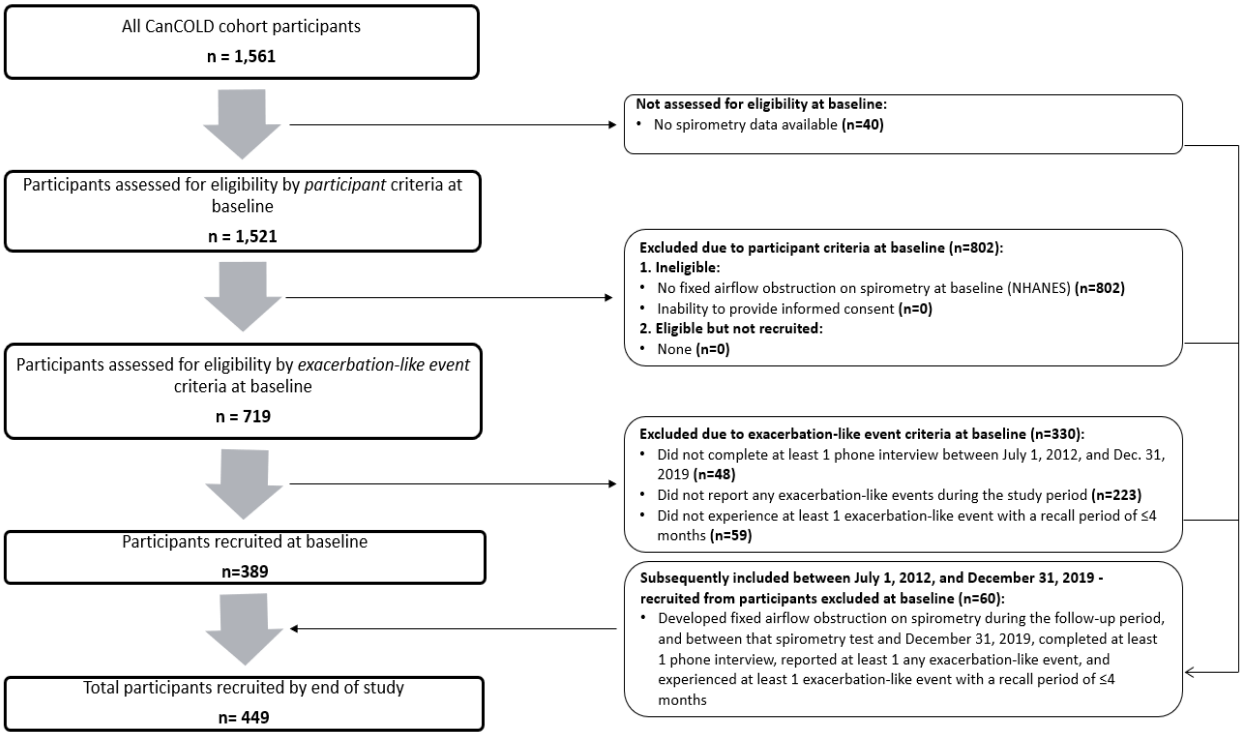

Figure 1. Flow diagram of study participants[169].

Table 1. Characteristics of CanCOLD participants who reported having at least 1 exacerbation-like event at baseline, and of all eligible COPD participants by the end of the study

	Total (Baseline)	**Non-COPD** (Baseline)	**COPD** (Baseline)	**COPD** (End-of-Study)
	n=729	**n=340**	**n=389**	**n=449**
Sex, male (%)	368 (50.5)	159 (46.8)	209 (53.7)	240 (53.5)
Age, years	68.7 ± 10.4	67.3 ± 10.0	69.9 ± 10.5	69.8 ± 10.2
Cigarette status				
Never-smoker	294 (40.3)	163 (47.9)	131 (33.7)	144 (32.1)
Former smoker	334 (45.8)	142 (41.8)	192 (49.4)	225 (50.1)
Current smoker	101 (13.9)	35 (10.3)	66 (17.0)	80 (17.8)
Smoking Hx (PYHx)	17.0 ± 22.0	11.1 ± 16.9	22.1 ± 24.4	23.0 ± 24.8
MRC ≥ 3	70 (10.3)	19 (6.0)	51 (14.0)	56 (13.3)
FEV_1, Litres	2.4 ± 0.8	2.6 ± 0.7	2.2 ± 0.8	2.2 ± 0.8
FEV_1/FVC, %	68.0 ± 11.2	77.0 ± 4.9	60.0 ± 8.8	60.4 ± 8.9
FEV_1, % predicted	88.7 ± 21.5	98.7 ± 17.8	80.1 ± 20.6	80.2 ± 20.4
GOLD stage 1 (%)	202 (27.7)	0 (0.0)	202 (51.9)	231 (51.4)
GOLD stage ≥2 (%)	187 (25.7)	0 (0.0)	187 (48.1)	218 (48.6)
MD Dx COPD (%)	192 (26.3)	47 (13.8)	145 (37.3)	175 (39.0)
MD Dx Asthma (%)	238 (32.6)	76 (22.4)	162 (41.6)	187 (41.6)

Hx = History; PYHx = Pack-Year History; FEV_1 = Forced expiratory volume in one second; FVC = Forced vital capacity; GOLD = Global initiative for chronic obstructive lung disease; COPD = Chronic obstructive pulmonary disease.

Air Pollution Exposure

The daily concentrations of the air pollutant exposures across all 9 study sites over the 2012-2019 study period (including median, 25th percentile, 75th percentile and IQR - dichotomized by Warm and Cool Seasons) during the case and control periods are listed in **Table 2**. Median estimates for NO_2 concentration were relatively higher in the Cool Season than in the Warm Season. Median estimates for $PM_{2.5}$ concentration were similar between Warm and Cool Seasons. Median estimates for O_3 concentration were slightly higher in the Cool Season than in the Warm Season.

Table 2. Air pollutant concentration estimates during case and control periods in the Warm and Cool Seasons

	Warm				**Cool**			
	Median (SD)	**25th perc.**	**75th perc.**	**IQR**	**Median (SD)**	**25th perc.**	**75th perc.**	**IQR**
NO_2 (ppb)	9.27 (4.9)	5.55	12.84	7.3	13.78 (6.82)	8.42	18.69	10.27
$PM_{2.5}$ ($\mu g/m^3$)	5.83 (5.01)	3.92	8.39	4.47	5.83 (4.67)	3.9	8.75	4.85
O_3 (ppb)	18.88 (8.99)	13.63	25.39	11.77	20 (9.85)	12.38	26.71	14.33

NO_2 = Nitrogen dioxide; ppb = parts per billion; $PM_{2.5}$ = particulate matter 2.5 microns or less in diameter; ug = microgram; m^3 = metre cubed; O_3 = ozone; SD = standard deviation; 25th perc. = 25th percentile; 75th perc. = 75th percentile; IQR = interquartile range.

Single-Pollutant Models

Figure 2, **Figure 3**, and **Figure 4** present generalized estimating equations (GEE) models for each pre-specified lag period (from Day 0 to Day -6) for NO_2, $PM_{2.5}$ and O_3, respectively. Unadjusted and adjusted (for mean temperature and mean relative humidity) results are provided in each figure. All data are dichotomized by Season (Cool and Warm), with symptom-based and event-based exacerbation-like events also reported separately. All data are presented per interquartile range increase for each air pollutant for each Season.

For NO_2, **Figure 2** demonstrates that in the Warm Season of the unadjusted model, on Lag Day -3, a 7.3 ppb increase in exposure to ambient NO_2 was associated with an increased odds of both symptom-based (OR 1.07 [0.99, 1.14]) and event-based (OR 1.11 [0.95, 1.29]) exacerbation-like events, though these did not reach statistical significance. Similarly, in the Warm Season of the adjusted model on Lag Day -3, every 7.3 ppb increase in exposure to ambient NO_2 was associated with an increased odds of symptom-based exacerbation-like events (OR 1.09 [1.01, 1.17]), and with an increased odds of event-based exacerbation-like events (OR 1.14 [0.98, 1.33]) which did not reach statistical significance.

In the Cool Season of both the unadjusted and adjusted models, no association and no consistent trend was observed for exposure to ambient NO_2 and the odds of symptom-based or event-based exacerbation-like events.

For $PM_{2.5}$, **Figure 3** demonstrates that in the Warm Season of both the unadjusted and adjusted models, no association and no consistent trend was observed for every 4.47 $\mu g/m^3$ increase in ambient $PM_{2.5}$ exposure and the odds of symptom-based or event-based exacerbation-like events. In the Cool Season of both the unadjusted and adjusted models on Lag Day -1, every 4.85 $\mu g/m^3$ increase in exposure to ambient $PM_{2.5}$ was associated with an increased odds of symptom-based exacerbation-like events (unadjusted: OR 1.07 [1.01, 1.13]; adjusted: OR 1.09 [1.02, 1.16]). No association and no consistent trend was observed between exposure to ambient $PM_{2.5}$ and the odds of event-based exacerbation-like events.

For O_3, **Figure 4** demonstrates that in the Warm Season of the unadjusted model, no association and no consistent trend was observed for exposure to ambient O_3 and the odds of symptom-based or event-based exacerbation-like events. In the Warm Season of the adjusted model, every 11.77 ppb increase in exposure to ambient O_3 on Lag Day -3 was associated with a *decreased* odds of symptom-based exacerbation-like events (OR: 0.94 [0.86, 1.03]) which did not reach statistical

significance, and with a *decreased* odds of event-based exacerbation-like events (OR: 0.81 [0.66, 0.99]).

In the Cool Season of the unadjusted model, every 14.33 ppb increase in exposure to ambient O_3 was associated with a trend towards a *decreased* odds of symptom-based exacerbation-like events on Lag Day -1 (symptom-based: OR 0.95 [0.90, 1.01] ; event-based: OR 0.93 [0.83, 1.06]) which did not reach statistical significance, and on Lag Day -2 (symptom-based: OR 0.96 [0.91, 1.01]; event-based: OR 0.94 [0.84, 1.05]) which also did not reach statistical significance. A similar trend was observed in the Cool Season of the adjusted model for Lag Day -1 (symptom-based: OR 0.95 [0.87, 1.03]; event-based: OR 0.90 [0.76, 1.07]) which did not reach statistical significance, and on Lag Day -2 (symptom-based: OR 0.93 [0.86, 1.00]; event-based: OR 0.91 [0.78, 1.06]) which did not reach statistical significance.

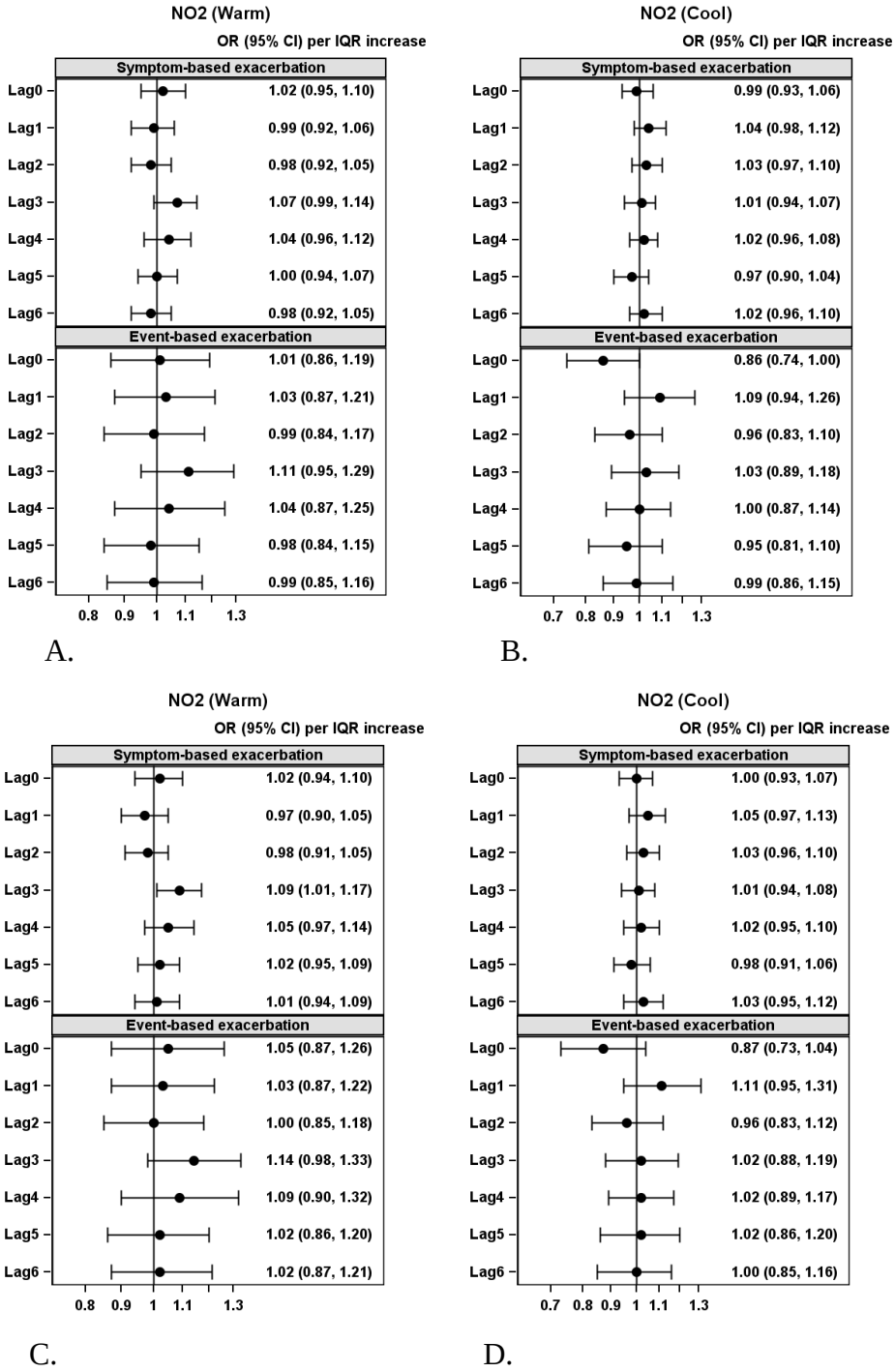

Figure 2. Single-pollutant generalized estimating equations (GEE) model for NO_2 and the odds of symptom-based and event-based exacerbation-like events. Unadjusted models (A. Warm, B. Cool) and adjusted models for mean temperature and relative humidity (C. Warm, D. Cool). Odds ratios (OR's) and 95% Confidence Intervals (95% CI's) are presented per interquartile range (IQR) increase in NO_2.

