Sources and composition of outdoor air pollution and adverse health outcomes in Canada

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September 2022

A thesis submitted to McGill University in partial fulfillment of the

requirements of the degree of Doctor of Philosophy

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Abstract

Ambient air pollution, including fine particulate matter ($PM_{2.5}$) and oxidant gases (ozone, nitrogen dioxide), contribute to disease outcomes such as cardiovascular and respiratory diseases and cancer through the mechanism of oxidative stress. The source of air pollution influences its composition, which in turn affects its toxicity. Recently, there has been an interest in understanding how specific constituents in particulate air pollution (including metals, sulfur) and oxidative properties, which differ depending on the source, are related to health outcomes. The overarching goal of this thesis is to fill several knowledge gaps on adverse health outcomes associated with specific sources, constituents and oxidative properties of air pollution in Canada.

In Objective 1, we performed a repeated-measures panel study with 71 children to examine associations between short-term and sub-chronic $PM_{2.5}$ or oxidant gases and two measures of cardiovascular health (retinal blood vessel diameter and blood pressure). The study took place in a region of Vancouver Island that is impacted by residential biomass burning. Multivariable linear mixed-effect models were used to estimate associations between outdoor air pollution ($PM_{2.5}$ or oxidant gases) and cardiovascular outcomes, and interactions between $PM_{2.5}$ and oxidant gases were also considered. We observed inverse associations between oxidant gases and retinal arteriolar diameter; for example, each 10 ppb increase in 7-day mean oxidant gases were associated with a 2.63 μm (95% confidence interval: -4.63, -0.63) decrease in retinal arteriolar diameter. Moreover, oxidant gases modified the associations between $PM_{2.5}$ and arteriolar diameter, with weak inverse associations observed between $PM_{2.5}$ and arteriolar diameter only when oxidant gases were elevated.

In Objective 2, we examined whether associations between short-term $PM_{2.5}$ or oxidant gases and respiratory hospitalizations were modified by metals or sulfur content in $PM_{2.5}$ or

particle oxidative potential in a case-crossover study of 10,500 Canadian children. Multivariable conditional logistic regression models were used to estimate associations between air pollutants and respiratory hospitalizations, above and below median values for particle metals, sulfur and oxidative potential. Lag-1 $PM_{2.5}$ mass was not associated with respiratory hospitalizations in analyses ignoring particle constituents and oxidative potential, but when models were examined above and below median metals, sulfur, and oxidative potential, positive associations were observed above the median. For example, the odds ratio and 95% confidence interval per 10 $\mu g/m^3$ increase in $PM_{2.5}$ were 1.084 (1.007–1.167) when copper was above the median and 0.970 (0.929–1.014) when copper was below the median. Similar trends were observed for oxidant gases.

In Objective 3, we investigated associations between wildfire exposure based on area burned within a 20 and 50 km radius of residential location and the incidence of lung and brain cancer, non-Hodgkin lymphoma, leukemia, and multiple myeloma among approximately 2 million participants in the 1996 Canadian Census Health and Environment Cohort. Using multivariable Cox proportional hazards models, we observed positive associations between wildfires and lung and brain cancer. For example, cohort members exposed to a wildfire within 50 km of residential locations in the past 10 years had a 4.9% (95% confidence interval: 2.8%-7.1%) relatively higher incidence of lung cancer than unexposed populations, and a 10% relatively higher incidence (95% confidence interval: 2.6%-17.9%) of brain tumours. Wildfires were not associated with haematologic cancers.

Overall, these findings demonstrate adverse health effects of exposure to different sources of air pollution, including residential biomass burning and wildfires, as well as specific constituents (metals, sulfur) and oxidative properties of air pollution in the Canadian population.

Abrégé

La pollution de l'air ambiant (extérieur), y compris les particules fines ($PM_{2.5}$) et les gaz oxydants (ozone, dioxyde d'azote), contribue au développement de nombreuses maladies telles que les maladies cardiovasculaires et respiratoires et le cancer par le mécanisme du stress oxydatif. La source de pollution de l'air influence sa composition, qui à son tour affecte sa toxicité. Récemment, il y a eu un intérêt croissant pour comprendre comment les constituants spécifiques de la pollution atmosphérique particulaire (y compris les métaux, le soufre) et les propriétés oxydatives, qui peuvent différer selon la source, sont liés aux résultats pour la santé. L'objectif principal de cette thèse est de combler plusieurs lacunes dans les connaissances sur les effets néfastes sur la santé associés à des sources, des constituants et des propriétés oxydatives spécifiques de la pollution atmosphérique dans la population canadienne.

Dans l'objectif 1, nous avons réalisé une étude par panel à mesures répétées auprès de 71 enfants (mesurés 6 fois chacun) pour examiner les associations entre les $PM_{2.5}$ ou les gaz oxydants à court terme et subchroniques et deux mesures de la santé cardiovasculaire (diamètre des vaisseaux sanguins rétiniens et pression artérielle). L'étude s'est déroulée dans une région de l'île de Vancouver touchée par la combustion résidentielle de biomasse. Des modèles linéaires multivariables à effets mixtes ont été utilisés pour estimer les associations entre les expositions moyennes le jour même, sur 3 jours, sur 7 jours et sur 21 jours et le diamètre des vaisseaux sanguins rétiniens et la pression artérielle, et les interactions entre les $PM_{2.5}$ et les gaz oxydants ont également été prises en compte. Nous avons observé des associations inverses entre les gaz oxydants et le diamètre artériolaire rétinien; par exemple, chaque augmentation de 10 ppb des gaz oxydants moyens sur 7 jours était associée à une diminution de 2.63 μm (IC à 95%: -4.63 - 0.63) du diamètre artériolaire rétinien. De plus, les gaz oxydants ont également modifié les

associations entre les $PM_{2.5}$ et le diamètre artériolaire, avec de faibles associations inverses observées entre les $PM_{2.5}$ et le diamètre artériolaire uniquement lorsque les gaz oxydants étaient élevés.

Dans l'objectif 2, nous avons examiné si les associations entre les $PM_{2.5}$ à court terme ou les gaz oxydants et les hospitalisations respiratoires étaient modifiés par la teneur en métal ou en soufre des $PM_{2.5}$ ou le potentiel oxydatif des particules dans une étude de croisement de cas constitué d'environ 10 500 enfants canadiens. Des moniteurs au sol ont été utilisés pour mesurer la concentration massique quotidienne de $PM_{2.5}$ et les concentrations de gaz oxydant, et des estimations mensuelles de la teneur en métal et en soufre dans les $PM_{2.5}$ ainsi que trois mesures du potentiel oxydatif des particules ont également été mesurées. Des modèles de régression logistique conditionnelle multivariés ont été utilisés pour estimer les associations entre les polluants atmosphériques et les hospitalisations respiratoires, au-dessus et en dessous des valeurs médianes pour les métaux particulaires, le soufre et le potentiel oxydatif. Les concentrations massiques de $PM_{2.5}$ Lag-1 n'étaient pas associées aux hospitalisations respiratoires dans les analyses ignorant les constituants des particules et le potentiel oxydatif, mais lorsque les modèles étaient examinés au-dessus et en dessous de la médiane des métaux, du soufre et du potentiel oxydatif, des associations positives ont été observées au-dessus de la médiane. Par exemple, le rapport de cotes et l'intervalle de confiance à 95% par augmentation de 10 $\mu g/m^3$ des $PM_{2.5}$ étaient de 1.084 (1.007-1.167) lorsque le cuivre était supérieur à la médiane et de 0.970 (0.929-1.014) lorsque le cuivre était inférieur à la médiane. Des tendances similaires ont été observées pour les gaz oxydants.

Dans l'objectif 3, nous avons étudié les associations entre l'exposition aux feux de forêt en fonction de la superficie brûlée dans un rayon de 20 et 50 km du lieu de résidence et

l'incidence du cancer du poumon et du cerveau, du lymphome non hodgkinien, de la leucémie et du myélome multiple chez environ 2 millions de participants de la cohorte santé et environnement du recensement canadien de 1996. En utilisant des modèles multivariables de risques proportionnels de Cox, nous avons observé des associations positives entre les incendies de forêt et le cancer du poumon et du cerveau. Par exemple, les membres de la cohorte exposés à un incendie de forêt à moins de 50 km d'emplacements résidentiels au cours des 10 dernières années avaient une incidence relativement plus élevée de cancer du poumon de 4.9% (IC à 95%: 2.8%-7.1%) et une incidence relativement plus élevée de 10% (IC à 95% : 2.6%-17.9%) de tumeurs cérébrales que les populations non exposées. Les incendies de forêt n'étaient pas associés aux cancers hématologiques dans cette étude.

Dans l'ensemble, les résultats présentés dans cette thèse démontrent les effets néfastes sur la santé de l'exposition à différentes sources de pollution atmosphérique, y compris la combustion de biomasse résidentielle et les incendies de forêt, ainsi que des constituants spécifiques (métaux, soufre) et des propriétés oxydantes de la pollution atmosphérique dans la population canadienne.

List of abbreviations

AIC	Akaike information criterion
As	Arsenic
BMI	Body mass incidence
Ca	Calcium
CanCHEC	Canadian Census Health and Environment Cohort
Canossem	Canadian Optimized Statistical Smoke Exposure Model
CI	Confidence interval
cIMT	Carotid intima-media thickness
CRAE	Central retinal arteriolar equivalent
CRVE	Central retinal venular equivalent
Cu	Copper
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DAD	Discharge Abstract Database
Fe	Iron
GIS	Geographic Information Systems
HANDS	Hotspot and Normalized Difference Vegetation Index Differencing Synergy
Hg	Mercury
HR	Hazard ratio
IQR	Interquartile range
K	Potassium

m	Metre
MAFiMS	Multi-Acquisition Fire Mapping System
Mg	Mercury
mm	Millimetre
Mn	Manganese
Na	Sodium
NBAC	National Burned Area Composite
Ni	Nickle
NO	Nitric oxide
NO_2	Nitrogen dioxide
NOx	Nitrogen oxides
O_3	Ozone
OP^{AA}	Ascorbic acid oxidative potential
OP^{DTT}	Dithiothreitol oxidative potential
OP^{GSH}	Glutathione oxidative potential
O_x	Redox-weighted average of nitrogen dioxide and ozone
OR	Odds ratio
PM	Particulate matter
$PM_{2.5}$	Fine particulate matter
PM_{10}	Particulate matter <10 μm
Pb	Lead
ppb	Parts per billion
SD	Standard deviation

SBP	Systolic blood pressure
TCDD	2,3,7,8-Tetrachlorodibenzodioxin
V	Vanadium
VOCs	Volatile organic compounds
Zn	Zinc

Acknowledgements

My doctoral studies were funded by the Max Stern Recruitment Fellowship (2018-2019), Alma Mater Fellowship (2018-2020), and Max E. Binz Fellowship (2019-2020) from the Faculty of Medicine, and a doctoral award from the Fonds de recherche en santé du Québec (2020-2022). I also received financial support from a CIHR Foundation Grant held by Scott Weichenthal, and scholarships from the Quebec Inter-university Centre for Social Statistics.

I am very grateful to my thesis supervisor, Scott Weichenthal, for his mentorship and encouragement throughout my doctoral training. He provided me with plenty of guidance to lead me in the right direction but trusted my abilities to make independent decisions, which allowed for immense academic and personal growth. I am also very lucky to have worked with Michal Abrahamowicz and Eric Lavigne, members of my thesis committee, whose thoughtful feedback greatly improved the quality of my work.

Thank you to the faculty and staff in the Department of Epidemiology, Biostatistics and Occupational Health at McGill for providing such a supportive and intellectually stimulating learning environment. I would also like to thank my PhD cohort; I couldn't think of a better group to have spent so many hours together with during our first couple years of coursework, as well as many coffee and drink dates. I love having friends to geek out about epidemiology with, I've learned so much from all of you.

Lastly, I am endlessly thankful to my family for their continuous support in my long and detouring academic career, and Marc for his 12+ years of love and companionship.

Contribution to original knowledge

Manuscript 1: This manuscript evaluates associations between short-term/sub-chronic fine particulate matter and oxidant gases and measures of cardiovascular health (retinal blood vessel diameter and blood pressure) in children living in a region impacted by residential biomass burning. This is one of a few existing studies to examine associations between air pollution and the retinal microvasculature, and the first that is performed in a rural location where the main source of air pollution is residential biomass burning.

Manuscript 2: This manuscript evaluates whether associations between short-term fine particulate matter or oxidant gases and respiratory hospitalizations in Canadian children are modified by metals or sulfur in fine particulate matter or particle oxidative potential. Limited evidence in adults support the hypothesis that metals, sulfur and particle oxidative potential are important effect modifiers, but to our knowledge this question has not been previously examined in children.

Manuscript 3: This manuscript was a comprehensive assessment of the associations between residential exposure to wildfires and the incidence of lung cancer, brain cancer, non-Hodgkin lymphoma, leukemia, and multiple myeloma. This is the first study in the world to assess associations between long-term wildfire exposure and cancer risk.

Contribution of authors

Manuscript 1: Korsiak J, Perepeluk K, Peterson NG, Kulka R, Weichenthal S

JK coordinated the study, analyzed the retinal images, performed statistical analyses and wrote the manuscript. KLP and NGP organized the fieldwork and collected all clinical data. RK coordinated the collection and analysis of exposure data. SW designed the study, obtained funding, oversaw all aspects of data collection and statistical analyses, and provided critical revisions of the manuscript. All authors have read and approved the final manuscript.

Manuscript 2: Korsiak J, Lavigne E, You H, Pollitt K, Hatzopoulou M, Evans G, Burnett RT, Weichenthal S

SW conceptualized the study. JK refined the research question and conducted the literature review. SW designed the study. JK, SW and EL prepared the data and verified the underlying data. HY and RK co-ordinated the collection of $PM_{2.5}$ filters from across Canada. GE led the oxidative potential analysis in collaboration with KP. JK performed all statistical analyses and all authors contributed to the interpretation of results. JK wrote the first draft of the manuscript, and all authors reviewed and revised the final draft. All authors had full access to the data.

Manuscript 3: Korsiak J, Pinault L, Christidis T, Burnett RT, Abrahamowicz M, Weichenthal S

SW conceptualised the study. JK refined the research question and did the literature review. RTB and SW designed the study. LP generated the exposure surfaces. JK, LP, and TC prepared the data and verified the underlying data. All authors contributed to statistical methods and MA

provided statistical oversight. JK did all statistical analyses and all authors contributed to the interpretation of the results. JK wrote the first draft of the manuscript, and all authors reviewed and revised the final draft. All authors had full access to the data.

CHAPTER 1: Introduction

Ambient (outdoor) air pollution is a leading contributor to disability-adjusted life years lost and mortality, exceeded only by several behavioural and metabolic risk factors[1]. Air pollution is a dynamic mixture of both gaseous and particulate pollutants that vary in space and time, and exposure is universal, affecting people of all ages and ethnicities throughout the globe. Due to the ubiquitous nature of ambient air pollution and its widespread health consequences, air quality is an important public health concern.

Perhaps the most well-studied outdoor air pollutant is fine particulate matter, composed of particles with a mass median aerodynamic diameter less than 2.5 μm ($PM_{2.5}$). $PM_{2.5}$ is a causal agent for the development of cardiovascular disease[2], lung cancer[3], and acute respiratory events[4,5], and is associated with a wide range of other health endpoints including neurological disorders[6] and adverse birth outcomes[7]. Although the exact biological mechanism by which $PM_{2.5}$ contributes to adverse health is not fully understood, oxidative stress is a probable mechanism[8]. Globally, concentrations of ambient $PM_{2.5}$ are increasing, and this is largely driven by industrialization in low-and-middle-income countries, whereas in high-income countries, concerted regulatory measures have led to a reduction in ambient $PM_{2.5}$ in the past 30 years[9]. Although Canada has some of the cleanest air in the world[10,11], health impacts of air pollution are still observed. For example, country-wide analyses have observed positive associations between $PM_{2.5}$ and non-accidental[12–14], cardiovascular[13,14] and respiratory mortality[14].