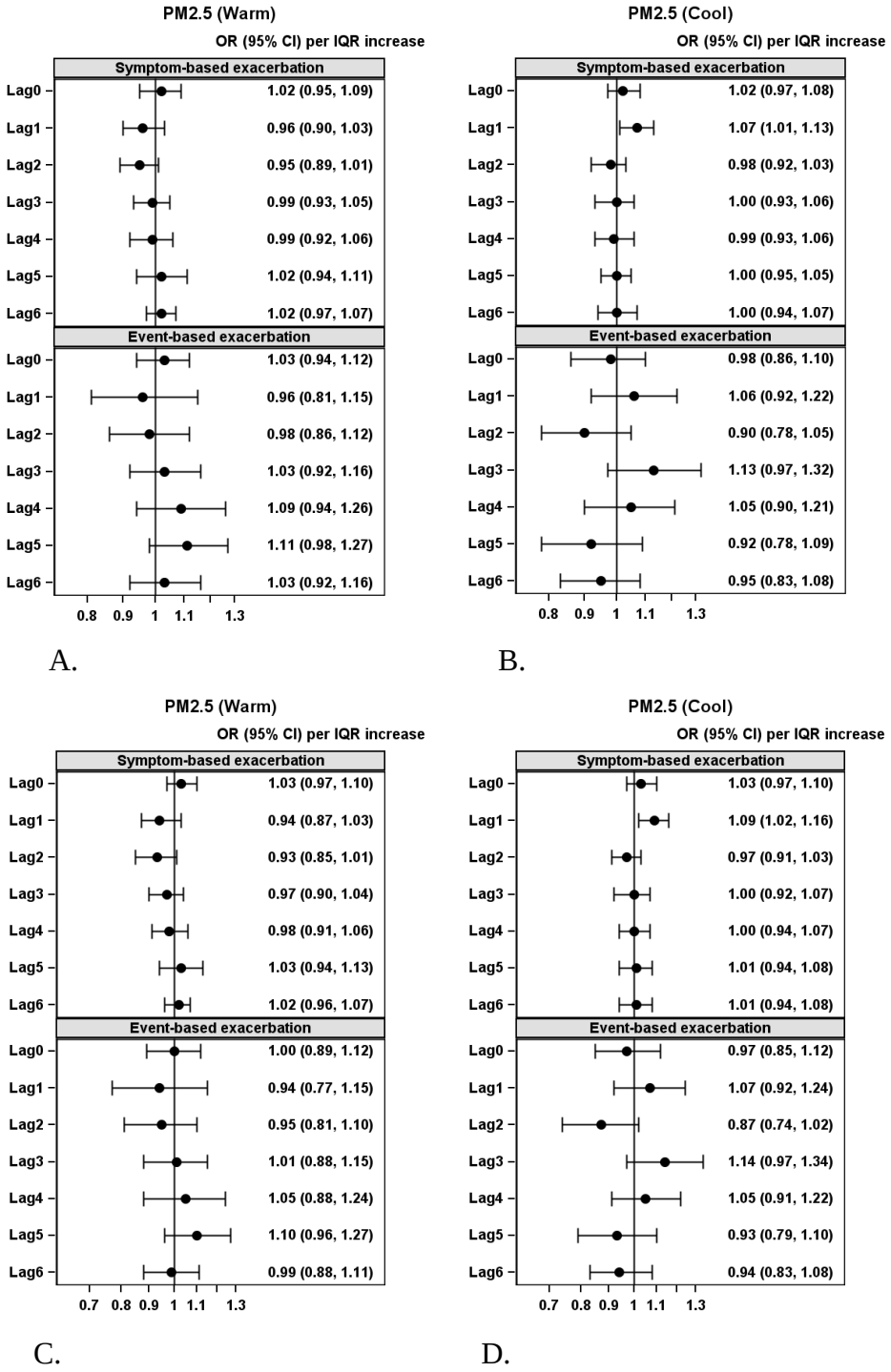

Figure 3. Single-pollutant generalized estimating equations (GEE) model for $PM_{2.5}$ and the odds of symptom-based and event-based exacerbation-like events. Unadjusted models (A. Warm, B. Cool) and adjusted models for mean temperature and relative humidity (C. Warm, D. Cool). Odds ratios (OR's) and 95% Confidence Intervals (95% CI's) are presented per interquartile range (IQR) increase in $PM_{2.5}$.

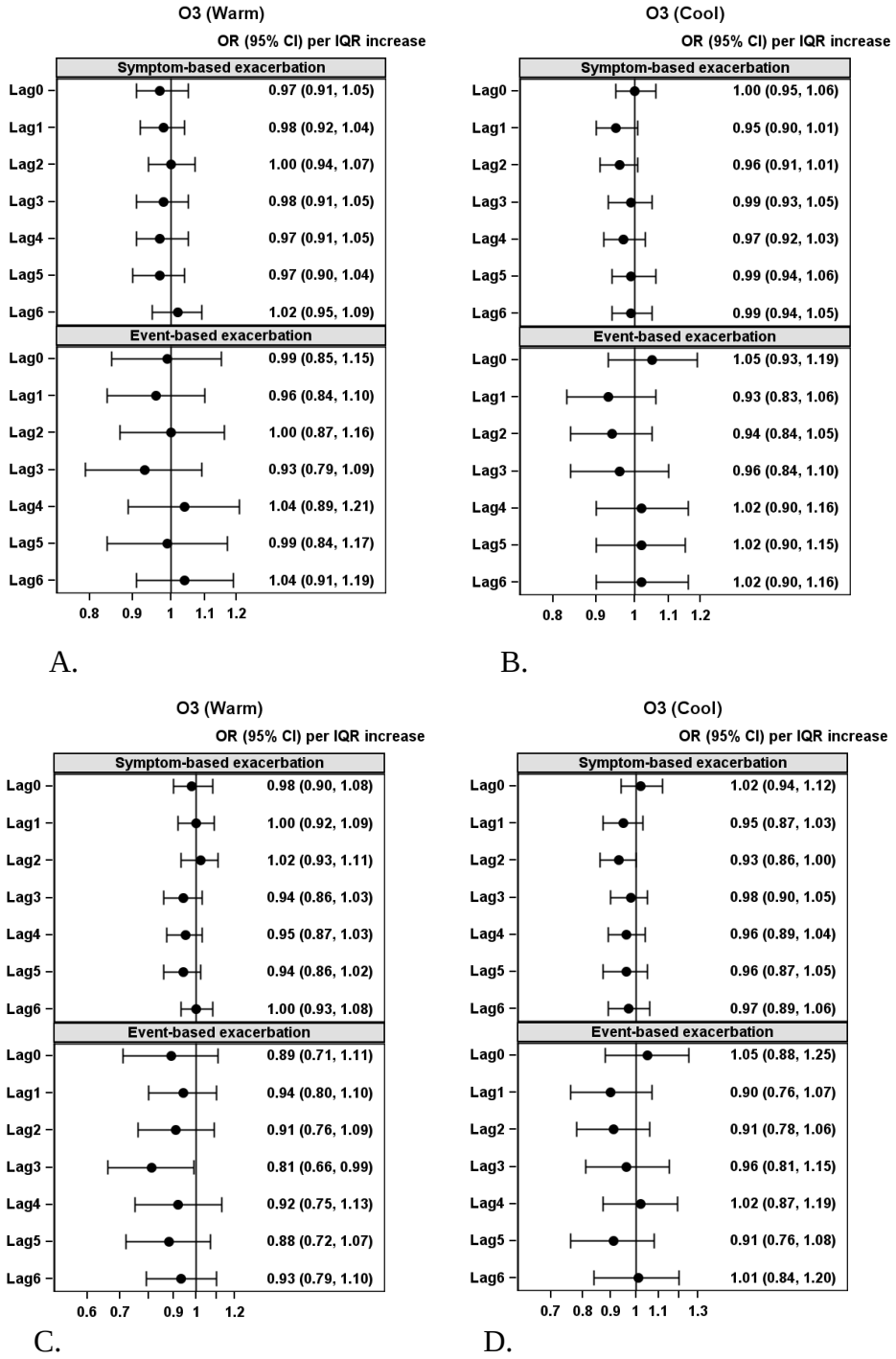

Figure 4. Single-pollutant generalized estimating equations (GEE) model for O_3 and the odds of symptom-based and event-based exacerbation-like events. Unadjusted models (A. Warm, B. Cool) and adjusted models for mean temperature and relative humidity (C. Warm, D. Cool). Odds ratios (OR's) and 95% Confidence Intervals (95% CI's) are presented per interquartile range (IQR) increase in O_3.

Two-Pollutant Models

Table 3 shows the correlation coefficients (R^2) between each of the three pollutants. Given the strong correlation between NO_2 and O_3 (R^2 = -0.61), two-pollutant models for only NO_2 and $PM_{2.5}$ and for $PM_{2.5}$ and O_3 are included.

Table 3. Correlation between air pollutants

Variable 1	Variable 2	Pearson Coefficient (R^2)
NO_2	$PM_{2.5}$	0.33
NO_2	O_3	**-0.61**
$PM_{2.5}$	O_3	-0.11

NO_2 = Nitrogen dioxide; $PM_{2.5}$ = particulate matter 2.5 microns or less in diameter; O_3 = ozone.

Two-pollutant generalized estimating equations (GEE) models (all adjusted for mean temperature and mean relative humidity) for each pre-specified lag period (from Day 0 to Day -6) are presented in **Figure 5** (NO_2 and $PM_{2.5}$) and **Figure 6** ($PM_{2.5}$ and O_3). All data are dichotomized by Season (Warm and Cool), with symptom-based and event-based exacerbation-like events also reported separately. All data are presented per interquartile range increase for each air pollutant for each Season.

For NO_2 and $PM_{2.5}$, **Figure 5** demonstrates that following adjustment for $PM_{2.5}$ in the Warm Season, every 7.3 ppb increase in exposure to ambient NO_2 on Lag Day -3 was associated with an increased odds of symptom-based exacerbation-like events (OR 1.10 [1.02, 1.19]), and with event-based exacerbation-like events (OR 1.14 [0.98, 1.34]) which did not reach statistical significance. Following adjustment for $PM_{2.5}$ in the Cool Season, no association and no consistent trend was observed for exposure to ambient NO_2 and the odds of symptom-based or event-based exacerbation-like events.

Following adjustment for NO_2 in the Warm Season, every 4.47 $\mu g/m^3$ increase in exposure to ambient $PM_{2.5}$ on Lag Day -2 was associated with a *decreased* odds of symptom-based exacerbation-like events (OR 0.91 [0.83, 0.99]).

Following adjustment for NO_2 in the Cool Season, every 4.85 $\mu g/m^3$ increase in exposure to

ambient $PM_{2.5}$ on Lag Day -1 was associated with an increased risk of symptom-based exacerbation-like events (OR 1.09 [1.02, 1.17]).

For $PM_{2.5}$ and O_3, **Figure 6** demonstrates that following adjustment for O_3 in the Warm Season, no association and no consistent trend was observed for exposure to ambient $PM_{2.5}$ and the odds of symptom-based or event-based exacerbation-like events.

Following adjustment for O_3 in the Cool Season, every 4.85 $\mu g/m^3$ increase in exposure to ambient $PM_{2.5}$ on Lag Day -1 was associated with an increased odds of symptom-based exacerbation-like events on Lag Day -1 (OR 1.09 [1.02, 1.17]), and with a *decreased* odds of event-based exacerbation-like events on Lag Day -2 (OR 0.82 [0.68, 0.98]).

Following adjustment for $PM_{2.5}$ in the Warm Season, every 11.77 ppb increase in exposure to ambient O_3 on Lag Day -3 was associated with a *decreased* odds of event-based exacerbation-like events (OR 0.81 [0.66, 0.99]).

Following adjustment for $PM_{2.5}$ in the Cool Season, every 14.33 ppb increase in exposure to ambient O_3 on Lag Day -2 was associated with a *decreased* odds of symptom-based exacerbation-like events (OR 0.90 [0.83, 0.98]), and with a *decreased* odds of event-based exacerbation-like events (OR 0.86 [0.71, 1.03]) which did not reach statistical significance.

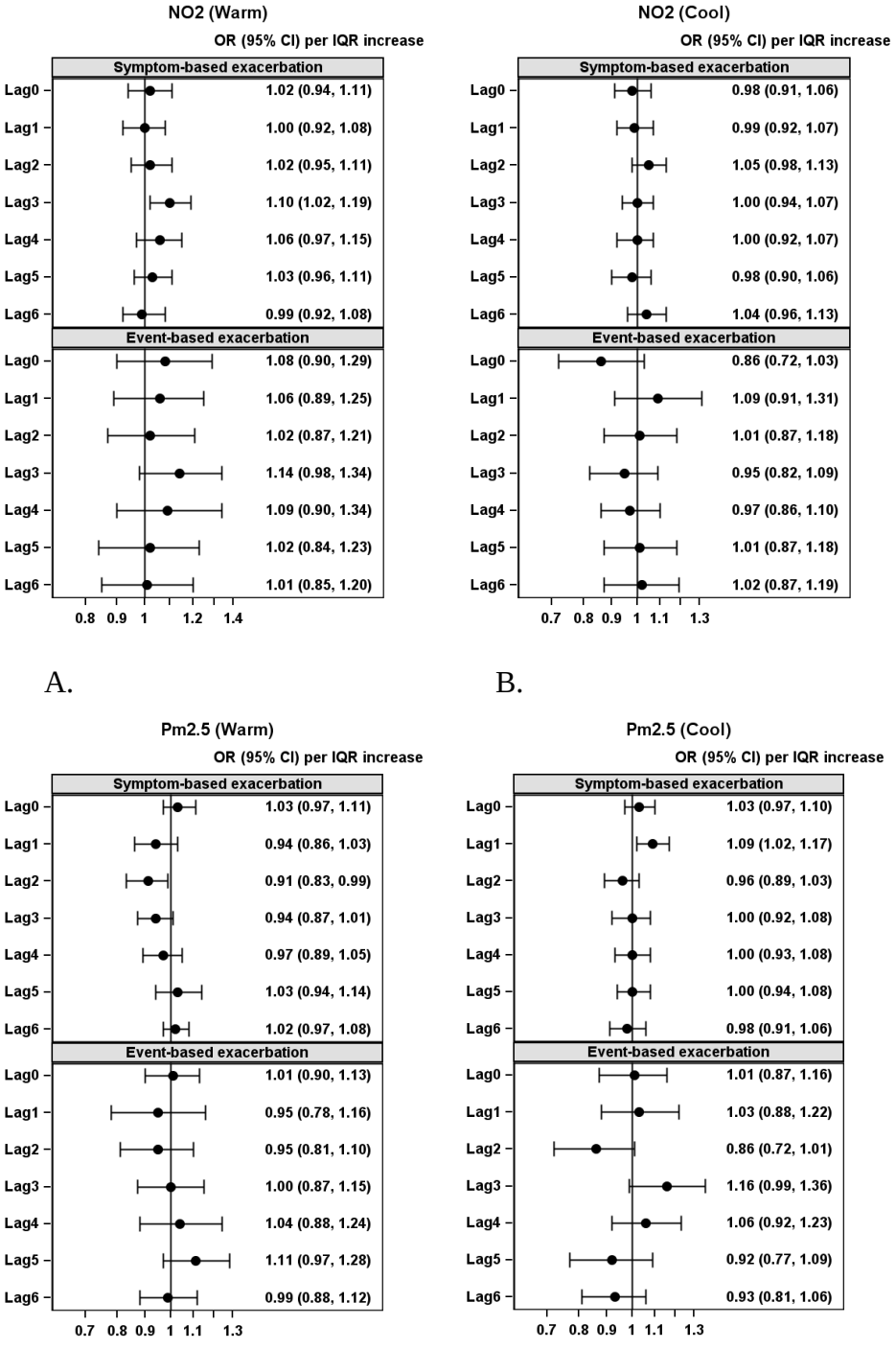

Figure 5. Two-pollutant generalized estimating equations (GEE) model for $PM_{2.5}$ and NO_2 and the odds of symptom-based and event-based exacerbation-like events. All models adjusted for mean temperature, mean relative humidity, and both pollutants (A. and C. Warm; B. and D. Cool). Odds ratios (OR's) and 95% Confidence Intervals (95% CI's) are presented per interquartile range (IQR) increase in NO_2, and per IQR increase in $PM_{2.5}$, respectively.

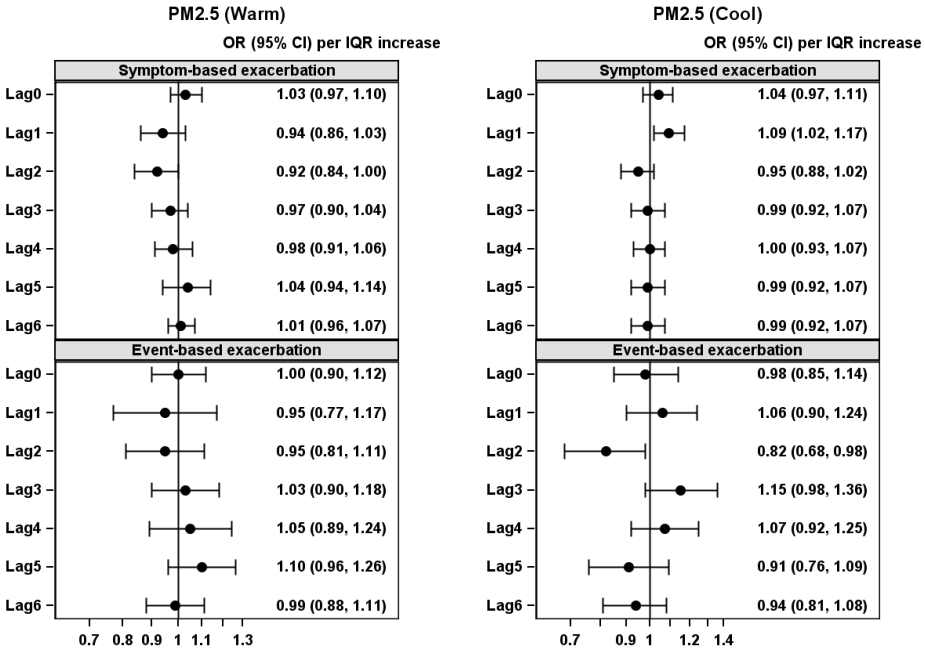

Figure 6. Two-pollutant generalized estimating equations (GEE) model for $PM_{2.5}$ and O_3 and the odds of symptom-based and event-based exacerbation-like events. All models adjusted for mean temperature, mean relative humidity, and both pollutants (A. and C. Warm; B. and D. Cool). Odds ratios (OR's) and 95% Confidence Intervals (95% CI's) are presented per interquartile

range (IQR) increase in $PM_{2.5}$, and per IQR increase in O_3, respectively.

The Effect of Sex

The effect of sex on the association between each air pollutant and exacerbation-like events are presented in **Table A3** (Warm Season) and **Table A4** (Cool Season)**.** All data are presented per interquartile range increase for each air pollutant for each Season.

NO_2:

In females in the Warm Season, every 7.3 ppb increase in exposure to ambient NO_2 on Lag Day -3 was associated with an increased odds of symptom-based (OR 1.14 [1.03, 1.28]) and event-based (OR 1.42 [1.09, 1.85]) exacerbation-like events. Similarly, in females in the Warm Season, every 7.3 ppb increase in exposure to ambient NO_2 on Lag Day -4 was associated with an increased odds of symptom-based (OR 1.11 [0.99, 1.25]) and event-based (OR 1.25 [0.94, 1.66]) which did not reach statistical significance. Conversely, in males in the Warm Season, no trend and no association was observed between exposure to ambient NO_2 and the odds of symptom-based and event-based exacerbation-like events.

In females and in males in the Cool Season, no trend and no association was observed between exposure to ambient NO_2 and the odds of symptom-based and event-based exacerbation-like events.

$PM_{2.5}$:

In females in the Warm Season, every 4.47 $\mu g/m^3$ increase in exposure to ambient $PM_{2.5}$ was associated with an increased odds of symptom-based exacerbation-like events on Lag Day 0 (OR 1.07 [1.00, 1.14]) and on Lag Day -5 (OR 1.12 [1.00, 1.26]) which did not reach statistical significance. In females in the Warm Season, every 4.47 $\mu g/m^3$ increase in exposure to ambient $PM_{2.5}$ was associated with an increased odds of event-based exacerbation-like events on Lag Day 0 (OR 1.06 [0.97, 1.16]) which did not reach statistical significance, and on Lag Day -5 (OR 1.23 [1.05, 1.43]). Conversely, in males in the Warm Season, every 4.47 $\mu g/m^3$ increase in exposure to ambient $PM_{2.5}$ was associated with a *decreased* odds of symptom-based exacerbation-like events on Lag Days -1 (OR 0.88 [0.79, 0.98]), -2 (OR 0.89 [0.80, 1.00]) and -3 (OR 0.89 [0.82, 0.97]). In females in the Cool Season, every 4.85 $\mu g/m^3$ increase in exposure to ambient $PM_{2.5}$ was associated with an increased odds of symptom-based exacerbation-like events on Lag Day -1 (OR 1.11 [1.02, 1.21]). Conversely, in males in the Cool Season, every 4.85 $\mu g/m^3$ increase in

exposure to ambient $PM_{2.5}$ was associated with a *decreased* odds of event-based exacerbation-like events on Lag Day -6 (OR 0.74 [0.60, 0.92]).

O_3:

In females in the Warm Season, every 11.77 ppb increase in exposure to ambient O_3 was associated with a *decreased* odds of symptom-based exacerbation-like events on Lag Day -5 (OR 0.89 [0.79, 1.00]) and with a *decreased* odds of event-based exacerbation-like events on Lag Day -1 (OR 0.80 [0.64, 1.00]). In males in the Warm Season, every 11.77 ppb increase in exposure to ambient O_3 was associated with a *decreased* odds of event-based exacerbation-like events on Lag Day -5 (OR 0.73 [0.52, 1.02]) which did not reach statistical significance.

In females in the Cool Season, no trend and no association was observed with every 14.33 ppb in exposure to ambient O_3 on the odds of symptom-based and event-based exacerbation-like events. In males in the Cool Season, every 14.33 ppb increase in exposure to ambient O_3 was associated with a *decreased* odds of symptom-based exacerbation-like events on Lag Day -5 (OR 0.77 [0.60, 1.00]) which did not reach statistical significance.

The Effect of the Severity of Chronic Obstructive Pulmonary Disease

The effect of severity of COPD (by *Global Initiative for Chronic Obstructive Lung Disease* spirometry criteria: GOLD1 vs. GOLD2+) on the association between each air pollutant and exacerbation-like events are presented in **Table A5** (Warm Season) and **Table A6** (Cool Season)**.** All data are presented per interquartile range increase for each air pollutant for each Season.

NO_2:

In GOLD1 participants in the Warm Season, every 7.3 ppb increase in exposure to ambient NO_2 on Lag Day -3 was associated with an increased odds of symptom-based (OR 1.14 [1.01, 1.30]) and event-based (OR 1.35 [1.07, 1.70]) exacerbation-like events. Conversely, in GOLD2+ participants in the Warm Season, no trend and no association was observed for exposure to ambient NO_2 and the odds of symptom-based and event-based exacerbation-like events.

In GOLD1 participants in the Cool Season, every 10.27 ppb increase in exposure to ambient NO_2 was associated with an increased odds of symptom-based exacerbation-like events on Lag Days 0 (OR 1.08 [1.03, 1.14]), -2 (OR 1.07 [1.00, 1.14]) -3 (OR 1.09 [1.04, 1.15]), -4 (OR 1.09 [1.04,

1.14]), and -6 (OR 1.07 [1.02, 1.12]); and on Lag Days -1 (OR 1.12 [1.00, 1.26]) and -5 (OR 1.06 [0.97, 1.16]) which did not reach statistical significance. In GOLD1 participants in the Cool Season, every 10.27 ppb increase in exposure to ambient NO_2 was associated with an increased odds of event-based exacerbations on Lag Day -1 (OR 1.30 [1.02, 1.65]) and on Lag Day -3 (OR 1.20 [0.98, 1.45]) which did not reach statistical significance. Conversely, in GOLD2+ participants, every 10.27 ppb increase in exposure to ambient NO_2 was associated with a *decreased* odds of event-based exacerbation-like events on Lag Day 0 (OR 0.77 [0.59, 1.01]) which did not reach statistical significance.

$PM_{2.5}$:

In GOLD1 participants in the Warm Season, every 4.47 $\mu g/m^3$ increase in exposure to ambient $PM_{2.5}$ was associated with an increased odds of symptom-based exacerbation-like events on Lag Days 0 (OR 1.06 [0.97, 1.15]), -5 (OR 1.12 [0.99, 1.26]) and -6 (OR 1.06 [1.00, 1.14]) which did not reach statistical significance. In GOLD1 participants in the Warm Season, every 4.47 $\mu g/m^3$ increase in exposure to ambient $PM_{2.5}$ was associated with an increased odds of event-based exacerbation-like events on Lag Days 0 (OR 1.41 [0.99, 2.02]) and -1 (OR 1.41 [1.00, 1.98]) which did not reach statistical significance, and on Lag Day -5 (OR 1.25 [1.05, 1.49]). Conversely, in GOLD2+ participants in the Warm Season, every 4.47 $\mu g/m^3$ increase in exposure to ambient $PM_{2.5}$ was associated with a *decreased* odds of symptom-based exacerbation-like events on Lag Day -2 (OR 0.88 [0.77, 0.99]) and of event-based exacerbation-like events on Lag Day -1 (OR 0.75 [0.59, 0.96]).

In GOLD1 participants in the Cool Season, every 4.85 $\mu g/m^3$ increase in exposure to ambient $PM_{2.5}$ was associated with an increased odds of symptom-based exacerbation-like events on Lag Day -1 (OR 1.11 [1.00, 1.24]) and of event-based exacerbation-like events on Lag Day -3 (OR 1.36 [1.10, 1.69]). In GOLD2+ participants in the Cool Season, every 4.85 $\mu g/m^3$ increase in exposure to ambient $PM_{2.5}$ was associated with an increased odds of symptom-based exacerbation-like events on Lag Day -1 (OR 1.07 [0.99, 1.16]) and with a *decreased* odds of event-based exacerbation-like events on Lag Day -2 (OR 0.84 [0.70, 1.00]) which did not reach statistical significance.

O_3:

In both GOLD1 and GOLD2+ participants in the Warm Season, no trend and no association was observed with every 11.77 ppb increase in exposure to ambient O_3 on the odds of symptom-

based and event-based exacerbation-like events.

In GOLD1 participants in the Cool Season, every 14.33 ppb increase in exposure to ambient O_3 was associated with a decreased odds of symptom-based exacerbation-like events on Lag Days 0 (OR 0.91 [0.85, 0.98]), -3 (OR 0.92 [0.85, 1.00]), -4 (OR 0.89 [0.82, 0.98]), -5 (OR 0.83 [0.73, 0.94]), and -6 (OR 0.90 [0.84, 0.96]), and on Lag Days -1 (OR 0.93 [0.81, 1.05]) and -2 (OR 0.95 [0.87, 1.03]) which did not reach statistical significance. In GOLD1 participants in the Cool Season, every 14.33 ppb increase in exposure to ambient O_3 was associated with a decreased odds of event-based exacerbation-like events on Lag Day -5 (OR 0.78 [0.60, 1.01]) which did not reach statistical significance. In GOLD2+ participants in the Cool Season, no trend and no association was observed with every 14.33 ppb increase in exposure to ambient O_3 on the odds of symptom-based and event-based exacerbation-like events.

Sensitivity Analyses on the Effect of Including All Exacerbation-Like Events Regardless of Recall Period

In the sensitivity analyses the exclusion criterion of recall period duration from the time of the exacerbation-like event was removed and all primary analyses were then repeated. A total of 1,646 symptom-based exacerbation-like events and a total of 993 event-based exacerbation-like events were included in the sensitivity analyses. Sensitivity analyses on all unadjusted models from the primary analysis are presented in **Table A7**, and sensitivity analyses on all adjusted models from the primary analysis are presented in **Table A8**. All data are presented per interquartile range increase for each air pollutant for each Season.

In the Warm Season, a 7.3 ppb increase in exposure to ambient NO_2 on Lag Day -3 was associated with an increased odds of symptom-based exacerbation-like events in both the unadjusted (OR 1.09 [1.02, 1.17]) and the adjusted (OR 1.11 [1.04, 1.19]) models. In the Cool Season, no trend and no association was observed with every 10.27 ppb increase in exposure to ambient NO_2 in the unadjusted and adjusted models.

In the Warm Season, every 4.47 $\mu g/m^3$ increase in exposure to ambient $PM_{2.5}$ on Lag Day -2 was associated with a *decreased* odds of symptom-based exacerbation-like events in both the unadjusted (OR 0.93 [0.88, 1.00]) and adjusted (OR 0.92 [0.84, 1.00]) models. In the Cool Season, every 4.85 $\mu g/m^3$ increase in exposure to ambient $PM_{2.5}$ on Lag Day -1 was associated with an increased odds of symptom-based exacerbation-like events in both the unadjusted (OR

1.06 [1.01, 1.12]) and adjusted (OR 1.08 [1.02, 1.14]) models. In the Cool Season, every 4.85 $\mu g/m^3$ increase in exposure to ambient $PM_{2.5}$ on Lag Day -2 was associated with a *decreased* odds of event-based exacerbation-like events for both unadjusted (OR 0.86 [0.75, 0.98]) and adjusted (OR 0.82 [0.72, 0.95]) models.

In the Warm Season in the unadjusted model, no trend and no association was observed with every 11.77 ppb increase in exposure to ambient O_3 on the odds of symptom-based and event-based exacerbation-like events. In the Warm Season in the adjusted model, every 11.77 ppb increase in exposure to ambient O_3 on Lag Day -5 was associated with a *decreased* odds of symptom-based exacerbation-like events (OR 0.92 [0.85, 0.99]). In the Cool Season, every 14.33 ppb increase in exposure to ambient O_3 on Lag Day -2 was associated with a *decreased* odds of symptom-based exacerbation-like events in both the unadjusted (OR 0.95 [0.90, 1.00]) and adjusted (OR 0.91 [0.84, 0.99]) models.

Chapter 5: Discussion

Summary of Findings

The major findings of the present study are that exposure to ambient nitrogen dioxide (NO_2) and to fine particulate matter ($PM_{2.5}$) was associated with an increased odds of exacerbation-like events in a Canadian multi-site cohort of participants with mild to moderate COPD. Regarding specific season and lag period, these associations were observed for NO_2 on the third day prior to the day of the exacerbation-like event in the Warm Season, and for $PM_{2.5}$ on the day prior to the day of the exacerbation-like event in the Cool Season. This specific pattern for NO_2 and for $PM_{2.5}$ was observed consistently across primary analyses including unadjusted and adjusted models, across secondary analyses including two-pollutant, sex, and disease severity models, and across sensitivity analyses.

Secondary analyses revealed that there are important sex-specific differences, and there may also be disease severity-specific differences, in the association between air pollutant exposure and exacerbation-like events: the overall pattern observed for NO_2 and $PM_{2.5}$ described above was observed specifically in females but not in males, and was observed specifically in patients with mild (*Global Initiative for Chronic Obstructive Lung Disease* GOLD1) COPD but not in patients with moderate (GOLD2) COPD. The limited sample size and the underrepresentation of individuals with GOLD3 (n=31) and GOLD4 (n=1) did not allow for this relationship to be explored further in more advanced disease.

Seemingly paradoxically, relative increases in O_3 concentrations were associated with a *decreased* odds of exacerbation-like events across the different primary, secondary and sensitivity analyses, with patterns that varied in regards to lag period and Season. Though not observed in the primary analysis (neither in the unadjusted nor in the adjusted models), this seemingly paradoxical negative association was also observed in some secondary and sensitivity analyses (particularly in *males* and particularly in participants with *GOLD2+* COPD) for $PM_{2.5}$ as well.

Study Participants and Setting

Data from the present study was collected from participants of 9 cities across 6 provinces in Canada over a roughly 7.5-year period, and therefore constitutes a good representation of the Canadian population living with mild-to-moderate COPD. By extension, the air pollutant

concentrations and weather co-variates reported in the present study are also a good representation of the Canadian landscape.