$PM_{2.5}$ is traditionally measured as a mass concentration (i.e., the total mass of particles less than 2.5 μm within a cubic meter, $\mu g/m^3$). As such, $PM_{2.5}$ is not a single chemical entity but is comprised of a mixture of relatively harmless (sand, sea salt, etc.) and more harmful (e.g., metals, polycyclic aromatic hydrocarbons, etc.) substances. This mass-based approach to

measure $PM_{2.5}$ does not account for differences in particle composition or toxicity and instead treats all particles as equally toxic. Unsurprisingly, heterogeneity in health impacts of $PM_{2.5}$ have been observed, in part due to variations in the source of pollution and/or its composition[15–19]. It is increasingly recognized that there is a need to move beyond only measuring and studying the health impacts of $PM_{2.5}$ mass concentration and instead focus on specific sources, constituents or chemical properties of $PM_{2.5}$[20,21]. Having a better understanding of what specifically about $PM_{2.5}$ contributes to adverse health can help inform more efficient public policy.

In addition to $PM_{2.5}$, individuals are simultaneously exposed to outdoor gaseous air pollutants such as ozone (O_3) and nitrogen dioxide (NO_2), which also contribute to adverse health outcomes through the mechanism of oxidative stress[8]. Given that $PM_{2.5}$ and oxidant gases share the same biological mechanism, it is biologically plausible that interactions between these air pollutants exist. For example, several studies have observed stronger health effects of $PM_{2.5}$ when individuals are also exposed to high concentrations of oxidant gases[22,23]. Therefore, it may be relevant to consider interactions between $PM_{2.5}$ and oxidant gases when evaluating their health impacts.

1.1 Research objectives

The overarching goal of this thesis is to fill several gaps in knowledge on adverse health outcomes associated with specific sources, constituents, or oxidative properties of air pollution in the Canadian population by leveraging both new and existing databases. Among children, we focus on acute cardiovascular and respiratory health outcomes, while in adults we focus on a chronic health outcome (cancer). The specific aims are as follows:

Objective 1) To estimate associations between ambient $PM_{2.5}$ (primarily from residential biomass burning) or oxidant gases and retinal blood vessel diameter and blood pressure (measures of cardiovascular health) in school-aged children living in rural British Columbia.

To address Objective 1, we performed a repeated-measures panel study at two elementary schools in the Comox Valley region of Vancouver Island between 2018-2020. We recruited 71 students and outcomes were measured for a median of 6 times per child, for a total of 344 retinal blood vessel measurements and 432 blood pressure measurements. We evaluated associations between air pollution ($PM_{2.5}$, oxidant gases) and markers of cardiovascular health (retinal blood vessel diameter, blood pressure) using multivariable linear mixed-effect models, and considered whether the associations between $PM_{2.5}$ and retinal arteriolar diameter were modified by concentrations of oxidant gases (and visa versa). This objective is addressed in Chapter 3: Manuscript 1.

Objective 2) To evaluate whether associations between short-term ambient $PM_{2.5}$ or oxidant gases and respiratory hospitalizations among Canadian children were modified by metals or sulfur content in $PM_{2.5}$ or particle oxidative potential.

To address Objective 2, we performed a case-crossover study across 34 Canadian cities from 2016-2017. Monthly mean estimates of particle oxidative potential, metals (copper, nickel, manganese, iron, zinc) and sulfur were measured in each city each month. Hospitalization data were obtained from administrative data sources. Associations were evaluated above and below median oxidative potential, metals and sulfur content using multivariable conditional logistic regression models. This objective is addressed in Chapter 4: Manuscript 2.

Objective 3) To estimate associations between long-term residential proximity to wildfires and the incidence of lung cancer, brain cancer, multiple myeloma, non-Hodgkin's lymphoma and leukemia in a national, population-based cohort study.

To address Objective 3, I used data from the 1996 Canadian Census Health and Environment Cohort; a nationally representative population-based cohort in which participants are followed for 20 years for mortality and cancer outcomes (N=2 million people). This database was linked to wildfire exposures (obtained from Natural Resources Canada) based on the area of forest burned within a given radius of residential postal codes, from 1986-2015. Multivariable Cox proportional hazards models were used to evaluate associations between wildfire exposures and cancer outcomes, adjusted for a wide range of individual and neighbourhood-level covariates. This objective is addressed in Chapter 5: Manuscript 3.

CHAPTER 2: Literature review

2.1 Major types of ambient air pollution

This section of the literature review will provide a brief overview of three major types of ambient air pollution: $PM_{2.5}$, NO_2, and O_3.

2.1.1 Fine particulate matter ($PM_{2.5}$)

$PM_{2.5}$ includes all solid and liquid particles found in the air with a mass median aerodynamic diameter less than 2.5 μm. It is comprised of a wide range of chemical species including elemental carbon, organic compounds (e.g., polycyclic aromatic hydrocarbons, organic carbon), metals, and different ions (e.g., sulfate, nitrate, ammonium, chloride)[24–26]. Sources of $PM_{2.5}$ are diverse and comprise both natural and anthropogenic direct emissions (including wildfires, windblown dust, transportation, industry, residential biomass burning), and secondary emissions formed in the atmosphere by chemical reactions involving primary gaseous emissions (such as sulfur dioxide, volatile organic compounds, ammonia, and nitrogen oxides). Concentrations of annual $PM_{2.5}$ in Canada are low and have decreased slightly over the past 30 years, from approximately 10 μg/m^3 in 1990 to 7 μg/m^3 in 2019[11]. As shown in Figure 1, Canada has some of the lowest concentrations of ambient $PM_{2.5}$ in the world. That being said, health-based air quality guidelines by the World Health Organization are set at 5 μg/m^3 for $PM_{2.5}$[27], and much of Canada exceeds this threshold[28].

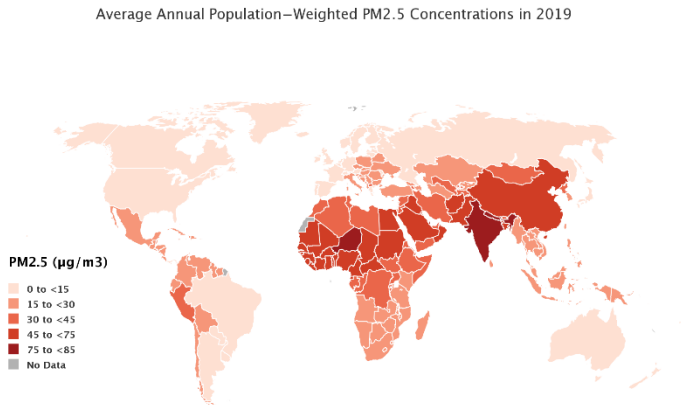

Figure 1: Average annual population-weighted $PM_{2.5}$ concentrations in 2019 https://www.stateofglobalair.org/data/#/air/map

The five leading sources of annual ambient $PM_{2.5}$ in Canada are wildfires (accounting for 17% of population-weighted average annual emissions), transportation (including mobile sources and dust resuspension, 15.9%), residential combustion (for heating, 15.1%), industry (e.g., petroleum, chemical, mineral, pulp and paper, aluminum, 14.2%) and agriculture (livestock and agriculture soils, 10.4%)[29]. However, the contribution of different sectors varies both temporally and spatially. In the winter months, residential combustion is the leading contributor to ambient $PM_{2.5}$ because many homes rely on wood burning as a heating source, followed by transportation[29]. In the summer, wildfires, biogenic secondary organic aerosols and industry are the leading sources of ambient $PM_{2.5}$[29]. On a regional scale, there are also differences in the relative contribution of different sectors to $PM_{2.5}$. In central Canada, residential combustion followed by transportation are the leading contributors to outdoor $PM_{2.5}$, while in western Canada, wildfires and agriculture are the major sources of $PM_{2.5}$. In Atlantic Canada, wildfires and secondary organic aerosols are the leading sources of $PM_{2.5}$, and in northern Canada, more than half of the $PM_{2.5}$ arises from wildfire emissions because there are minimal anthropogenic sources in this region[29].