Notably, 32.1% (at baseline) and 33.7% (by end-of-study) of the participants with COPD included in the present study were lifelong non-smokers (**Table 1**). Though this proportion of individuals with COPD that are lifelong non-smokers is seemingly high, this has previously been reported within the CanCOLD cohort[14] and in COPD populations around the world[16]. CanCOLD is unique in that the disease status of every participant is confirmed by spirometry and therefore this high proportion of never-smokers with fixed airflow obstruction is likely more accurate compared with prior estimates from reports in which spirometry was not performed. One possible explanation for this finding is that there is also a high percentage of physician-diagnosed asthma (41.6% at baseline and at end-of-study) in the present CanCOLD-derived study population, in which case airway remodeling (i.e. transitioning from reversible airflow obstruction to irreversible airflow obstruction over years/decades in the asthmatics in this older participant population, with a mean age of 69.8-69.9 years) is possible. Conversely, and similar to the notion that non-infectious etiologies (such as air pollution) may be important precipitants of acute exacerbations of COPD, it is possible that long-term non-cigarette inhaled noxious exposures such as air pollution over many years may play a larger role in the pathogenesis of COPD than has been previously attributed, though this was not the focus of the present study.

The air pollutant concentrations observed in this study are notably lower in comparison to prior descriptions of ambient air pollutant concentrations in the literature. For example, the largest systematic review and meta-analysis published to date, conducted mostly in Asian populations, reported overall mean (and standard deviation) 24-hour average exposure levels of 64.56 ± 20.32 $\mu g/m^3$ (34.33 ± 10.81 ppb) for NO_2; 14.84 ± 8.05 $\mu g/m^3$ for $PM_{2.5}$; and 54.90 ± 22.87 $\mu g/m^3$ (27.98 ± 11.66 ppb) for O_3[129] – compared with mean 24-hour average exposure levels during the Warm and Cool Seasons (respectively) of 9.51 ± 4.9 and 13.9 ± 6.82 ppb (NO_2), 6.78 ± 5.01 and 7.01 ± 4.67 $\mu g/m^3$ ($PM_{2.5}$) and 20.08 ± 8.99 and 19.64 ± 9.85 ppb (O_3) in the present study. On the international stage Canada is known to have lower annual ambient air pollutant concentrations than in most other countries[106], however importantly the maximum values observed in the present study (which were sampled around the time of exacerbation-like events) do approach or exceed the Canadian 2020 annual air pollution concentration upper limit standards[105]. These results highlight that even patient populations living in countries with

relatively 'cleaner' air may be susceptible to acute and transient/episodic relative increases in air pollutant concentrations. By extension, these results also support increasing actions in the scientific community to further intensify international air pollution regulations and restrictions[112].

NO_2, $PM_{2.5}$ and O_3 Exposure and Odds of Exacerbation-Like Events

In the present case-crossover study, NO_2 and to $PM_{2.5}$ exposure was associated with an increased odds of exacerbation-like events. NO_2 exposure was associated with an increased odds of exacerbation-like events *three days prior* to the event in the *Warm* Season rather than in the Cool Season in a consistent manner. It is possible that this may relate to less time spent outdoors during the Cool Season than during the Warm Season in the Canadian climate, though this is only speculative. Nitrogen dioxide is formed largely from the incomplete combustion of nitrogen-containing chemicals and fossil fuels. Despite the fact that ambient NO_2 concentrations can tend to be higher in the Cool months than in the Warm months, which was observed in this and other Canadian studies[161], prior studies have also demonstrated positive associations between NO_2 exposure and acute respiratory events in patients with COPD specifically in the *warm* months and not in the cool months. Lin *et al.*[147] performed a case-crossover study in Taiwan in which all data were similarly dichotomized into "cooling down" and "warming up" seasons. Rather than lag days, week-long sampling averages were used. During the "warming up" season, an association between NO_2 and O_3 (but not $PM_{2.5}$ or PM_{10}) and hospitalizations for acute exacerbations of COPD was observed. Also similar to the present study, a positive association between PM_{10} (but not NO_2 or O_3) and hospitalization for acute exacerbation of COPD was observed during the "cooling down" season of that study. Unlike the present study, no associations between $PM_{2.5}$ and hospitalization for acute exacerbation of COPD was observed in either season in that study. The lag effect and positive association between NO_2 exposure and acute respiratory events in participants with COPD have been well-described in previous time series and case-crossover studies in both developing and developed countries,[117, 129, 142, 150, 170]. Therefore, the results of the present study further support and confirm this positive association. In the present study, $PM_{2.5}$ exposure was associated with an increased odds of exacerbation-like events *one day prior* to the event in the *Cool* Season rather than in the Warm Season in a

consistent manner. Because both fine and coarse particulate matter are a complex mixture of solid particles and liquid droplets suspended in air, there are known seasonal, geographic and temporal variations in its composition. Hand *et al.* assessed the composition of fine particulate matter ($PM_{2.5}$) in different seasons across 176 urban sites and 168 rural sites in the United States[171]. Notably, the amount of ammonium nitrate levels comprising $PM_{2.5}$ were found to peak specifically in the wintertime. These differences in $PM_{2.5}$ composition between Cool and Warm Seasons may have offset any influence of seasonal differences in the amount of time spent outdoors in the present study. While this seasonal pattern in $PM_{2.5}$ composition was similar between urban and rural sites, urban sites demonstrated higher concentrations of both $PM_{2.5}$ and of ammonium nitrate-containing levels within $PM_{2.5}$ than was observed in rural sites. A separate study analyzing $PM_{2.5}$ composition from major Canadian urban cities demonstrated that a sizeable proportion of the prevalent $PM_{2.5}$ concentration in these cities originated from the United States[116]. This trans-boundary reality supports the likelihood that Canadian urban seasonal patterns in $PM_{2.5}$ concentration and distribution are very similar to those reported by Hand *et al.* Since participants were recruited from large Canadian urban cities, the phenomenon of an increased odds of exacerbation-like events following $PM_{2.5}$ exposure specifically in the Cool Season may relate to these described season-specific and urban-specific characteristics of fine particulate matter composition and concentration.

Similar to the present study, Devries *et al.*[117] performed a case-crossover study in a well-characterized cohort of participants with COPD confirmed by spirometry; similarly used a sensitive outcome (collected via COPD nurse telephone visits and defined by a worsening of symptoms requiring oral corticosteroids or antibiotics); and similarly performed the study in a North American setting with air pollutant concentrations below recommended ambient air quality standards (using area-level averages from fixed site monitors). The study was conducted over a 15-month period and employed a unidirectional, non-time stratified (1-3 random control periods during 'healthy weeks') sampling strategy. Rather than lag days, multi-day sampling averages were used in that study. Temperature and relative humidity were collected (relative humidity was ultimately not used in modeling), and seasonality was factored into the analysis. Single-pollutant and two-pollutant models were performed. Similar to the present study, Devries *et al.* found a positive association between NO_2 and the odds of acute exacerbations of COPD in the single-pollutant model (which became statistically non-significant following adjustment for

temperature), and also found a positive association between NO_2 and the odds of COPD exacerbations in the two-pollutant model following adjustment for $PM_{2.5}$. The effects of O_3 exposure were not investigated. Surprisingly, a paradoxical association of *reduced* odds of COPD exacerbation was found for $PM_{2.5}$ in the single-pollutant model (both unadjusted and adjusted for temperature) in that study. This surprising paradoxical association was also observed in the present study in certain secondary and sensitivity models but not in the primary analyses, and was also demonstrated in the outpatient East London cohort study by Peacock *et al*.[148] and in an inconsistent manner in the time series study by To *et al*. (where the negative association was observed specifically for outpatient visits and hospitalizations)[150]. Devries *et al*.[117] attributed the paradoxical associations between $PM_{2.5}$ and COPD exacerbations to the high variability of $PM_{2.5}$ compositions over time, however that is likely insufficient to fully explain these associations.
In the present study, 24-hour Lag Days were used to assess for delayed effects of the pollutants, and exposure to ambient O_3 was associated with a *decreased* odds of exacerbation-like events across most models in a consistent fashion, including in the adjusted model of the primary analysis. An initial interpretation of this result might be that relative increases in O_3 concentration have a *protective* effect on the odds of experiencing an exacerbation-like event. Similar to the present study, in the systematic review and meta-analysis by Li *et al.*[129], 24-hour period lag days of 0 to -6 were assessed and overall positive associations for each of NO_2, $PM_{2.5}$ and O_3 and acute exacerbations of COPD were reported. Associations were noted to be strongest on Lag Day 0 for gaseous pollutants, and strongest on Lag Day -3 for particulate pollutants. Notably, that meta-analysis reported that on Lag Day 0, exposure to O_3 was associated with a significantly *reduced* odds of acute exacerbations of COPD while exposure to NO_2 was associated with a significantly *increased* odds of acute exacerbations of COPD. This same paradoxical association was observed between short-term increases in O_3 concentration and all 'COPD visit' types in the Canadian time series study performed by To *et al*.[150] Because the association between O_3 concentration and other acute health events such as myocardial infarction has previously been documented to uniquely differ from the associations with each of the other main pollutants studied[172], it is possible that O_3 may simply be a 'bystander' as one of many components of a complex mixture of gaseous and particulate pollutants. Notably, there is an 'inverse relationship' in the literature between O_3 and the other air pollutants. This was demonstrated convincingly in the Canadian setting by the multi-site time series study conducted

by Stieb *et al*.[143]. NO_2 and O_3 in particular appear to have an inverse relationship which may stem from the known typical geographical distribution of these pollutants. While NO_2 is formed by incomplete combustion of nitrogen-containing chemicals and is largely found at or near major roadways, O_3 is formed in the presence of sunlight following chemical reaction of oxides of nitrogen and is largely found in nearby suburbs[173]. Thus, the seemingly paradoxical 'protective' effects of O_3 concentration on acute respiratory events reported here and previously in the literature[129, 148, 149] may partially be explained by inverse geographical and temporal relationships between NO_2 and O_3, and by the previously reported possibility of O_3 as a 'bystander' pollutant amongst the many other harmful air pollutants.

In the present study, similar to prior reports,[149] there was an effect of sex on the observed associations between air pollutants and exacerbation-like events. Specifically, the principal study findings of a positive association between NO_2 (Warm Season Lag Day -3 in) and $PM_{2.5}$ (Cool Season Lag Day -1) and exacerbation-like events were observed only in female participants and were not observed in male participants. In fact, the seemingly *paradoxical* associations (*negative* associations between $PM_{2.5}$ and exacerbation-like events described above) were observed only in males and not in females. While both particulate ($PM_{2.5}$) and gaseous (NO_2) air pollutants were associated with an increased odds of exacerbation-like events in females in the present study, in the case-crossover study performed by Szyszkowicz *et al.* associations in females were mostly observed for gaseous pollutants (O_3 and SO_2)[149]. Since the conventional mechanism of action of air pollutants in the precipitation of acute respiratory events in patients with COPD is thought to be due to the pro-inflammatory and possibly immune-modulated effects of air pollutants on the airways[131], and since there are sex-specific differences in T-cell expression patterns and pro-inflammatory cytokine release between men and women[44], biological and potentially hormonally-mediated immune responses may help explain the important sex-specific findings of the present study.

Interestingly, the study findings observed in the primary analyses and observed specifically in females were also observed specifically in participants with mild (*Global Initiative for Chronic Obstructive Lung Disease* GOLD1) COPD but not in participants with moderate-severe (GOLD2+) COPD. It is possible that the individual-level behaviour of exposure avoidance of known respiratory triggers (for example, the tendency to stay indoors on days characterized by particularly high concentrations of ambient air pollution) may be a disease severity-specific

phenomenon occurring disproportionately in participants with moderate, severe, and very severe forms of disease than in participants with mild COPD. Such heterogeneity in exposure between GOLD1 and GOLD2+ subgroups might help explain why the main study findings were observed in GOLD1 and not in GOLD2+ participants. Unfortunately, the GOLD2+ subgroup consisted mainly of moderate ('GOLD2') disease, with under-/non-representation of severe ('GOLD3') and very severe ('GOLD4') disease, which limits the ability to further test this hypothesis.

The sex-specific and disease severity-specific findings are interesting since multiple reports have described the phenomenon whereby women are at a higher risk of developing *early-onset* COPD than in men[49], and women with *mild* COPD tend to exhibit more severe dyspnea scores than men with mild COPD[48]. Therefore, an interaction between female sex and mild disease in the susceptibility of acute air pollutant exposure is possible in patients with COPD. Furthermore, there was a remarkable positive association between NO_2 exposure and the odds of symptom-based exacerbation-like events in the Cool Season specifically in patients with GOLD1 COPD which spanned across Lag Days 0 through -6. These notable associations spanning throughout the entire lag period with NO_2 in the Cool Season were not observed in any of the other primary or secondary analyses and indicate that the subgroup of patients with mild COPD may be uniquely susceptible to NO_2 exposure in the cooler months for as-of-yet undetermined reasons.

Because this study was performed in a unique cohort of participants (with spirometry-confirmed disease, with milder disease forms than have been published previously), used a more sensitive outcome which includes the capturing of outpatient events (which may not have been captured in prior studies which utilized hospital-based codes), and was conducted in a relatively lower pollutant setting compared with studies performed in developing nations, it has allowed for the confirmation of interesting subgroup manifestations of the main study findings. These results will need to be externally validated in other studies on similar population-based cohorts.

Strengths

There are several unique strengths of the present study, including study design, study population, study setting, and choice of study outcome.

Regarding the ***study design***, the principal strength of the case-crossover study method is that all individual-level, non-time varying confounders are controlled for. This is accomplished by 'self-matching' such that covariates that are constant *within* individuals are controlled for over the sampling period[145].

Regarding the ***study population***, the CanCOLD cohort is a well-characterized group of participants. The majority of prior studies used international classification of disease codes and hospital administrative data to classify both disease status (i.e. 'COPD' vs. 'non-COPD' participants) and outcome (i.e. 'hospitalization for an acute exacerbation of COPD'), though other prior studies have successfully employed telephone-based[117] and diary card-based[148] methods of collecting outpatient exacerbation events in well-characterized COPD cohorts. CanCOLD participants have disease status (COPD/non-COPD) confirmed by spirometry and outcomes of interest (in this case, prospectively-collected exacerbation-like events) well-characterized and meticulously documented. As such, the risk of disease misclassification is minimized. Having a well-characterized cohort also allowed for more accurate secondary analyses (such as by severity of disease as confirmed by spirometry) to be explored in the present study.

Regarding the ***study setting***, the present study is a multi-city study with participants across several different Canadian provinces and is therefore a unique and representative sampling of the Canadian COPD population, particularly the mild-to-moderate COPD patient population. The positive associations observed between NO_2 and $PM_{2.5}$ and exacerbation-like events in the relatively 'low-pollutant' Canadian setting is an important finding not only for Canadians living with mild/moderate COPD, but also for mild/moderate COPD patient populations living in developed countries around the world.

Regarding the choice of the ***study outcome***, the 'exacerbation-like event' has been used effectively in a number of previously published studies to capture important acute respiratory events and characterize the respiratory burden in patients with COPD[101], in patients living with COPD which remains undiagnosed by a physician[80], in never-smokers living with COPD[14] and even in patients without COPD[102]. Symptom-based exacerbation-like events in particular, which do not necessitate any prescription of treatment or any healthcare contact including no clinic or emergency department visit or hospitalization, provide a unique, sensitive and clinically relevant[96, 99] outcome. The absence of treatment or healthcare contact that is characteristic of the symptom-based exacerbation-like event does not necessarily imply that these events are mild, or that they are without short- or long-term clinical consequence to the patient[81, 82]. Symptom-based exacerbation-like events are very likely to not be detected in studies were health administrative data or international classification of disease codes are used to determine the occurrence of the

respiratory outcome, and even within the present study which did not use health administrative data to determine outcome, the clear difference between the number of symptom-based (1,400) and event-based (841) exacerbation-like events captured over the study period supports this fact. There remains ongoing debate regarding what the most appropriate case definition for an acute exacerbation of COPD should actually be[174], which have ongoing implications in the clinical and research arenas alike. The use of exacerbation-like events as the outcome in this study specifically in the Canadian landscape and specifically in participants with predominantly mild-moderate disease is a study strength and has allowed for the estimation of the association between short-term air pollution and respiratory health, beyond what is possible using more severe case definitions for an acute exacerbation of COPD and/or administrative health data-derived outcomes.