2.1.2 Nitrogen dioxide (NO_2)

Nitric oxide (NO) and nitrogen dioxide (NO_2) are two nitrogen oxides (NO_X) primarily generated from combustion processes, including heating, power generation, engine exhaust, and wildfires[30,31]. Combustion processes typically emit 90-95% of NO_X as NO and only 5-10% as NO_2, but in ambient air NO is quickly oxidized by available oxidants, including oxygen, ozone and volatile organic compounds (VOCs) to form NO_2[32]. In urban areas, vehicular exhaust is the main source of NO_2 such that NO_2 is often used as a marker of traffic-related air pollution[33]. Concentrations of NO_2 in urban areas typically follow daily, weekly and seasonal road traffic

patterns, where peak concentrations are often observed during rush hour, while concentrations at night and on weekends are typically much lower[25]. NO_2 in Canada has decreased over time largely due to regulations related to vehicle emissions; average concentrations decreased by almost 50% over the period of 1988-2013, from approximately 20 ppb in 1988 to 11 ppb in 2013[34]. With reductions in NO_2 emissions from anthropogenic sources, wildfires are becoming a relatively more important source of ambient NO_2[30].

2.1.3 Ozone (O_3)

Ground-level O_3 is a secondary pollutant that is not directly emitted but instead formed in the atmosphere through complex, non-linear photochemical reactions between NO_X and VOCs in the presence of sunlight. O_3 is generally less spatially variable than $PM_{2.5}$ and NO_2. Regulatory actions to reduce ground-level O_3 typically target precursors to ozone formation (NO_X and VOCs), but due to the complex processes by which O_3 is formed, reductions in O_3 precursors do not necessarily translate into reduced ambient O_3[35]. As such, O_3 is challenging to regulate and ambient concentrations in Canada have remained relatively stable since the 1990s at approximately 37 ppb[36]. Moreover, because temperature is a strong driver of O_3 formation, O_3 is also expected to increase into the future with climate change[37], and may become increasingly difficult to regulate

2.2 Oxidative stress

This section of the literature review will provide a brief discussion of oxidative stress, an important mechanism by which $PM_{2.5}$ and oxidant gases contribute to adverse health outcomes. I will also discuss metals in $PM_{2.5}$ in the context of oxidative stress, as well as different approaches to measure the oxidative properties of particulate matter.

2.2.1 Oxidative stress

Oxidative stress is involved in many disease pathologies, including cardiovascular[38] and respiratory[39] diseases, and cancer[40,41], and is well recognized as a main mechanism underlying the toxic effects of air pollution[8]. Oxidative stress occurs when there is an excess of reactive oxygen species (a subset of free radicals which contain oxygen) in cells compared to antioxidant defenses[8]. Reactive oxygen species react indiscriminately with different molecules, including lipids, proteins, and nucleic acids, by "stealing" electrons (known as "oxidation")[8]. This can potentially lead to cellular damage and an influx of inflammatory cells to the injured site, which can lead to a second wave of oxidative stress because inflammatory cells generate reactive oxygen species themselves[8,42]. On the other hand, the body contains antioxidants which preferentially react with reactive oxygen species to form less toxic secondary products. The respiratory tract lining fluid, a thin layer of fluid comprised of many different substances that line the respiratory tract epithelial cells, contains high concentrations of the antioxidants glutathione, uric acid and ascorbic acid, and acts as a first line of defense against the toxic effects of inhaled pollutants[8,43]. Oxidant gases and $PM_{2.5}$ both cause oxidative stress[8].

2.2.2 Oxidative stress and oxidant gases

Both O_3 and NO_2 are oxidant gases[8], although O_3 is a stronger oxidizing agent than NO_2 (the redox potential of O_3 is 2.075 volts compared to 1.07 volts for NO_2)[44,45]. Upon inhalation, O_3 and NO_2 preferentially react with antioxidants in the respiratory tract lining fluid, but when concentrations O_3 or NO_2 are high or when antioxidant defences are compromised, these gases can react with lipids and proteins[8]. When O_3 and NO_2 react with substrates in the respiratory tract lining fluid, they are consumed and are therefore unlikely to interact directly with the pulmonary epithelium[8]. However, reactions between oxidant gases and lipids or proteins lead to the

generation of harmful secondary oxidation products, which transmit toxic signals to the underlying pulmonary epithelium and initiate numerous cellular responses that can lead to an influx of inflammatory cells to the lungs[46].

2.2.3 Oxidative stress and $PM_{2.5}$

As with oxidant gases, inhaled $PM_{2.5}$ reacts with antioxidants present in the respiratory tract lining fluid but can quickly deplete these defenses. Unlike O_3 and NO_2, where the generation of oxidative stress is mainly attributed to the concentration of gases, the ability of $PM_{2.5}$ to generate reactive oxygen species is driven by both the concentration of $PM_{2.5}$ as well as its composition[8,42]. This is because O_3 and NO_2 are single chemical entities, while $PM_{2.5}$ is comprised of a wide range of different particles that vary in their toxicity. For example, redox-active transition metals such as iron (Fe) and copper (Cu) can act as catalysts in the formation of reactive oxygen species including superoxide, hydrogen peroxide and hydroxyl radicals, all of which cause oxidative stress[42]. Moreover, organic components of particulate matter, including quinones and polycyclic aromatic hydrocarbons, also contribute to oxidative stress[42]. Quinones are highly-redox active molecules that can directly reduce oxygen and generate reactive oxygen species, while polycyclic aromatic hydrocarbons indirectly contribute to the formation of reactive oxygen species by first biotransforming into redox-active quinones[42]. Less harmful constituents found in particulate matter include sand and sea salt, among others.

2.2.3.1 Metals in $PM_{2.5}$

Transition metals play an important role in the toxicity of ambient $PM_{2.5}$ through their ability to participate in redox reactions. Metals originate from a variety of different sources including engine, break and tire wear, tail-pipe emissions, coal-fired power plants, residual oil combustion processes, and metal refineries, among others[47–49]. Certain sources of $PM_{2.5}$ are

elevated in specific metals; for example, tail pipe emissions from gasoline-fueled vehicles are characterized by elevation in calcium (Ca), Cu and nickel (Ni), oil combustion emissions (from power plants, industrial boilers, maritime/shipping industry) are elevated in Ni and vanadium (V), and coal combustion emissions are elevated in crustal materials (sodium (Na), Fe, Ca, magnesium (Mg), etc.) and trace metals (Cu, Ni, lead (Pb), zinc (Zn), arsenic (As), etc.)[49]. Several metals in particulate matter, including Cu, Fe, manganese (Mn), Ni and Zn have been frequently associated with several measures of particle oxidative potential[47].

The solubility of transition metals is an import determinant of metal toxicity because soluble metals are more mobile and bioavailable than non-soluble metal components[47,48,50]. Acid processing of aerosols by inorganic ions such as sulfate help increase the solubility of metals[47,49,50]. Therefore, particulate matter that contains high concentrations of both metals and sulfur particles may be particularly harmful to health[48].

The health effects of metals in particulate matter have been examined in several systematic reviews and meta-analyses. A 2017 review by Achilleos and colleagues[51] examined associations between short-term exposure to $PM_{2.5}$ constituents, including metals (Na, Mg, potassium (K), Ca, V, Mn, Fe, Ni, Cu, Zn) and mortality in time-series and case-crossover studies. Overall, the authors found some evidence for associations between certain metals, including Ca, Cu, Fe, K, Mn, Mg, V and Zn, with all-cause, cardiovascular, and/or respiratory mortality, but there was a high degree of heterogeneity between studies. Another systematic review and meta-analysis from 2019 by Yang and colleauges[52] looked at associations between both short-term and long-term exposures to $PM_{2.5}$ constituents, including metals, and mortality and morbidity. In this meta-analyses, they detected positive associations between all-cause mortality and short/long-term exposures to K, as well as long-term exposure to Zn. For

cardiovascular mortality, the authors observed positive associations with short-term K, long-term Fe, and both short and long-term Zn, with some evidence for Ni, V, and Na[52].

There are no existing systematic reviews/meta-analyses that summarize the health effects of metals in particulate matter among children specifically, but metals in particulate matter have previously been associated with negative respiratory health outcomes in numerous studies. For example, short-term ambient exposure to several metals including Ni, V, and Fe have been positively associated with airway inflammation[53,54], while two time-series studies observed associations between various trace metals (e.g., Zn, Cu and Fe) and respiratory hospitalizations[55,56]. In a recent case-crossover study that performed source apportionment of $PM_{2.5}$, metals were more strongly associated with respiratory hospitalizations than other sources[57].

2.2.3.2 Measures of particulate oxidative potential

To move beyond only measuring $PM_{2.5}$ mass concentration, many studies have aimed to quantify the oxidative properties of particulate matter. There are several different existing approaches to measure particle oxidative potential, including a-cellular assays, in-vitro and ex-vivo methods (based off cell cultures), and in-vivo methods[26]. In Objective 2 of this thesis, we use three a-cellular assays to measure particle oxidative potential: the ascorbic acid (AA), glutathione (GSH), and dithiothreitol (DTT) assays[26].

A-cellular tests measure the consumption of a molecule (generally an antioxidant) after exposure to a known concentration of particulate matter. AA and GSH are antioxidants that are found in high concentrations in the respiratory tract lining fluid. With these assays, physiologically relevant concentrations of AA and GSH are incubated with $PM_{2.5}$ in a simulated respiratory tract lining fluid and the extent to which AA and GSH are depleted over time reflects

particle oxidative potential, expressed as OP^{AA} and OP^{GSH}[47]. The DTT assay differs slightly because DTT is not an antioxidant but is used as a surrogate of cellular reductants, such as nicotinamide adenine dinucleotide /nicotinamide adenine dinucleotide phosphate[47]. The DTT assay involves incubating DTT with $PM_{2.5}$ and measuring the consumption of DTT over time; when DTT is in excess, the consumption rate of DTT is proportional to the generation of reactive oxygen species, and is thus used as a measure of particle oxidative potential (OP^{DTT})[26,47,58]. Often, several acellular assays are used simultaneously in epidemiological analyses because each assay is sensitive to different properties of particulate matter[26]. For example, OP^{GSH} and OP^{AA} are sensitive to metals including Cu and Fe, while OP^{DTT} is sensitive to metals as well as organic carbon species and products of combustion[47].

Measures of particle oxidative potential have been incorporated into several studies investigating the respiratory health impacts of $PM_{2.5}$ (in addition to other health outcomes which are not discussed here because they are not directly relevant to the subject matter of this thesis). In a time-series study in Atlanta, United States, 3-day mean OP^{DTT} was associated with emergency department visits for respiratory diseases[59], while evidence from another time-series study in London, England, did not find consistent associations between short-term OP^{AA} or OP^{GSH} and respiratory mortality[60]. Moreover, two studies in children have observed more consistent associations between measures of particle oxidative potential and respiratory outcomes than with particle mass. For example, in a study of almost 4000 children in the Netherlands, long-term OP^{DTT} was more strongly associated with asthma and rhinitis than particle mass[61], while in another study among asthmatic Canadian children, associations between airway inflammation and short-term OP^{GSH} (but not particle mass) were observed[62]. To our knowledge, one other study investigated whether associations between short-term $PM_{2.5}$ mass

concentrations and respiratory health outcomes were modified by measures of oxidative potential, and found stronger associations between short-term $PM_{2.5}$ mass and respiratory hospitalizations when OP^{GSH} but not OP^{AA} was elevated[63]. However, this study was limited because only long-term estimates of oxidative potential were available, when oxidative potential may also vary on a temporal scale[64].

2.2.4 Interactions between air pollutants

Given that oxidative stress is likely responsible for the adverse health effects of both particulate and gaseous air pollutants[8], it is relevant to consider interactions or effect modification by co-pollutants in epidemiological analyses. For example, the health impacts of $PM_{2.5}$ mass concentration may be stronger when individuals are simultaneously exposed to higher concentrations of oxidant gases, or similarly the health effects of oxidant gases may be greater when individuals are exposed to $PM_{2.5}$ comprised of more toxic constituents (e.g., metals). Although many studies generate multi-pollutant models, whereby co-pollutants are conceptualized as confounders, markedly fewer studies consider interactions or effect modification by co-pollutants. In a human-controlled exposure study, heart rate variability and diastolic blood pressure were adversely impacted by simultaneous exposure to $PM_{2.5}$ and O_3, but not by each pollutant alone[65]. Moreover, three epidemiological studies performed in Canada observed stronger associations between long-term[14,23] and short-term[22] $PM_{2.5}$ and non-accidental all-cause[14,22,23], cardiovascular[14,22,23] and respiratory[23] mortality when oxidant gas concentrations were higher, while a study in 29 European cities observed stronger associations between short-term PM_{10} and non-accidental mortality when long-term NO_2 concentrations were elevated[66]. In addition, a large time-series study in Hong Kong (where air pollution concentrations are much

higher than most places in North America and Europe) observed synergistic interaction between short-term ambient PM_{10} and NO_2 on hospitalizations for cardiovascular disease[67].

2.3 Sources of pollution: residential biomass burning and wildfires

Objectives 1 and 3 of this dissertation focus on the health impacts of residential biomass burning and wildfires, two important sources of ambient air pollution in Canada. This section of the literature review will discuss what is known about the various health impacts of these two pollution sources.

2.3.1 Residential biomass burning

Residential biomass burning is a significant source of ambient $PM_{2.5}$ in Canada[29], and it is also well-known that combustion processes are an important source of NO_2 and O_3. Historically, burning wood was the main source of heating in Canada and fireplaces or woodstoves are still used as a primary or secondary heating source in many households, particularly in rural communities, because it is a cost-efficient and a reliable source of heat. Some regulatory efforts have been made to limit air pollution attributed to residential biomass burning; for example, the province of British Columbia offers an exchange program to swap out old woodstoves for cleaner options, including heat pumps, gas or pellet stoves, and newer more energy-efficient woodstoves, and the city of Montreal enforced a ban on some types of woodstoves in 2018. However, the use of residential woodstoves is a contentious issue and most governing bodies have been reluctant to regulate residential wood burning, largely because so many people are reliant on this energy source and regulations are challenging to enforce.

2.3.1.1 Health effects of exposure to ambient residential biomass burning

It is relevant to consider the health effects of residential biomass because $PM_{2.5}$ from biomass burning is enriched in organic compounds which may be particularly toxic; for example, OP^{DTT} is especially sensitive to biomass burning sources[68]. Many studies have investigated the health impacts of indoor air pollution from biomass fuel, particularly in low-and-middle-income countries where this cooking practice is most common[69–73], while most studies of outdoor air pollution influenced by biomass burning focus on wildfire exposures or perform source apportionment of $PM_{2.5}$ without distinguishing between the source of biomass burning[74]. It is important to differentiate between the type of biomass burning (e.g., residential wood burning vs. wildfires) opposed to grouping all sources of biomass burning together because the nature of these exposures differ; for example, wildfires cause periodic episodes of highly polluted air, while residential biomass burning typically leads to more moderate elevations in air pollution for a longer period of time.

To our knowledge, only two studies have specifically investigated how ambient air impacted by residential biomass burning affects health[74]. In a case-crossover study in British Columbia, Canada, associations between short-term $PM_{2.5}$ and myocardial infarction in older Canadians during the winter season (when residential biomass burning is common) were stronger when more of the ambient $PM_{2.5}$ was from biomass-burning sources (as determined through measuring levoglucosan, a marker of biomass burning)[75]. In a second study performed in a region of Phoenix, Arizona where both indoor and outdoor fireplaces are used as a heat source during the winter months, $PM_{2.5}$ >35 $\mu g/ m^3$ during the winter heating season was associated with an approximately 20% increased risk in asthma-related hospitalizations among adults compared to when $PM_{2.5}$ was ≤35 $\mu g/ m^3$, while no associations were observed among children[76].

2.3.2 Wildfires

Although wildfires have important ecological purposes[77], they are increasingly recognized as a population health problem; for example, the potential threat of wildfires to human health with the changing climate was discussed in several prominent medical journals[78–80] in 2020, and in a comprehensive report commissioned by the United Nations in 2021[81]. In Canada, the total area burned and the number of large fires (≥200 hectares) have significantly increased since the late 1950s, and the fire season has also extended by approximately two weeks[82]. Robust predictions on a global scale anticipate wildfires to become more frequent, severe and longer in duration in the future, largely because of climate change[83–86]. Moreover, urban sprawl has led to an expansion of the wildland-urban interface (an area where human infrastructure and wildland vegetation meet), which increases human exposure to wildfires[87,88].