Limitations

There are several important limitations of the present study, including potential unmeasured time-varying confounding factors, date-of-event collection limitations, recall bias, selection bias, sample size constraints, exposure measurement error and the large number of associations tested, and spectrum of disease severity.

Regarding ***unmeasured time-varying confounders***, while the case-crossover method does control for confounders that do not vary between the hazard period and the control periods for each participant, it does *not* control for any confounders which do differ on hazard period and control period days. These are referred to as time-varying confounders. In order to control for their confounding effects, these time-varying variables need to be i) measured, or appropriately estimated, and ii) included in analyses. For example, if a study participant did not usually adhere to taking their daily inhaler medications on most days (including on control days) but did opt to take inhaler medications on the hazard day (which by definition is around the time of the exacerbation-like event in the present study), and if this was not measured/adjusted for in the analysis, then these short-term 'variations' in inhaler adherence would confound the association under investigation such that the effect of air pollutant concentration on the odds of an exacerbation-like event would be underestimated. Other possible time-varying confounders include physical activity level or time spent outdoors, if these behaviours differed on hazard period and control period days. For example, if air pollutant concentrations were indeed higher on hazard days and if this led to respiratory trigger mitigation behaviours such as remaining

indoors longer during hazard days than during control days, this would lead to a reduced actual air pollutant exposure by participants in relation to the estimates measured by fixed monitoring stations. This would confound the association under investigation such that, once again, the effect of air pollutant concentration on the odds of an exacerbation-like event would be underestimated. Data on the potential time-varying confounders of daily medication adherence and daily time spent outdoors were not available within the scope of the study, and therefore this is a limitation. However, the study was able to control for confounding i) by non-time varying confounders (such as sex, age, disease severity, co-morbidities and smoking history) by the case-crossover method used; ii) by day of the week, season, and long-term trend through the use of a time-stratified control period sampling approach; and iii) by the important time-varying covariates of mean temperature and mean relative humidity (which can differ sizably on hazard period and control period days) in the adjusted models as part of the primary and secondary analyses.

Another important limitation of the present study is that there was no ability to confirm the ***date of onset*** of each acute exacerbation-like event. Though participants were instructed to record this information prospectively between telephone visits, inaccurate reporting of such dates could have serious consequence particularly when the case-crossover design is used since the date of onset defines both the hazard period date as well as the control period dates. This is therefore an important limitation of the present study. Even in large clinical trials there has been a great deal of uncertainty and heterogeneity regarding how to determine the precise date of onset of acute exacerbations of COPD[175]. For example, two patterns of acute exacerbations of COPD were described in an observational cohort study on 212 patients with COPD followed for nearly 3 years: a 'sudden onset' pattern (where the predefined threshold characterizing an acute exacerbation was crossed on the same day as the first onset of symptoms), and a 'gradual onset' pattern (where the predefined threshold characterizing an acute exacerbation was crossed only after roughly 4 days following symptom onset)[176]. Since the capacity of transient air pollutants to act as triggers in precipitating acute respiratory events is the focus of the present study and of all prior case-crossover and time series studies discussed, defining exact onset dates represents a significant and ongoing challenge which applies to even those studies which used health administrative data to record the precise date of the event. This illustrates an important and pervasive limitation on how to accurately define the correct date of onset of an acute

exacerbation, and represents a limitation not only of this study but moreover on the entire field of research on acute exacerbations of COPD.

As described above, the precise collection of event dates in the conduct of a case-crossover study is critical. Therefore, it was deemed to be of paramount importance to establish inclusion and exclusion criteria that would maximize precision in reporting the correct date of the event, even if doing so was at the expense of possibly creating a selection bias or of further compounding sample size constraints. Regarding ***recall bias***, it is highly likely that events recalled on a date which is further from the time of the telephone questionnaire is a possible source of error in the present study. Although telephone visits were performed every 3 months, over the roughly 7.5 years of follow-up of CanCOLD participant data used in the present study it was possible for participants to miss an occasional telephone visit (in which case the recall period between the event of interest and the telephone visit to report the event of interest could be 6 months or even greater). Though participants were instructed to record events prospectively as they occurred, such that the information provided during telephone visits would be as accurate as possible, the inclusion of dates recalled very remotely from the time of the event could reasonably affect the precision of the date of the event. To address and minimize the study limitation of recall bias, an exclusion criterion for all events used was to limit recall to 4 months or less between the date of the event and the date of reporting the event by telephone visit.

It is possible that the very action of implementing the recall period exclusion criterion (meant to minimize recall bias and improve precision of event dates) subsequently led to the *creation* of a ***selection bias*** (which could bias the associations being estimated). To address the possibility of selection bias, sensitivity analyses were performed in which the unadjusted and adjusted models of the primary analysis were repeated using all exacerbation-like events. Compared with a total of 1,400 symptom-based exacerbation-like events and a total of 841 event-based exacerbation-like events included in the primary and secondary analyses of the present study, a total of 1,646 symptom-based exacerbation-like events and a total of 993 event-based exacerbation-like events were included in the sensitivity analyses. Therefore, roughly 15% of all symptom-based and event-based exacerbation-like events were excluded from the primary and secondary analyses of the present study by the implementation of the exclusion criterion. While a paradoxical association (a *decreased* odds on Lag Day -2 of $PM_{2.5}$ exposure in the Warm Season with symptom-based exacerbation-like events and in the Cool Season with event-based exacerbation-

like events) was observed in the sensitivity analyses, reassuringly, the main pattern observed in the primary and secondary analyses of the study - a positive association between NO_2 and symptom-based exacerbation-like events in the Warm Season on Lag Day -3, and between $PM_{2.5}$ and symptom-based exacerbation-like events in the Cool Season on Lag Day -1 - were again observed in the unadjusted and adjusted models of the sensitivity analyses. The choice to implement the recall period selection criterion was a balance between the risk of recall bias versus the risk of selection bias and the risk of further compounding sample size constraints, and therefore this is an important limitation.

Because this was a case-crossover study conducted on a well-characterized cohort of participants with COPD, ***sample size constraints*** represent a study limitation. These constraints may have limited further subgroup analyses (for example, by 'severe' and 'very severe' disease severity) and were further compounded by the choice to implement the recall period exclusion criterion. The number of events in the present study are far fewer than what is observed in the time series literature which, as summarized nicely by the systematic review and meta-analysis by Li *et al.*, can include event counts which can reach into the hundreds of thousands at a population level[129]. By the end of the present study, a total of 1,400 symptom-based exacerbation-like events and a total of 841 event-based exacerbation-like events from 449 participants with COPD were included in the primary and secondary analyses. The use of spirometry not only at baseline but longitudinally over the study period allowed for the addition of events from 60 additional participants above and beyond those eligible at baseline since they were subsequently diagnosed with COPD and experienced an eligible exacerbation-like event following their diagnosis. This has allowed for a more accurate determination of disease status over the duration of this longitudinal study (thereby reducing misclassification errors) and as it relates to sample size constraints, has allowed for the appropriate inclusion and analysis of more eligible participants and events. Furthermore, the decision to employ a generalized estimating equation (GEE) methodology allowed for multiple events per participant to be collected over the study period (as demonstrated by **Figure A3**) which also allowed for the appropriate inclusion of more eligible events while minimizing violating the assumption of independent observations. By comparison, the important North American case-crossover study conducted by Devries *et al.* which similarly studied a well-characterized COPD cohort and similarly investigated exacerbations not necessarily requiring emergency department visit or hospitalization included 231 'exacerbation

periods' from 168 patients with COPD. The East London cohort study by Peacock *et al.* did not report the number of exacerbations that were collected in the article however since the study was performed on 94 participants with COPD (compared to 449 participants) over a median follow-up period of under 1.5 years (compared to a follow-up period of roughly 7.5 years), the sample size of that study was also likely much lower than that of the present study. Therefore, the total number of events captured and included in the present study is much smaller when compared to the time series literature, however it is either similar or larger when compared to similar published case-crossover studies.

Regarding ***exposure measurement error***, the present study assigned an area-level exposure (i.e. city-level air pollutant concentration estimate) to all participants living in a given city. This is an important limitation to acknowledge. This *exposure* measurement error is *non-differential* since there is an equal degree of bias between the measurements taken on hazard period days and the measurements taken on control period days[177]. The potential impact of non-differential measurement error in continuous exposure variables such as air pollutant concentration is that the estimate will be closer to the null than the true association, and that there will be an increase in the standard errors[177]. The present study uses the *National Air Pollution Surveillance program* database, the only database available which can provide short-term (hourly/daily) estimates necessary to assess the association between acute/transient changes in air pollutant concentration and exacerbation-like events, however these are reported from fixed-location monitoring stations scattered throughout each study city. The exposure measurement methodology used in the present study is in keeping with the methodology used in the published literature of air pollution case-crossover and time series studies, and therefore this is a limitation that is systematic in this field. Furthermore, ***a large number of associations*** were tested in the present study given that three different pollutants, two Seasons (Warm and Cool), and seven different lags (0 to -6 inclusive) were included. Though this approach is also in keeping with the methodology used in the published literature of air pollution case-crossover and time series studies, it is important to consider the large number of associations tested in the interpretation of the study results.

Lastly, regarding the ***spectrum of disease severity*** of the study population, the CanCOLD cohort is a non-clinical, population-based sample of participants. The severity of disease in the study population was limited mainly to mild and moderate COPD. This population sampling approach may have also skewed the selection and recruitment of individuals with lesser symptom burdens

to participate. ‘Severe’ and ‘very severe’ disease is under-represented or not represented in this cohort, which limited the capacity to further assess the association between air pollution exposure and exacerbation-like events across multiple levels of disease severity.

Summary and Conclusion

The occurrence of acute exacerbation-like events in COPD, a condition which is among the commonest chronic lung diseases in Canadian adults, is of immediate relevance to patients, clinicians, researchers, and health systems alike. Despite the relatively low levels of air pollutants in Canada, transient increases in ambient exposure to nitrogen dioxide (NO_2) and fine particulate matter ($PM_{2.5}$) appear to increase the likelihood of subsequent acute respiratory events. Many prior epidemiological studies on acute exacerbations of COPD and air pollutants used administrative health data and hospital visit data and studied this association primarily in patients with clinically diagnosed COPD with severe forms of disease. These studies may have missed clinically relevant milder events, and many others were limited to only one city or state/province rather than reporting on a national sampling. Much larger time series studies than the present study were performed at the population level and provided important insights into this association, and the present study provides additional information on this association through a separate study design and on a well-characterized cohort with disease status and severity documented by longitudinal spirometry. The unique features and strengths of the present study support the validity of the main findings: that ambient NO_2 concentrations in the Warm Season and ambient $PM_{2.5}$ concentrations in the Cool Season may precipitate acute respiratory events in the following 72 hours and on the following day, respectively, in patients living with mild/moderate COPD. Females with mild COPD represent a particularly vulnerable subgroup of the COPD patient population and may be a particularly high-risk group regarding the effects of transient ambient nitrogen dioxide and fine particulate matter exposure.

Furthermore, this study addresses important gaps in the literature and should play a supportive role in public health policy. At the international level, these findings support even more aggressive ambient air pollution regulatory policies, even in nations with levels which were below the conventional standards. In particular, adoption of more aggressive daily maximum air pollutant cutoffs may reduce the likelihood of developing acute respiratory events. Fortunately, this is being increasingly recognized as an important global intervention. This is evidenced by the ambitious lowering of acceptable 24-hour levels of NO_2 (from previously being undefined to

now being 25μg/m^3), $PM_{2.5}$ (from 25μg/m^3 to now being 15μg/m^3), and of other pollutants in the new World Health Organization Air Quality Guidelines released in September 2021[112] as a timely update to the 2005 recommendations[178]. At the national level, these findings support industry and urban planning policies and incentives to minimize specific sources of NO_2 and $PM_{2.5}$ production and circulation. Communication measures to at-risk subpopulations during relatively higher air pollutant concentration days could be adopted by local public health authorities and municipal governments. These could include air pollutant public broadcasting warnings and advisories when NO_2 and $PM_{2.5}$ concentrations are measured to be relatively higher than typical values, and can be personalized (ex. smartphone applications, 'apps', for individual high-risk patients to specifically alert them). At the local health systems-level, resource planning/allocation for urgent access care around the time of these high relatively air pollutant concentration days could similarly be arranged. For example, extra acute care resources may be allocated for the roughly 24- to 72-hour period following documented relative increases in NO_2 and $PM_{2.5}$ concentrations. Lastly, individual-level patient interventions for patients living with COPD on exposure avoidance can be pursued through self-management education strategies.

Given the increasingly serious realities of climate change and the recurrent problem of wildfires, further studies confirming and supporting the findings of the present study will be an important area of future research. The consequences of acute respiratory exacerbations in vulnerable individuals such as those living with COPD being provoked by transient increases in air pollutant concentrations goes well beyond the limited issue of acute health system burden; it impacts a considerably larger proportion of the outpatient population living with mild/moderate and even undiagnosed COPD. The effectiveness of public health implementations, as a result of this and of future studies, will be of increasingly important value in comprehensively tackling the growing climate and air pollution crisis and in implementing better and more targeted public health policies.

Chapter 6: References

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Appendix

Figure A1. CanCOLD telephone interview case report form

CASE REPORT FORM
(CRF)

PHONE INTERVIEW

English Questionnaire

Please note the following:

1. The following phone interview is done every 3-months. The upcoming dates will always be calculated from the date were the first interview was done.

2. Update CanCOLD Database and indicate whether the subject completed the Phone interview or not (if not indicate reasons.)

3. Scan and e-mail all your new available phone interview forms in PDF to the National Coordination Office (NCO) on the 15th and the 30th of each month (for monitoring and data entry).

Version 12DEC15

PHONE INTERVIEW

Subject: | | | | | | **Date** (dd-mmm-yyyy): | | | **Interview:** | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 | 57 | 60 |

Page 1 – GENERAL OVERVIEW
Mandatory page for all interviews

PLEASE HAVE ALL YOUR MEDICATIONS AND A CALENDAR, THIS WILL FACILITATE ANSWERING THE QUESTIONNAIRE

1. During the last 3 months (or since this questionnaire was last administered, on _____ _____ _____
read date to subject) have you smoked? dd mmm yyyy

No ○ Yes ○

2. In the last 3 months (or since this questionnaire was last administered) have you **experienced an episode with new or changes in any respiratory symptoms** (cough, phlegm, wheeze, breathlessness) that **became worse for at least 2 days**?

No ○ *(end of questionnaire)* Yes ○ → Complete section on **Page 2 - Respiratory Symptoms**

If yes:

2.1 How many episodes* did you experience that became worse for at least 2 days that were separated by at least 3 days? _____

2.2 Have you had any increases, additions or changes in medication related to these respiratory symptoms?

No ○ Yes ○ → Complete section on **Page 3 - Medication**

2.3 Have you felt as though your work has been affected by these respiratory symptoms?

I am retired ○ No ○ Yes ○ → Complete section on **Page 4 - Work**

2.4. Have you had any health care visits related to these respiratory symptoms?

No ○ Yes ○ → Complete section on **Page 5 - Health care visits** (including unplanned physician visits, emergency department use and hospitalization)

Notes to the coordinator:
- *If the answer to these 2.2, 2.3 and 2.4 is "No", then end the questionnaire.*
- *If subject experienced more than one episode of changes/new respiratory symptoms that lasted for at least 2 days and that are separated by at least 3 days, fill out a separate questionnaire for each episode.*

Completed by ID #:|_____|_____|_____|_____|

PHONE INTERVIEW

Subject: | | | | | | **Date** (dd-mmm-yyyy): | | | **Interview:** | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 | 57 | 60 |

Page 2 - RESPIRATORY SYMPTOMS
Repeat this page for each episode of new or changes in respiratory symptoms occurring in the last 3 months (or since this questionnaire was last administered)

1. In the last 3 months (or since this questionnaire was last administered) when did you experience an episode with **new or changes in any respiratory symptoms** that became worse for at least 2 days:

_____ _____ _____
dd mmm yyyy

For approximately how many days did you experience these symptoms? _____
(minimum 2 days)

2. Did any of the following respiratory symptoms change :

Indicate with an X new or changes in the following respiratory symptoms

Major respiratory symptoms

- ○ Worsening dyspnea (worsening difficulty breathing)
- ○ Increased production of sputum (more mucus produced)
- ○ Increased sputum purulence (ex. change in colour from white to yellow, or yellow to green)

Minor respiratory and related symptoms

New onset of:

- ○ Cough
- ○ Wheezing
- ○ Sore throat
- ○ Fever or chills (A fever is a temperature above 38°C or 100°F)
- ○ Cold or flu-like symptoms *(coryzal symptoms)*
- ○ Chest tightness
- ○ Fatigue
- ○ Difficulty with expectoration
- ○ Night time awakening

PHONE INTERVIEW

Subject: | | | | | | **Date** (dd-mmm-yyyy): | | | **Interview:** 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 | 57 | 60

[BLUE FORM]

Page 3 - MEDICATION

Repeat this page for <u>each episode</u> of new or changes in respiratory symptoms occurring in the last 3 months (or since this questionnaire was last administered)

***Note to coordinator:** Identify the date that this episode started* _____ _____ _____
dd mmm yyyy

In the last 3 months (or since this questionnaire was last administered), because of your **respiratory symptoms**, did you:

1. Have to increase any of your regular medication?

Yes ○ No ○ *(go to question 2)*

1.1 If yes, did these include increases in:
Indicate with an X increases in the following respiratory medication

○ Bronchodilators

○ Inhaled corticosteroids

○ Both bronchodilators and inhaled corticosteroids

2. Begin taking any new medication related to these respiratory symptoms (new meaning not regular)?

Yes ○ No ○ *(go to question 3)*

2.1 If yes, did these include:
Indicate with an X the addition of the following respiratory medication

○ Short-acting bronchodilators (such as Ventolin, etc.)
What was the approximate date that you started to take short-acting bronchodilators? _____ _____ _____
dd mmm yyyy

○ Oral corticosteroids (such as Prednisone, etc)
What was the approximate date that you started to take oral corticosteroids? _____ _____ _____
dd mmm yyyy

○ Antibiotics
What was the approximate date that you started to take antibiotics? _____ _____ _____
dd mmm yyyy

○ Others (prescription)
What was the approximate date that you started to take any other medication? _____ _____ _____
dd mmm yyyy

3. Take any non-prescription medication (i.e. cough medicine, decongestant)?

Yes ○ No ○

4. Take any non-prescription natural medication?

PHONE INTERVIEW

Subject: | | | | | | **Date** (dd-mmm-yyyy): | | | **Interview:**

0	3	6	9	12	15	18	21	24	27	30	33	36
		39	42	45	48	51	54	57	60			

Yes ○ No ○ [YELLOW FORM]

PHONE INTERVIEW

Subject: | | | | | | **Date** (dd-mmm-yyyy): | | | **Interview:** 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 | 57 | 60

Page 4 - WORK

Repeat this page for <u>each episode</u> of new or changes in respiratory symptoms occurring in the last 3 months (or since this questionnaire was last administered)

***Note to coordinator:** Identify the date that this episode started* _____ _____ _____
dd mmm yyyy

1. In the last 3 months (or since this questionnaire was last administered), have you been working?

Yes ○ No ○ *(end of this section/page)*

1.1 If yes, did changes in your **respiratory** symptoms prevent you from going to work?

Yes ○ *(answer 1.1.1)* No ○ *(answer 1.1.2)*

1.1.1 If yes, how many days of work did you miss? _____

1.1.2 If no, was your job performance negatively affected by changes in your **respiratory** symptoms?

Yes ○ No ○

PHONE INTERVIEW

Subject: | | | | | | **Date** (dd-mmm-yyyy): | | | **Interview:** | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 | 57 | 60 |

[PINK FORM]

Page 5 - MEDICAL VISITS

Repeat this page for each episode of new or changes in respiratory symptoms occurring in the last 3 months (or since this questionnaire was last administered)

Note to coordinator: Identify the date that this episode started _____ _____ _____
dd mmm yyyy

In the last 3 months (or since this questionnaire was last administered), because of changes in your **respiratory symptoms**, did you...

Doctor visits

1. Visit a doctor or did a doctor visit you (such as a doctor's office, clinic or at home)?

Yes ○ No ○ *(go to question 2)*

Doctor visit (event number)	1	2	3
1.1 If yes, month of visit			
1.2 If yes, was this visit unscheduled (meaning that you saw a doctor as an emergency)?	Yes ○ No ○	Yes ○ No ○	Yes ○ No ○

Emergency visits

2. Have to visit the Emergency Room?

Yes ○ No ○ *(go to question 3)*

ER visit (event number)	1	2	3
2.1 If yes, month of visit			
2.2 If yes, how long did you stay in the ER? (* *SAE log)*	○ ≥ 24 hrs *(*)* ○ < 24 hrs	○ ≥ 24 hrs *(*)* ○ < 24 hrs	○ ≥ 24 hrs *(*)* ○ < 24 hrs

*Indicate with an X if stay was greater or equal to 24 hours or less than 24 hours, 24 hours meaning one day time **AND** one night time.*

1. Approximate date admitted to the ER _____ *# of days* _____ *Reason* _____
2. Approximate date admitted to the ER _____ *# of days* _____ *Reason* _____
3. Approximate date admitted to the ER _____ *# of days* _____ *Reason* _____

Hospital visits

3. Have to be admitted to the hospital?

Yes ○ No ○ *(end)*

Hospitalizations (event number)	1	2	3
3.1 If yes, month of visit			
3.2 Were you admitted to the ICU during your hospitalization?	Yes ○ No ○	Yes ○ No ○	Yes ○ No ○
3.3 For approximately how many days* were you in the hospital? *(* SAE log)*			

1. Approximate date admitted _____ *# of days* _____ *Reason* _____
2. Approximate date admitted _____ *# of days* _____ *Reason* _____
3. Approximate date admitted _____ *# of days* _____ *Reason* _____

PHONE INTERVIEW

Subject: | | | | | | **Date** (dd-mmm-yyyy): | | **Interview:**

0	3	6	9	12	15	18	21	24	27	30	33	36
			39	42	45	48	51	54	57	60		

** Record in the SAE log each admission/ER visit lasting greater or equal to 24 hours (occurring after the subject has signed Consent Form and since last questionnaire was administered).*

[GREEN FORM]

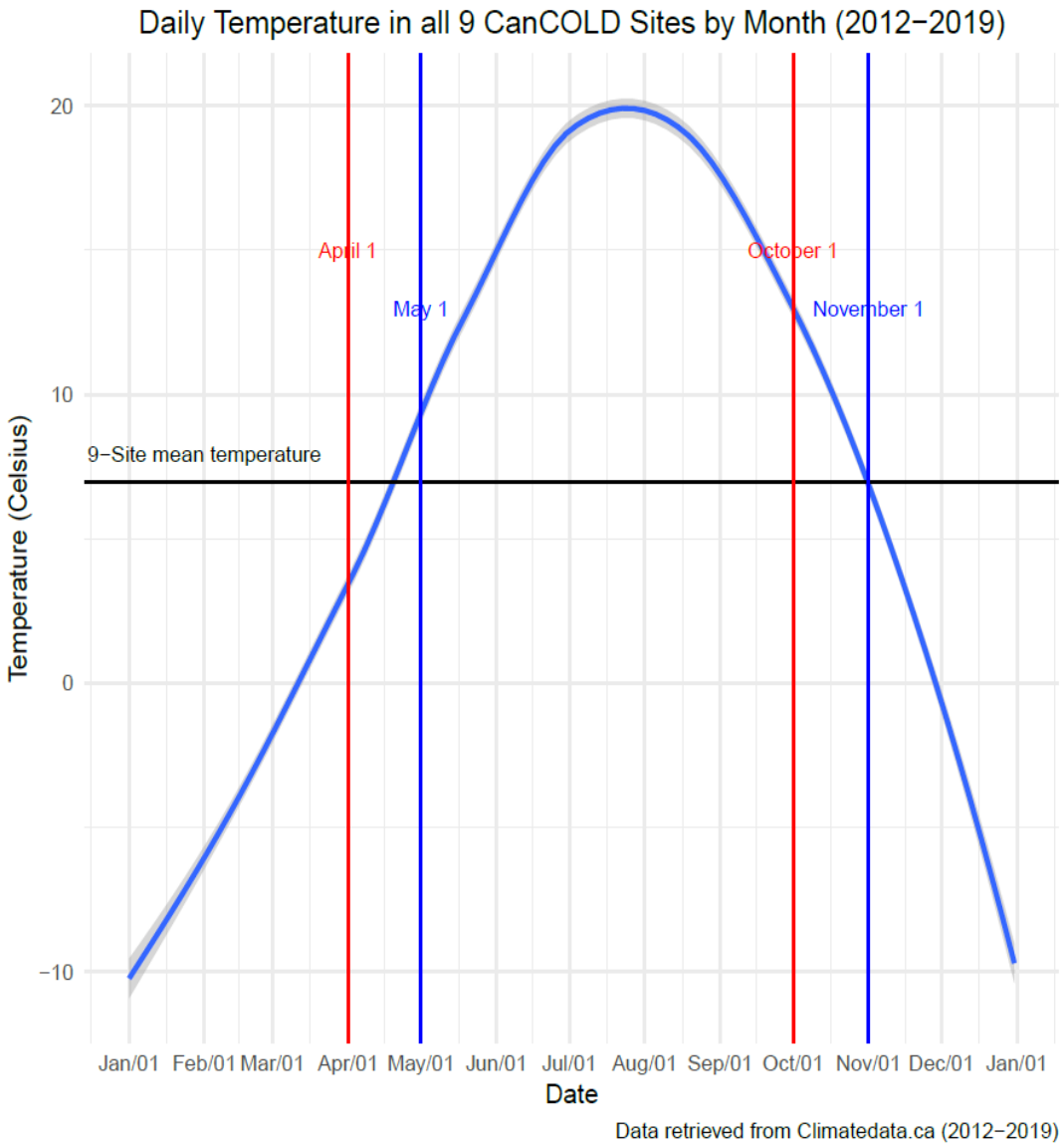


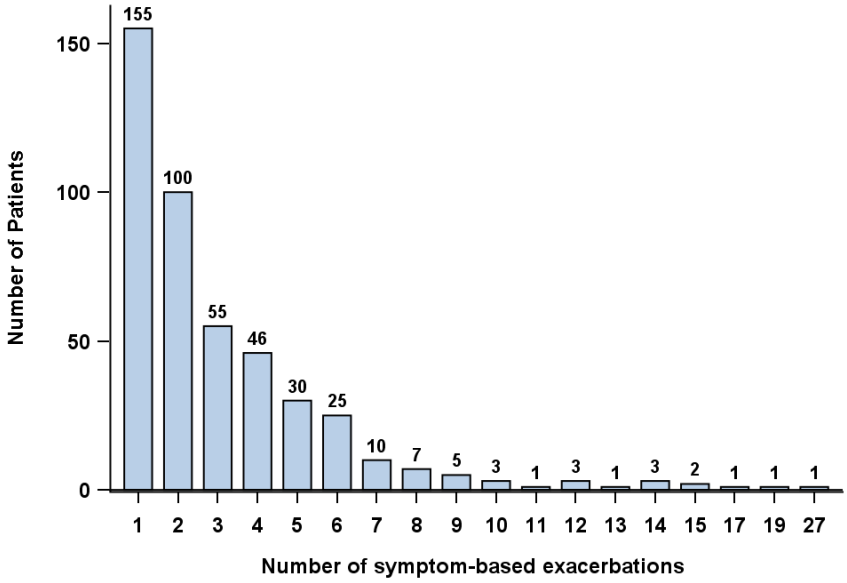
Figure A2. Selection of 'Warm' and 'Cool' Seasons through plotting 9-city monthly average versus 9-city total average between 2012-2019. Points of intersection most closely matched May 1st and November 1st, supporting a 'Warm' Season of May-October inclusive and a 'Cool' Season of November-April inclusive.

Table A1. Quasi-likelihood under the independence model criterion (QIC) from all univariable models in the Warm Season using Exchangeable and Unstructured correlation structures

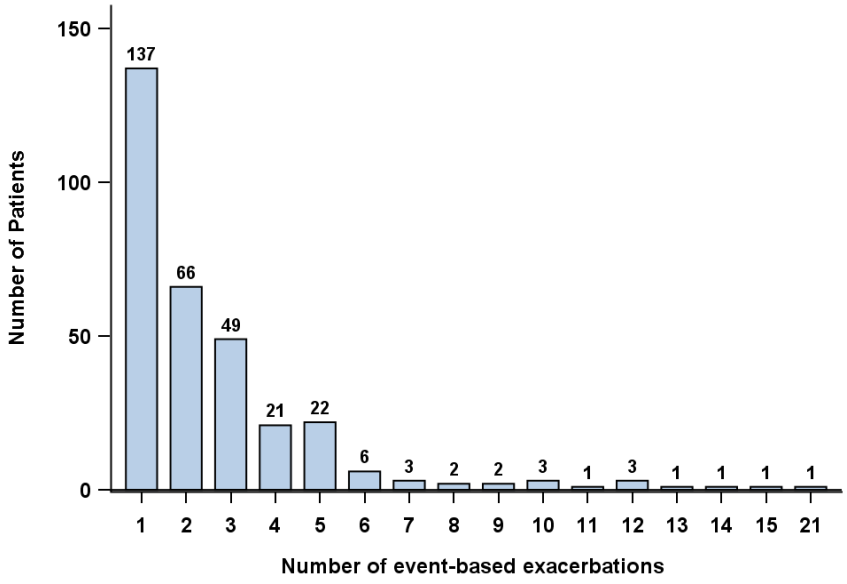
	Warm Season			
	Exchangeable QIC		Unstructured QIC	
	Symptom-based	**Event-based**	**Symptom-based**	**Event-based**
NO_2 — per increase in Interquartile Range				
Lag 0	2689.1624	577.2688	2689.9106	576.3783
Lag 1	2695.7576	583.7048	2696.9897	582.5184
Lag 2	2696.1196	583.7047	2698.3176	582.6694
Lag 3	2695.9241	583.7042	2698.0557	582.149
Lag 4	2697.2167	583.7048	2698.6935	582.4785
Lag 5	2694.3028	583.2582	2699.6585	582.1845
Lag 6	2691.1394	579.1471	2695.3756	578.2249
$PM_{2.5}$ — per increase in Interquartile Range				
Lag 0	2658.844	567.7071	2665.4988	566.9075
Lag 1	2651.8025	568.6003	2656.4091	568.5676
Lag 2	2645.8816	568.1545	2649.7265	569.0447
Lag 3	2643.9643	563.5961	2646.4489	562.9518
Lag 4	2650.1265	567.257	2654.7434	566.4456
Lag 5	2660.3975	568.152	2665.7659	567.0633
Lag 6	2653.7969	570.4763	2661.1309	569.4245
O_3 — per increase in Interquartile Range				
Lag 0	2715.3353	581.38	2718.1653	580.3514
Lag 1	2716.2962	584.5977	2719.6175	583.465
Lag 2	2717.4915	584.5979	2723.4746	583.5349
Lag 3	2715.9572	584.5973	2720.0323	583.2084
Lag 4	2716.403	584.5978	2720.3443	583.5777
Lag 5	2715.8563	584.598	2720.3586	583.3916
Lag 6	2711.8076	583.7044	2718.2512	582.5075