2.3.2.1 Health effects of wildfires

There have been several reviews on the various health impacts of wildfires[89–98], including four reviews that have summarized the various health outcomes associated with wildfires in the general population[89–93], as well as specific reviews on child health outcomes[94], birth outcomes[98], occupational exposures[95], and respiratory health outcomes[96,97]. Of the review papers that have focused on numerous health outcomes in the general population, the 2016 review by Reid and colleagues[89] is the most comprehensive. In this review, the authors found consistent evidence for associations between wildfire smoke and acute respiratory health outcomes, including medication prescriptions, physician visits, emergency department visits, and hospitalizations[89]. Growing evidence also suggests an increased risk of all-cause mortality, while evidence for acute cardiovascular morbidity was inconclusive, with many studies noting no associations between wildfires and physician visits, emergency department visits and hospitalizations for

cardiovascular events[89]. Moreover, growing evidence also suggests associations between wildfire exposure and adverse birth outcomes, including low birth weight[89,98] and pre-term birth[98]. More recently, a global time-series study across 749 cities in 43 countries found that short-term exposure to wildfire-derived $PM_{2.5}$ was associated with small risk increases (approximately 2%) in all-cause, cardiovascular and respiratory mortality[99].

In contrast to what is known about the short-term health effects of wildfires, virtually nothing is known about the long-term health effects of wildfire exposure[78,89,92,94], but whether wildfires impact long-term health is relevant for several reasons. First, in North America (and many regions of the world), wildfires tend to occur in similar regions each year so nearby communities may be exposed to wildfire-derived pollutants on a seasonal basis, year after year. Moreover, the wildfire season is getting longer, so air quality may be impacted for months at a time in some regions. In addition, although some pollutants emitted from wildfires return to normal levels shortly after the fire has stopped burning (e.g., particulate matter), other chemicals may persist in the environment for long periods of time; for example, wildfires emit heavy metals and polycyclic aromatic hydrocarbons which are resistant to environmental degradation[100,101]. As such, exposure to harmful environmental pollutants may continue beyond the period of active burning.

2.3.2.2 Wildfires and cancer

Associations between wildfires and cancer have not been assessed previously, but several pollutants emitted from wildfires are established carcinogens. Objective 3 of this thesis investigated associations between wildfires and lung cancer, brain cancer and three hematologic cancers (leukemia, non-Hodgkin lymphoma, multiple myeloma). We selected these specific

cancer outcomes based on evidence linking known wildfire pollutants to these types of cancers, which is discussed in the next paragraph.

$PM_{2.5}$, a major component of wildfire smoke, is a group 1 carcinogen (carcinogenic to humans) and causes lung cancer[102]. Epidemiological research has demonstrated that biomass burning sources of particulate matter may have a greater impact on respiratory health than particulate matter emitted from other sources[103], while toxicological studies have also shown that particulate matter from wildfires is more toxic to lungs than particulate matter collected from normal ambient air[104,105]. Wildfires also emit many ultrafine particles (less than 0.1 μm) which are able to pass the blood-brain barrier[106] and have recently been associated with increased risk of brain tumours in a large Canadian study[107]. Wildfires are also a significant source of human exposure to benzene[108], and benzene is classified as a group 1 carcinogen (carcinogenic to humans) because it causes acute myeloid leukemia[109], a common type of leukemia in adults. Positive associations have also been observed between benzene and non-Hodgkin lymphoma, multiple myeloma, lung cancer and brain cancer[109,110]. Although most evidence pertaining to the ability of benzene to cause cancer in humans is from occupational cohorts[109], some evidence also supports the carcinogenicity of long-term, low-dose exposure to ambient benzene[110–112]. In addition, there is sufficient evidence in humans that 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD; a dioxin released from wildfires, among other sources) is carcinogenic and generally positive associations have been found between TCDD and lung cancer and non-Hodgkin lymphoma[113]. There is also strong evidence that 1-3 butadiene and formaldehyde, both group 1 carcinogens resulting from incomplete combustion, cause tumors of the hematopoietic and lymphoid tissues[114,115]. Heavy metals, including arsenic, lead, cadmium, mercury and aluminum, are able to pass the blood-brain barrier[116] and have been implicated in the development of brain

cancer, although evidence is limited[117]. Several heavy metals are also established causes of lung cancer[118].

When selecting cancer outcomes for Objective 3, we also considered the literature surrounding cancer risk in firefighters. Evidence from a large meta-analysis provides some evidence of an association between firefighting and brain cancer, non-Hodgkin lymphoma, multiple myeloma, and leukemia[119]. Regarding cancer risk among wildland firefighters in particular, the literature is scarce but limited evidence supports an association with lung cancer[120]. However, firefighters are very different than the general population (i.e., much healthier), and different pathways beyond environmental pollutants/chemical exposures are likely involved in explaining the elevated cancer risk among firefighters (e.g., working patterns including shift work, psychological stress, etc.), so we did not rely too heavily on this literature when selecting the outcomes for Objective 3.

2.4 Air pollution and child cardiorespiratory health

Children are particularly vulnerable to the adverse impacts of air pollution owing to several physiological and behavioural factors, including their underdeveloped lungs and immune system, tendency for mouth-breathing (thus reduced nasal filtration), and higher baseline breathing rate (leading to more pollutant intake) compared to adults[121]. This section of the literature review will focus on the cardiorespiratory health effects of air pollution in children because Objectives 1 and 2 of this thesis focus on child cardiovascular and respiratory health.

2.4.1 Cardiovascular outcomes

Given that cardiovascular disease is a chronic condition that manifests in adulthood, studies in children focus on preclinical markers of cardiovascular health, including blood pressure, measures of endothelial function, and microvascular health.

Associations between short and long-term ambient air pollution (including particulate matter and NO_2) and blood pressure in children and adolescents were evaluated in two recent systematic reviews/meta-analyses published in 2021[122,123]. The reviews included 14[123] and 15[122] studies and meta-analyses were only performed for a few air pollutants because data were too sparse for other air pollutants. For short-term exposures, both studies performed a meta-analysis for associations between PM_{10} and blood pressure, and observed very small increases in systolic and diastolic blood pressure (less than 1 mm Hg) per 10 $\mu g/m^3$ increase in PM_{10}[122,123]. Regarding long-term exposures, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 1.8 mm Hg increase in systolic blood pressure (where the 95% CIs excluded the null) in both meta-analyses, while associations between $PM_{2.5}$ and diastolic blood pressure were slightly smaller (β and 95% CI: 1.06 (0.32-1.80)[122]; 0.931 (0.157, 1.705)[123]). Both studies also observed small positive associations between long-term NO_2 and systolic and diastolic blood pressure (less than 1 mm Hg in blood pressure per 10 ppb increase in NO_2)[122,123].

Regarding measures of endothelial function, one recent study among approximately 1000 11-12 year old children living in Australia observed positive associations between lifetime average $PM_{2.5}$ and carotid intima-media thickness (cIMT, a marker of atherosclerosis), while no associations were observed with other measures of carotid wall structure or function (diameter, distensibility, elasticity), or between NO_2 and carotid outcomes[124]. On the other hand, in another study of approximately 700 5-year old children in the Netherlands, long-term exposure to several

air pollutants ($PM_{2.5}$, PM_{10}, NO_2, and NO_x) were associated with carotid distensibility, while no associations with other markers of carotid artery wall structure or function (cIMT, elasticity) were observed[125]. Moreover, traffic-related air pollution (based on residential proximity) has also been associated with carotid arterial markers in two studies in Ecuador[126] and Italy[127], and short-term exposures to O_3, PM_{10} and NO_2 have been associated with markers of serum thrombomodulin and tissue factor (two other markers of endothelial dysfunction) in a cross-sectional study of approximately 120 children in Iran[128].

Two studies in children investigated the impact of air pollution on the microcirculation based on retinal blood vessel (arterioles and venules) diameter. The microcirculation represents a large component of the circulatory system and microvascular dysfunction is an important predictor of cardiovascular disease events[129]. Measuring the structure of the retinal microvasculature through fundus photography is a simple, non-invasive method to evaluate microvascular health[130], as the retinal microcirculation is anatomically and physiologically similar to the cerebrovascular[131] and coronary[132] microcirculation. Of the various parameters that can be estimated with fundus photography, the most common and easily estimated parameters are the diameters of retinal blood vessels. In one study of school-aged children living in an urban centre in Belgium, short-term $PM_{2.5}$ was associated with narrower retinal arteriolar diameter and wider venular diameter[133], while in another study of children ages 4-6 years (also living in Belgium), short-term $PM_{2.5}$ was associated with both narrower and wider retinal arterial diameter, depending on the exposure lag, while NO_2 was not associated with retinal blood vessel diameter[134].