Table A2. Quasi-likelihood under the independence model criterion (QIC) from all univariable models in the Cool Season using Exchangeable and Unstructured correlation structures

	Cool Season			
	Exchangeable QIC		**Unstructured QIC**	
	Symptom-based	**Event-based**	**Symptom-based**	**Event-based**
NO_2 — per increase in Interquartile Range				
Lag 0	3660.121	755.4555	3660.2314	755.2951
Lag 1	3653.9488	755.0072	3654.7321	752.9136
Lag 2	3666.153	755.9031	3667.4251	755.4684
Lag 3	3668.5997	759.1203	3669.9983	758.0632
Lag 4	3669.4988	759.1214	3670.1789	758.1395
Lag 5	3666.7619	759.1218	3668.3546	757.8872
Lag 6	3663.5307	759.1205	3665.753	757.7377
$PM_{2.5}$ — per increase in Interquartile Range				
Lag 0	3701.8735	756.795	3706.8972	756.3901
Lag 1	3690.3238	747.1401	3695.3541	747.1129
Lag 2	3693.8513	749.4641	3696.7925	749.5452
Lag 3	3694.0811	756.7892	3696.7634	755.1972
Lag 4	3697.8787	757.2419	3702.1342	756.6403
Lag 5	3701.7495	757.2423	3708.4566	757.7912
Lag 6	3698.9374	757.689	3705.1569	757.2707
O_3 — per increase in Interquartile Range				
Lag 0	3658.6281	749.0201	3660.0321	748.6631
Lag 1	3652.2115	747.6793	3655.2321	745.9881
Lag 2	3660.2717	751.3422	3664.5532	749.0046
Lag 3	3666.0142	754.5616	3669.7982	752.7587
Lag 4	3667.2393	755.0095	3670.8532	753.689
Lag 5	3668.1692	755.0094	3672.9981	753.3677
Lag 6	3665.0513	755.0095	3671.4259	753.4498



A.



B.

Figure A3. Histogram of the number of eligible symptom-based (A.) and event-based (B.) exacerbation-like events experienced by study participants between July 1, 2012 and December 31, 2019.

Table A3. Secondary analysis on the effect of sex during the Warm Season

	Male					**Female**			
	Symptom-based		**Event-based**			**Symptom-based**		**Event-based**	
	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value		Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
NO_2									
Lag 0	1.07 (0.95, 1.22)	0.259	1.00 (0.77, 1.32)	0.981		1.00 (0.89, 1.11)	0.941	1.15 (0.89, 1.50)	0.279
Lag 1	0.95 (0.85, 1.07)	0.414	0.90 (0.69, 1.17)	0.414		1.01 (0.91, 1.12)	0.814	1.19 (0.96, 1.48)	0.109
Lag 2	0.95 (0.85, 1.07)	0.387	0.93 (0.74, 1.17)	0.554		1.04 (0.94, 1.15)	0.458	1.09 (0.87, 1.36)	0.449
Lag 3	1.05 (0.94, 1.17)	0.348	0.95 (0.80, 1.14)	0.609		1.14 (1.03, 1.28)	0.016 *	1.42 (1.09, 1.85)	0.01*
Lag 4	1.02 (0.90, 1.15)	0.762	0.97 (0.75, 1.26)	0.827		1.11 (0.99, 1.25)	0.082	1.25 (0.94, 1.66)	0.121
Lag 5	1.01 (0.92, 1.11)	0.835	0.98 (0.75, 1.29)	0.91		1.05 (0.95, 1.15)	0.379	1.05 (0.85, 1.30)	0.649
Lag 6	0.99 (0.88, 1.10)	0.802	0.91 (0.72, 1.15)	0.421		1.06 (0.97, 1.17)	0.195	1.17 (0.90, 1.52)	0.236
$PM_{2.5}$									

Lag 0	0.93 (0.84, 1.04)	0.224	0.87 (0.69, 1.09)	0.227		1.07 (1.00, 1.14)	0.056	1.06 (0.97, 1.16)	0.189
Lag 1	0.88 (0.79, 0.98)	0.019 *	0.83 (0.61, 1.13)	0.229		0.99 (0.90, 1.10)	0.882	1.04 (0.79, 1.36)	0.769
Lag 2	0.89 (0.80, 1.00)	0.041 *	0.88 (0.69, 1.12)	0.299		0.95 (0.84, 1.07)	0.381	0.97 (0.79, 1.20)	0.797
Lag 3	0.89 (0.82, 0.97)	0.006 *	0.98 (0.83, 1.17)	0.854		1.07 (0.95, 1.22)	0.275	1.00 (0.76, 1.30)	0.972
Lag 4	0.92 (0.84, 1.02)	0.108	0.99 (0.78, 1.26)	0.945		1.04 (0.93, 1.17)	0.499	1.07 (0.85, 1.36)	0.548
Lag 5	0.93 (0.82, 1.05)	0.244	0.93 (0.74, 1.16)	0.494		1.12 (1.00, 1.26)	0.054	1.23 (1.05, 1.43)	0.01*
Lag 6	0.96 (0.88, 1.06)	0.423	1.10 (0.88, 1.37)	0.407		1.03 (0.97, 1.10)	0.305	0.93 (0.82, 1.05)	0.24
O_3									
Lag 0	0.91 (0.81, 1.02)	0.109	0.92 (0.65, 1.31)	0.644		1.01 (0.90, 1.12)	0.93	0.83 (0.61, 1.13)	0.229
Lag 1	1.00 (0.90, 1.11)	0.968	1.11 (0.85, 1.45)	0.428		0.98 (0.87, 1.10)	0.77	0.80 (0.64, 1.00)	0.047 *
Lag 2	1.08 (0.96,	0.2	0.99 (0.77,	0.934		0.92 (0.82,	0.189	0.83 (0.63,	0.172

	1.22)		1.27)			1.04)		1.09)	
Lag 3	0.89 (0.78, 1.02)	0.089	0.82 (0.65, 1.04)	0.106		0.98 (0.88, 1.09)	0.724	0.80 (0.58, 1.12)	0.2
Lag 4	0.95 (0.85, 1.06)	0.329	0.87 (0.63, 1.22)	0.433		0.95 (0.86, 1.05)	0.282	0.95 (0.74, 1.22)	0.688
Lag 5	0.98 (0.89, 1.08)	0.686	0.73 (0.52, 1.02)	0.062		0.89 (0.79, 1.00)	0.045 *	1.02 (0.82, 1.27)	0.86
Lag 6	0.98 (0.87, 1.10)	0.695	0.98 (0.75, 1.29)	0.903		0.95 (0.86, 1.05)	0.317	0.91 (0.74, 1.11)	0.343

Odds ratios (OR's) and 95% Confidence Intervals (95% CI's) are presented per interquartile range (IQR) increase in $PM_{2.5}$, in NO_2 and in O_3, respectively. * symbol indicates $P < 0.05$.

Table A4. Secondary analysis on the effect of sex during the Cool Season

	Male					**Female**			
	Symptom-based		**Event-based**			**Symptom-based**		**Event-based**	
	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value		Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
NO_2									
Lag 0	0.99 (0.90, 1.09)	0.83	0.87 (0.71, 1.08)	0.207		1.01 (0.92, 1.11)	0.857	0.86 (0.64, 1.14)	0.28
Lag 1	1.04 (0.94, 1.16)	0.444	1.07 (0.88, 1.31)	0.502		1.05 (0.96, 1.16)	0.283	1.16 (0.89, 1.50)	0.27
Lag 2	1.01 (0.92, 1.10)	0.906	0.98 (0.79, 1.21)	0.827		1.06 (0.97, 1.16)	0.232	0.96 (0.78, 1.18)	0.698
Lag 3	1.02 (0.92, 1.12)	0.749	1.04 (0.85, 1.28)	0.705		1.02 (0.93, 1.12)	0.724	1.01 (0.81, 1.27)	0.916
Lag 4	0.98 (0.90, 1.08)	0.745	0.90 (0.74, 1.09)	0.281		1.08 (0.98, 1.18)	0.137	1.13 (0.93, 1.38)	0.212
Lag 5	1.02 (0.92, 1.14)	0.71	1.11 (0.89, 1.39)	0.354		0.97 (0.87, 1.07)	0.506	1.00 (0.78, 1.28)	0.985
Lag 6	1.02 (0.92, 1.14)	0.658	0.85 (0.70, 1.04)	0.114		1.05 (0.94, 1.16)	0.371	1.17 (0.92, 1.50)	0.207
$PM_{2.5}$									
Lag 0	1.03	0.435	1.02	0.838		1.02	0.57	0.92	0.474

	(0.95, 1.12)		(0.85, 1.23)			(0.95, 1.10)		(0.75, 1.15)	
Lag 1	1.05 (0.97, 1.13)	0.223	1.03 (0.81, 1.30)	0.827		1.11 (1.02, 1.21)	0.013*	1.10 (0.90, 1.35)	0.332
Lag 2	0.94 (0.85, 1.03)	0.202	0.88 (0.66, 1.17)	0.377		0.99 (0.90, 1.07)	0.737	0.88 (0.72, 1.07)	0.191
Lag 3	0.95 (0.86, 1.06)	0.372	1.09 (0.91, 1.32)	0.351		1.04 (0.94, 1.14)	0.48	1.22 (0.95, 1.57)	0.116
Lag 4	1.00 (0.92, 1.08)	0.917	1.12 (0.90, 1.40)	0.306		1.01 (0.93, 1.10)	0.763	1.03 (0.84, 1.26)	0.782
Lag 5	1.01 (0.92, 1.10)	0.894	1.06 (0.85, 1.33)	0.597		1.00 (0.92, 1.09)	0.948	0.87 (0.68, 1.10)	0.25
Lag 6	0.95 (0.85, 1.06)	0.375	0.74 (0.60, 0.92)	0.006*		1.05 (0.96, 1.14)	0.297	1.11 (0.93, 1.32)	0.27
O_3									
Lag 0	1.02 (0.90, 1.15)	0.765	1.03 (0.79, 1.34)	0.847		1.02 (0.91, 1.13)	0.774	1.05 (0.83, 1.32)	0.701
Lag 1	0.96 (0.84, 1.10)	0.554	0.84 (0.66, 1.08)	0.18		0.94 (0.85, 1.04)	0.229	0.95 (0.75, 1.21)	0.69
Lag 2	0.93 (0.83, 1.04)	0.189	0.85 (0.66, 1.09)	0.192		0.92 (0.83, 1.02)	0.099	0.96 (0.79, 1.17)	0.662

Lag 3	0.96 (0.85, 1.08)	0.465	0.87 (0.66, 1.15)	0.325		0.97 (0.88, 1.08)	0.582	1.05 (0.83, 1.33)	0.669
Lag 4	0.97 (0.86, 1.08)	0.548	1.14 (0.90, 1.43)	0.285		0.93 (0.83, 1.03)	0.168	0.93 (0.75, 1.14)	0.484
Lag 5	0.90 (0.79, 1.02)	0.097	0.77 (0.60, 1.00)	0.053		0.98 (0.88, 1.11)	0.788	1.00 (0.78, 1.28)	0.981
Lag 6	0.94 (0.84, 1.06)	0.338	1.02 (0.80, 1.29)	0.88		0.98 (0.87, 1.11)	0.773	0.98 (0.75, 1.30)	0.907

Odds ratios (OR's) and 95% Confidence Intervals (95% CI's) are presented per interquartile range (IQR) increase in $PM_{2.5}$, in NO_2 and in O_3, respectively. * symbol indicates $P < 0.05$.

Table A5. Secondary analysis on the effect of *Global Initiative for Chronic Obstructive Lung Disease* (GOLD) grade during the Warm Season

	GOLD1					**GOLD2+**			
	Symptom-based		**Event-based**			**Symptom-based**		**Event-based**	
	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value		Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
NO_2									
Lag 0	0.96 (0.85, 1.08)	0.497	1.09 (0.86, 1.38)	0.488		1.05 (0.95, 1.16)	0.343	1.06 (0.79, 1.43)	0.703
Lag 1	0.90 (0.81, 1.01)	0.063	1.17 (0.96, 1.43)	0.128		1.02 (0.93, 1.13)	0.607	0.94 (0.73, 1.21)	0.638
Lag 2	0.96 (0.88, 1.06)	0.435	1.05 (0.83, 1.34)	0.68		1.00 (0.90, 1.10)	0.944	0.97 (0.78, 1.20)	0.758
Lag 3	1.14 (1.01, 1.30)	0.032*	1.35 (1.07, 1.70)	0.013*		1.05 (0.96, 1.14)	0.292	1.01 (0.83, 1.23)	0.929
Lag 4	1.11 (0.98, 1.25)	0.094	1.04 (0.78, 1.39)	0.771		1.02 (0.91, 1.13)	0.771	1.12 (0.87, 1.45)	0.372
Lag 5	1.04 (0.93, 1.16)	0.483	1.02 (0.77, 1.34)	0.908		1.01 (0.93, 1.11)	0.783	0.99 (0.80, 1.24)	0.957
Lag 6	1.03 (0.92, 1.15)	0.6	1.06 (0.80, 1.41)	0.663		0.99 (0.90, 1.10)	0.916	0.97 (0.79, 1.20)	0.798
$PM_{2.5}$									

Lag 0	1.06 (0.97, 1.15)	0.218	1.41 (0.99, 2.02)	0.058		1.02 (0.93, 1.11)	0.726	0.93 (0.76, 1.14)	0.481
Lag 1	0.99 (0.88, 1.13)	0.934	1.41 (1.00, 1.98)	0.053		0.93 (0.84, 1.04)	0.185	0.75 (0.59, 0.96)	0.02*
Lag 2	0.99 (0.88, 1.10)	0.821	1.10 (0.86, 1.39)	0.452		0.88 (0.77, 0.99)	0.032*	0.84 (0.68, 1.05)	0.12
Lag 3	0.99 (0.91, 1.08)	0.814	1.06 (0.89, 1.27)	0.528		0.93 (0.83, 1.05)	0.229	0.96 (0.78, 1.19)	0.738
Lag 4	1.01 (0.91, 1.13)	0.787	1.08 (0.83, 1.42)	0.568		0.94 (0.84, 1.05)	0.266	1.01 (0.82, 1.23)	0.954
Lag 5	1.12 (0.99, 1.26)	0.077	1.25 (1.05, 1.49)	0.011*		0.99 (0.88, 1.11)	0.871	0.99 (0.83, 1.18)	0.916
Lag 6	1.06 (1.00, 1.14)	0.067	0.99 (0.74, 1.33)	0.948		0.98 (0.91, 1.06)	0.672	0.98 (0.86, 1.10)	0.684
O_3									
Lag 0	0.95 (0.81, 1.11)	0.492	0.90 (0.65, 1.24)	0.516		1.02 (0.91, 1.13)	0.773	0.85 (0.63, 1.15)	0.301
Lag 1	1.04 (0.93, 1.16)	0.508	0.99 (0.80, 1.23)	0.934		0.98 (0.88, 1.10)	0.779	0.88 (0.69, 1.12)	0.299
Lag 2	1.08 (0.94,	0.297	0.96 (0.72, 1.29)	0.795		0.97 (0.87, 1.08)	0.566	0.88 (0.70, 1.11)	0.268

	1.24)								
Lag 3	0.97 (0.85, 1.11)	0.668	0.83 (0.58, 1.19)	0.313		0.92 (0.82, 1.04)	0.182	0.82 (0.65, 1.03)	0.088
Lag 4	0.94 (0.81, 1.08)	0.362	0.75 (0.52, 1.08)	0.124		0.96 (0.87, 1.06)	0.434	1.06 (0.85, 1.34)	0.587
Lag 5	0.88 (0.76, 1.03)	0.115	0.82 (0.59, 1.12)	0.211		0.96 (0.87, 1.06)	0.44	0.95 (0.74, 1.23)	0.699
Lag 6	0.97 (0.85, 1.11)	0.689	0.89 (0.69, 1.13)	0.326		1.01 (0.93, 1.11)	0.795	1.00 (0.80, 1.27)	0.969

Odds ratios (OR's) and 95% Confidence Intervals (95% CI's) are presented per interquartile range (IQR) increase in $PM_{2.5}$, in NO_2 and in O_3, respectively. * symbol indicates $P < 0.05$.