2.4.2 Respiratory outcomes

Many studies have investigated associations between both short and long-term exposures to ambient air pollution and various respiratory health outcomes in children. A 2017 systematic review and meta-analysis observed positive associations between exposure to traffic-related air pollution (including black carbon. NO_2, $PM_{2.5}$ and coarse particulate matter) and asthma incidence[135], while a narrative review reported strong evidence supporting associations between long-term traffic-related air pollution and reduced lung function in children[136]. Another narrative review performed in 2021 noted that most evidence supports associations between exposures to short-term and long-term ambient particulate matter, long-term O_3, and short-term NO_2 and reduced lung function, while evidence for short-term O_3 and long-term NO_2 was mixed[137]. Moreover, a 2017 systematic review and meta-analysis of case-crossover studies investigating associations between short-term ambient $PM_{2.5}$ and NO_2 and asthma exacerbations in children observed small (approximately 2-4%) risk increases for each 10-unit increase in $PM_{2.5}$ and NO_2[138]. In addition, respiratory infections are also likely impacted by short-term ambient pollution exposure. A systematic review and meta-analysis found that a 10-unit increase in $PM_{2.5}$, O_3 and NO_2 were associated with a 1-2% increased risk of pneumonia hospitalizations or emergency room visits in children[139].

2.5 Summary of knowledge gaps

Outdoor air pollution has a negative impact on many health outcomes including cardiovascular and respiratory diseases and cancer. This thesis aims to fill some specific knowledge gaps related to the health impacts of different sources of ambient air pollution

(residential biomass burning and forest fires) and constituents (metals, sulfur) or oxidative properties of $PM_{2.5}$ in Canada.

Objective 1 evaluates associations between ambient air pollution and acute cardiovascular markers in children living in a region impacted by residential biomass burning. Despite many Canadian households relying on this fuel source (in rural locations particularly), few epidemiological studies have examined the health impacts of exposure to ambient air impacted by residential biomass burning, which is relevant information to inform efficient regulatory measures. In addition, much evidence supports associations between ambient air pollution and adverse cardiovascular health in adults, but a limited body of evidence exists in children. Given that cardiovascular disease is a chronic condition that develops over time, it is relevant to examine associations between outdoor air pollution and cardiovascular health outcomes in children.

Objective 2 evaluates whether associations between short-term $PM_{2.5}$ or oxidant gases and respiratory hospitalizations in children are modified by the metal or sulfur content in $PM_{2.5}$ or particle oxidative potential. This aim is motivated by the observations that the health effects per unit mass of $PM_{2.5}$ or ppb of oxidant gases is not consistent across studies[140,141]. Here we investigate whether differences in the composition of $PM_{2.5}$ is a possible source of this heterogeneity.

Objective 3 examines associations between long-term wildfire exposure and the incidence of several cancers in Canadian adults. Whether wildfires impair health in the long-term has been recognized as an important knowledge gap[78,89,92,93,95] and there is essentially nothing known about whether wildfires contribute to cancer risk specifically. By leveraging rich data on historical wildfire events that are unique to Canada and linking these data to a large population-

based cohort, this objective intends to provide the first evidence on the relationship between wildfire exposures and cancer risk.

CHAPTER 3: Manuscript 1

3.1 Preface

This chapter contains the first of three manuscripts in this dissertation. In this chapter, I investigated the acute cardiovascular effects of ambient air pollution ($PM_{2.5}$ and O_x [the combined redox-weighted average oxidant capacity of NO_2 and O_3]) among children living in a region impacted by residential biomass burning. Specifically, we examined the impacts of $PM_{2.5}$ and O_x on retinal blood vessel diameter and blood pressure in a repeated-measures panel study of children living in the Comox Valley region of British Columbia. In addition to considering whether $PM_{2.5}$ or O_x individually impact retinal blood vessel diameter or blood pressure, we also considered whether health effects of $PM_{2.5}$ were modified by co-exposures to O_x, and visa versa. This manuscript was peer-reviewed and published in *Scientific Reports*.

Citation: Korsiak J, Perepeluk K, Peterson NP, Kulka R, Weichenthal S. Air pollution and retinal vessel diameter and blood pressure in school-aged children in a region impacted by residential biomass burning. *Scientific Reports* 2021;11: 12790. Doi: 10.1038/s41598-021-92269-x.

3.2 Air pollution and retinal vessel diameter and blood pressure in school-aged children in a region impacted by residential biomass burning

Abstract

Background: Little is known about the early-life cardiovascular health impacts of fine particulate air pollution ($PM_{2.5}$) and oxidant gases.

Methods: A repeated-measures panel study was used to evaluate associations between outdoor $PM_{2.5}$ and the combined oxidant capacity of O_3 and NO_2 (using a redox-weighted average, O_x) and retinal vessel diameter and blood pressure in children living in a region impacted by residential biomass burning. A median of 6 retinal vessel and blood pressure measurements were collected from 64 children (ages 4-12 years), for a total of 344 retinal measurements and 432 blood pressure measurements. Linear mixed-effect models were used to estimate associations between $PM_{2.5}$ or O_x (same-day, 3-day, 7-day, and 21-day means) and retinal vessel diameter and blood pressure. Interactions between $PM_{2.5}$ and O_x were also examined.

Results: O_x was inversely associated with retinal arteriolar diameter; the strongest association was observed for 7-day mean exposures, where each 10 ppb increase in O_x was associated with a 2.63 μm (95% CI: -4.63, -0.63) decrease in arteriolar diameter. Moreover, O_x modified associations between $PM_{2.5}$ and arteriolar diameter, with weak inverse associations observed between $PM_{2.5}$ and arteriolar diameter only at higher concentrations of O_x.

Conclusions: Our results suggest that outdoor air pollution impacts the retinal microvasculature of children and interactions between $PM_{2.5}$ and O_x may play an important role in determining the magnitude and direction of these associations.

Introduction

Outdoor air pollution is associated with adverse cardiovascular outcomes[2,142]. Although cardiovascular disease (CVD) manifests in adulthood, preclinical changes that contribute to and accelerate the development of CVD begin in childhood[143]. Therefore, identifying early-life modifiable exposures that adversely affect cardiovascular health may provide important information to help prevent CVD in later life.

Most research on associations between ambient air pollution and cardiovascular outcomes has focused on particulate matter exposure and consistent evidence from epidemiological and animal studies support a causal relationship[2]. Oxidant gases, such as ozone (O_3) and nitrogen dioxide (NO_2), have also been associated with adverse cardiovascular outcomes, although results have been less consistent[144,145]. Individuals are exposed to both particulate matter and oxidant gases simultaneously, and some evidence suggests these pollutants interact to affect health outcomes. For example, stronger associations between long-term[23] and short-term[22] fine particulate matter air pollution ($PM_{2.5}$) and mortality were found when the combined oxidant capacity of NO_2 and O_3 (using a redox-weighted average, O_x) was higher, highlighting the importance of considering O_x when evaluating $PM_{2.5}$ health effects.

The microcirculation represents a large component of the circulatory system and microvascular dysfunction is an important predictor of CVD events[129]. Measuring the structure of the retinal microvasculature through fundus photography can serve as a simple, non-invasive method to evaluate microvascular health[130], as the retinal microcirculation is anatomically and physiologically similar to the cerebrovascular[131] and coronary[132] microcirculation. Of the various parameters that can be estimated with fundus photography, the most common and easily estimated parameters are the diameters of retinal blood vessels. The relationship between air

pollution and retinal blood vessel diameter has been examined several times in adults in cross-sectional[146] and repeated-measures studies[147–149], and twice in children in repeated-measures studies[133,134]. In one study of school-aged children living in an urban centre in Belgium, short-term $PM_{2.5}$ (measured on the same day as the retinal image and the day before) was associated with narrower retinal arteriolar diameter and wider venular diameter[133]. In another study of children ages 4-6 years (also living in Belgium), $PM_{2.5}$ measured during the same day as the retinal image, the day before the retinal image, and the week before the retinal image was associated with both narrower and wider retinal arterial diameter, depending on the exposure lag, while NO_2 was not associated with retinal vessel diameter[134]. Due to the limited number of studies that have explored these associations in children and inconsistent results, these relationships necessitate further exploration.