Table A6. Secondary analysis on the effect of *Global Initiative for Chronic Obstructive Lung Disease* (GOLD) grade during the Cool Season

	GOLD1					**GOLD2+**			
	Symptom-based		**Event-based**			**Symptom-based**		**Event-based**	
	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value		Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
NO_2									
Lag 0	1.08 (1.03, 1.14)	0.002*	1.01 (0.82, 1.25)	0.905		0.95 (0.86, 1.05)	0.31	0.77 (0.59, 1.01)	0.062
Lag 1	1.12 (1.00, 1.26)	0.059	1.30 (1.02, 1.65)	0.034*		0.97 (0.89, 1.06)	0.545	1.00 (0.80, 1.25)	0.989
Lag 2	1.07 (1.00, 1.14)	0.044*	1.09 (0.88, 1.36)	0.411		0.99 (0.90, 1.08)	0.817	0.88 (0.72, 1.06)	0.182
Lag 3	1.09 (1.04, 1.15)	<0.001*	1.20 (0.98, 1.45)	0.071		0.95 (0.87, 1.04)	0.308	0.90 (0.72, 1.13)	0.352
Lag 4	1.09 (1.04, 1.14)	<0.001*	1.15 (0.95, 1.40)	0.152		0.99 (0.90, 1.09)	0.794	0.93 (0.77, 1.13)	0.485
Lag 5	1.06 (0.97, 1.16)	0.183	1.06 (0.84, 1.33)	0.646		0.92 (0.83, 1.02)	0.125	1.01 (0.80, 1.28)	0.947
Lag 6	1.07 (1.02, 1.12)	0.002*	0.98 (0.80, 1.21)	0.883		1.02 (0.91, 1.14)	0.738	1.02 (0.81, 1.29)	0.884

$PM_{2.5}$									
Lag 0	1.07 (0.98, 1.17)	0.155	0.93 (0.76, 1.15)	0.511		1.01 (0.94, 1.09)	0.799	1.00 (0.83, 1.20)	0.982
Lag 1	1.11 (1.00, 1.24)	0.046*	0.94 (0.72, 1.23)	0.667		1.07 (0.99, 1.16)	0.097	1.14 (0.95, 1.36)	0.154
Lag 2	0.97 (0.88, 1.08)	0.619	0.91 (0.66, 1.24)	0.547		0.96 (0.88, 1.04)	0.315	0.84 (0.70, 1.00)	0.055
Lag 3	1.02 (0.93, 1.13)	0.635	1.36 (1.10, 1.69)	0.004*		0.99 (0.89, 1.09)	0.787	1.01 (0.81, 1.25)	0.943
Lag 4	1.00 (0.93, 1.08)	0.939	1.01 (0.84, 1.22)	0.91		1.02 (0.93, 1.12)	0.648	1.09 (0.87, 1.36)	0.439
Lag 5	0.98 (0.89, 1.09)	0.716	0.86 (0.63, 1.18)	0.358		1.01 (0.93, 1.10)	0.773	0.99 (0.81, 1.22)	0.917
Lag 6	0.97 (0.88, 1.07)	0.536	0.85 (0.68, 1.08)	0.182		1.04 (0.95, 1.14)	0.393	0.99 (0.84, 1.15)	0.857
O_3									
Lag 0	0.91 (0.85, 0.98)	0.011*	0.91 (0.72, 1.16)	0.447		1.08 (0.97, 1.21)	0.169	1.18 (0.91, 1.51)	0.21
Lag 1	0.93 (0.81, 1.05)	0.243	0.84 (0.65, 1.10)	0.2		0.98 (0.88, 1.09)	0.683	0.94 (0.74, 1.20)	0.637
Lag 2	0.95	0.194	0.87 (0.70,	0.219		0.92 (0.83,	0.103	0.92	0.464

	(0.87, 1.03)		1.08)			1.02)		(0.73, 1.16)	
Lag 3	0.92 (0.85, 1.00)	0.038*	0.90 (0.71, 1.13)	0.354		0.99 (0.90, 1.09)	0.847	1.01 (0.78, 1.32)	0.922
Lag 4	0.89 (0.82, 0.98)	0.012*	0.98 (0.79, 1.21)	0.854		0.99 (0.89, 1.09)	0.77	1.05 (0.84, 1.31)	0.669
Lag 5	0.83 (0.73, 0.94)	0.004*	0.78 (0.60, 1.01)	0.058		1.06 (0.95, 1.18)	0.267	0.99 (0.77, 1.27)	0.938
Lag 6	0.90 (0.84, 0.96)	0.001*	0.93 (0.69, 1.25)	0.623		1.03 (0.91, 1.15)	0.656	1.05 (0.83, 1.31)	0.706

Odds ratios (OR's) and 95% Confidence Intervals (95% CI's) are presented per interquartile range (IQR) increase in $PM_{2.5}$, in NO_2 and in O_3, respectively. * symbol indicates $P < 0.05$.

Table A7. Sensitivity analysis of the effect of including all exacerbation-like events (regardless of recall period from the time of the event) in the analysis of all unadjusted models of the primary analysis

	Warm					**Cool**			
	Symptom-based		Event-based			Symptom-based		Event-based	
	Crude OR (95% CI)	P-value	Crude OR (95% CI)	P-value		Crude OR (95% CI)	P-value	Crude OR (95% CI)	P-value
NO_2									
Lag 0	1.03 (0.97, 1.11)	0.321	1.04 (0.89, 1.20)	0.644		1.00 (0.94, 1.06)	0.885	0.89 (0.78, 1.02)	0.104
Lag 1	1.00 (0.94, 1.07)	0.947	1.00 (0.86, 1.15)	0.959		1.04 (0.97, 1.11)	0.241	1.08 (0.94, 1.25)	0.262
Lag 2	0.98 (0.92, 1.05)	0.606	0.97 (0.85, 1.12)	0.708		1.04 (0.98, 1.11)	0.195	0.92 (0.81, 1.05)	0.23
Lag 3	1.09 (1.02, 1.17)	0.009*	1.11 (0.96, 1.27)	0.151		1.02 (0.96, 1.09)	0.546	1.03 (0.90, 1.17)	0.678
Lag 4	1.05 (0.97, 1.13)	0.195	1.09 (0.92, 1.29)	0.311		1.02 (0.95, 1.08)	0.612	0.99 (0.87, 1.12)	0.869
Lag 5	1.00 (0.94, 1.06)	0.999	0.98 (0.85, 1.13)	0.776		0.97 (0.90, 1.04)	0.329	0.94 (0.82, 1.08)	0.364
Lag 6	0.97 (0.90, 1.04)	0.351	0.98 (0.85, 1.12)	0.751		1.03 (0.96, 1.10)	0.399	1.00 (0.88, 1.15)	0.958

$PM_{2.5}$									
Lag 0	1.02 (0.97, 1.08)	0.478	1.01 (0.92, 1.11)	0.816		1.03 (0.97, 1.08)	0.343	0.99 (0.89, 1.10)	0.858
Lag 1	0.94 (0.89, 1.00)	0.061	0.96 (0.81, 1.13)	0.589		1.06 (1.01, 1.12)	0.029*	1.04 (0.92, 1.18)	0.489
Lag 2	0.93 (0.88, 1.00)	0.039*	0.96 (0.84, 1.10)	0.532		0.98 (0.93, 1.03)	0.446	0.86 (0.75, 0.98)	0.023*
Lag 3	0.99 (0.93, 1.05)	0.773	1.01 (0.90, 1.14)	0.802		1.02 (0.96, 1.08)	0.609	1.13 (0.98, 1.29)	0.082
Lag 4	1.00 (0.93, 1.06)	0.913	1.07 (0.92, 1.23)	0.387		1.00 (0.93, 1.06)	0.885	1.04 (0.91, 1.19)	0.565
Lag 5	1.01 (0.94, 1.08)	0.778	1.06 (0.91, 1.22)	0.461		1.00 (0.95, 1.06)	0.949	0.95 (0.81, 1.10)	0.467
Lag 6	0.99 (0.94, 1.03)	0.537	0.99 (0.90, 1.10)	0.89		1.01 (0.95, 1.08)	0.669	0.96 (0.85, 1.07)	0.444
O_3									
Lag 0	0.96 (0.90, 1.02)	0.217	0.97 (0.85, 1.11)	0.677		0.98 (0.93, 1.04)	0.467	1.05 (0.94, 1.17)	0.413
Lag 1	0.97 (0.91, 1.02)	0.233	0.98 (0.87, 1.11)	0.785		0.94 (0.89, 1.00)	0.052	0.95 (0.85, 1.06)	0.378
Lag 2	0.99	0.702	1.00	0.979		0.95 (0.90,	0.031*	0.97	0.512

	(0.93, 1.05)		(0.88, 1.13)			1.00)		(0.88, 1.07)	
Lag 3	0.97 (0.91, 1.04)	0.391	0.94 (0.82, 1.08)	0.368		0.96 (0.91, 1.02)	0.186	0.96 (0.85, 1.09)	0.537
Lag 4	0.99 (0.93, 1.06)	0.787	1.02 (0.89, 1.17)	0.789		0.96 (0.91, 1.01)	0.159	1.02 (0.91, 1.14)	0.738
Lag 5	0.95 (0.89, 1.02)	0.176	0.96 (0.83, 1.12)	0.629		0.99 (0.94, 1.05)	0.74	1.01 (0.90, 1.13)	0.881
Lag 6	1.01 (0.95, 1.07)	0.771	1.01 (0.89, 1.15)	0.832		0.98 (0.93, 1.03)	0.438	1.01 (0.90, 1.13)	0.882

Odds ratios (OR's) and 95% Confidence Intervals (95% CI's) are presented per interquartile range (IQR) increase in $PM_{2.5}$, in NO_2 and in O_3, respectively. * symbol indicates $P < 0.05$.

Table A8. Sensitivity analysis of the effect of including all exacerbation-like events (regardless of recall period from the time of the event) in the analysis of all adjusted models of the primary analysis

	Warm					**Cool**			
	Symptom-based		**Event-based**			**Symptom-based**		**Event-based**	
	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value		Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
NO_2									
Lag 0	1.03 (0.95, 1.11)	0.474	1.07 (0.91, 1.26)	0.394		0.99 (0.92, 1.06)	0.748	0.90 (0.77, 1.06)	0.201
Lag 1	0.99 (0.92, 1.06)	0.716	0.99 (0.86, 1.15)	0.902		1.04 (0.97, 1.12)	0.259	1.11 (0.95, 1.30)	0.175
Lag 2	0.98 (0.92, 1.05)	0.606	0.98 (0.85, 1.13)	0.793		1.04 (0.97, 1.11)	0.29	0.93 (0.80, 1.06)	0.275
Lag 3	1.11 (1.04, 1.19)	0.003 *	1.13 (0.98, 1.30)	0.096		1.02 (0.95, 1.09)	0.631	1.00 (0.86, 1.15)	0.973
Lag 4	1.06 (0.98, 1.15)	0.15	1.13 (0.95, 1.34)	0.178		1.02 (0.95, 1.10)	0.51	1.00 (0.88, 1.14)	0.987
Lag 5	1.02 (0.95, 1.09)	0.556	1.00 (0.86, 1.17)	0.997		0.98 (0.90, 1.06)	0.562	0.99 (0.85, 1.15)	0.855
Lag 6	0.99 (0.92,	0.72	1.00 (0.86,	0.984		1.03 (0.95,	0.458	1.00 (0.86,	0.965

	1.06)		1.16)			1.12)		1.15)	
$PM_{2.5}$									
Lag 0	1.03 (0.97, 1.09)	0.331	0.99 (0.88, 1.11)	0.822		1.03 (0.98, 1.09)	0.265	0.99 (0.88, 1.12)	0.896
Lag 1	0.93 (0.86, 1.00)	0.06	0.94 (0.78, 1.13)	0.492		1.08 (1.02, 1.14)	0.014 *	1.05 (0.92, 1.21)	0.433
Lag 2	0.92 (0.84, 1.00)	0.048 *	0.93 (0.79, 1.09)	0.35		0.96 (0.90, 1.02)	0.175	0.82 (0.72, 0.95)	0.007 *
Lag 3	0.97 (0.91, 1.04)	0.436	1.00 (0.88, 1.14)	0.985		1.01 (0.95, 1.08)	0.689	1.12 (0.97, 1.29)	0.124
Lag 4	0.99 (0.92, 1.07)	0.885	1.04 (0.89, 1.23)	0.614		1.00 (0.94, 1.07)	1	1.04 (0.91, 1.19)	0.573
Lag 5	1.03 (0.95, 1.12)	0.523	1.06 (0.90, 1.24)	0.486		1.01 (0.94, 1.08)	0.828	0.95 (0.82, 1.11)	0.512
Lag 6	0.98 (0.93, 1.04)	0.591	0.97 (0.87, 1.07)	0.546		1.01 (0.95, 1.08)	0.654	0.95 (0.85, 1.06)	0.351
O_3									
Lag 0	0.97 (0.90, 1.05)	0.497	0.88 (0.73, 1.06)	0.185		1.01 (0.93, 1.10)	0.812	1.06 (0.91, 1.23)	0.482
Lag 1	0.98 (0.91, 1.06)	0.665	0.96 (0.83, 1.12)	0.604		0.94 (0.87, 1.03)	0.183	0.91 (0.78, 1.06)	0.225

Lag 2	1.00 (0.93, 1.08)	0.935	0.93 (0.80, 1.08)	0.36		0.91 (0.84, 0.99)	0.035 *	0.95 (0.82, 1.11)	0.532
Lag 3	0.96 (0.89, 1.04)	0.29	0.88 (0.75, 1.03)	0.108		0.94 (0.87, 1.02)	0.149	1.01 (0.86, 1.19)	0.906
Lag 4	0.98 (0.91, 1.06)	0.609	0.95 (0.81, 1.12)	0.531		0.94 (0.87, 1.02)	0.149	1.03 (0.89, 1.19)	0.696
Lag 5	0.92 (0.85, 0.99)	0.032 *	0.89 (0.74, 1.06)	0.184		0.96 (0.88, 1.05)	0.389	0.95 (0.81, 1.11)	0.502
Lag 6	0.99 (0.92, 1.06)	0.819	0.95 (0.83, 1.09)	0.49		0.97 (0.89, 1.07)	0.564	1.00 (0.85, 1.18)	0.979

Odds ratios (OR's) and 95% Confidence Intervals (95% CI's) are presented per interquartile range (IQR) increase in $PM_{2.5}$, in NO_2 and in O_3, respectively. * symbol indicates $P < 0.05$.