Another preclinical cardiovascular outcome that may be adversely affected by outdoor air pollution is blood pressure,[144,145,150] but associations between short-term air pollution and blood pressure have not been extensively studied in children. In a recent meta-analysis of four studies that looked at associations between short-term air pollution (defined as <30 days) and blood pressure in children, each 10 $\mu g/m^3$ increase in particulate matter <10 μm (PM_{10}) was associated with a very small (<1 mm Hg) increase in systolic blood pressure, while no clear associations were observed between PM_{10} or $PM_{2.5}$ and diastolic blood pressure[123]. An understanding of the relationship between air pollution and blood pressure in children is important because childhood blood pressure tracks into adulthood[151] and elevated blood pressure is an important risk factor for the development of cardiovascular disease.

To our knowledge, no studies have explored how the combined oxidant capacity of NO_2 and O_3 (O_x) affects retinal blood vessel diameter or blood pressure, or whether associations

between $PM_{2.5}$ and these health outcomes are modified by O_x. In addition, no studies have focused specifically on the impact of residential biomass burning-related $PM_{2.5}$ to changes in the retinal microvasculature or blood pressure. This is an important consideration because residential biomass burning is a major source of $PM_{2.5}$ in rural Canada[29,152] due to the prevalence of wood burning to heat homes, and biomass-burning sources of $PM_{2.5}$ may be harmful to cardiovascular health[152].

To address gaps in our current understanding of air pollution impacts on cardiovascular health of children, we conducted a panel study to examine associations between outdoor $PM_{2.5}$ and O_x on changes to retinal vessel diameter and blood pressure in children living in a region of Canada known to be impacted by residential biomass burning. We also considered whether the impact of $PM_{2.5}$ on retinal blood vessel diameter or blood pressure was modified by outdoor concentrations of O_x.

Materials and methods

Study design and population

We conducted a repeated-measures panel study at two elementary schools in the neighbouring communities of Courtenay and Cumberland on the east coast of central Vancouver Island, in the province of British Columbia, Canada. The distance between the two schools is approximately 8 km. This is a rural area of Canada, with a population size of approximately 26,000 in Courtenay and 4,000 in Cumberland in 2016 (the most recent census year). The study took place from September 2018 to June 2019 in Courtenay, and from September 2019-March 2020 in Cumberland (the study was terminated three months early in Cumberland because of school closures due to the COVID-19 pandemic). The study took place over sequential school

years (instead of at both schools in the same school year) because study equipment and research staff were limited. This area has elevated outdoor $PM_{2.5}$ concentrations during the cold season (approximately November-April) because many households rely on wood burning as their primary heating source[152]. During the warmer season, outdoor $PM_{2.5}$ concentrations are typically very low (i.e. <5 $\mu g/m^3$)[152].

Children at each school were eligible to participate if they were 4-12 years of age at enrollment, lived in a non-smoking home, and resided in the community surrounding either school. Recruitment occurred during September of each school year, and health outcome measurements began in October. Exams were scheduled at intervals of approximately one month and were staggered throughout each month (as opposed to measuring everyone on the same day) in order to increase exposure variation and minimize the impact on regular school activities. Exams took place on Thursday and Friday mornings at the school site in Courtenay, and throughout the week in the morning and early afternoon in Cumberland. Oral assent was obtained from children and written informed consent was obtained from their parent/guardian. At baseline, parents/guardians of each participant completed a questionnaire to collect basic sociodemographic and household information. The study was approved by McGill University Research Ethics Board and the Health Canada Research Ethics Board and all methods were performed in accordance with the relevant guidelines and regulations.

Air pollutants and meteorological data

In the first year of the study, daily mean outdoor $PM_{2.5}$ concentrations in Courtenay were measured using a BAM (Beta-Attenuation Monitor) 1020 instrument located at the provincial air monitoring station situated on the playground of the school. In case there were any problems or gaps in data collection with the government-run monitor, we also set up a Partisol 2025i

sequential air sampler at the same location, which collected daily integrated $PM_{2.5}$ samples that were subsequently sent for gravimetric analysis. However, for this year of the study, we ended up only using $PM_{2.5}$ measurements from the BAM instrument in our analyses because there were fewer missing data. In the second year of the study in Cumberland, the school was not located at a provincial monitoring station so $PM_{2.5}$ was only measured using a Partisol 2025i sequential air sampler that we set up on the roof of the school. Although the $PM_{2.5}$ values used in analysis were from different instruments each year of the study, we observed a strong correlation in duplicate measurements in Courtenay (r=0.94) and both instruments are considered acceptable methods to monitor $PM_{2.5}$ by the United States Environmental Protection Agency[153].

For both years of the study, ozone and nitrogen dioxide were measured at the provincial air monitoring site in Courtenay with an API T400 UV Absorption O_3 analyzer and an API T200 chemiluminescence $NO/NO_2/NO_x$ analyzer, respectively; due to equipment limitations, we were unable to set up our own monitors for O_3 and NO_2 in Cumberland so relied on measurements from Courtenay as approximations. The combined weighted oxidant capacity (O_x) of NO_2 and O_3 was calculated as a weighted average of NO_2 and O_3, with weights equivalent to the respective redox potentials using the formula $O_x=[(1.07\times NO_2) + (2.075 \times O_3)]/3.145)$, as previously described[44,154]. Indoor air pollution was not measured in this study. Meteorological data, including mean daily temperature, wind speed, precipitation, and humidity were available from a provincial monitoring station located approximately 8 km from the school in Courtenay and 15 km from the school in Cumberland.

In the second year of the study (in Cumberland), there were some days with missing $PM_{2.5}$ data due to a delay in setting up the $PM_{2.5}$ monitor at the start of the study and occasional technical issues throughout the study. A model to predict missing $PM_{2.5}$ was developed, and

predicted values were used to impute missing $PM_{2.5}$. The prediction model regressed log-transformed $PM_{2.5}$ on several predictors including same-day $PM_{2.5}$, NO_2, temperature, wind speed, and precipitation measured at a nearby provincial monitoring station. Global search regression using the *gsreg* command in Stata was used to select the final prediction model, considering all possible combinations of interactions and square terms of predictor variables. The best fitting model had a R^2 of 0.72. There was a total of 58 days in which $PM_{2.5}$ was imputed (approximately 12% of $PM_{2.5}$ values in the time series).

Clinical exams

Clinical exams were conducted by two trained research assistants (one research assistant at each site) and involved imaging the retinal microvasculature and measuring blood pressure, height, and weight. All exams took place in a designated, quiet room in each school.

The fundus of the left and right eye of participants was photographed with a Canon CR2-AF 45° 20.2-megapixel digital nonmydriatic retinal camera in a darkened room. Images were analyzed by one grader (J.K.) using the semi-automatic MONA-REVA software (version 3.0.0, VITO Health, Mol, Belgium). For each participant, images from either the left or right eye were analyzed; the choice of whether to analyze the left or right eye of each participant depended on which eye had the most high quality images (where image quality was judged by how sharp the image was, whether the optic disc was centered, and whether the arterioles and venules were distinguishable from one another). Epidemiological studies have demonstrated a high correlation in retinal vessel diameters between the left and right eye[155,156]. When analyzing the images, the diameter of the optic disc was first determined, then the width of the retinal arterioles and venules were measured within an area equal to 0.5-1 times the disc diameter from the optic disc margin (Figure S1 in the Supplemental Material). Diameters of the 6 largest arterioles and

venules were used in the revised Parr Hubbard formula[157] to estimate Central Retinal Arteriolar Equivalent (CRAE) and Central Retinal Venular Equivalent (CRVE), summary measures reflecting average arteriolar and venular diameter. For each participant, the same 6 arterioles and venules were used to calculate CRAE and CRVE in repeated measurements.

Following fundus photography, blood pressure was measured with the SunTech CT40 vital signs device. While sitting upright in a chair with their non-dominant arm resting on a table, an appropriately sized arm cuff was selected based on the circumference of the child's upper arm, and blood pressure was measured twice with one minute between each reading. If systolic or diastolic blood pressure from the two successive readings were >10 mm Hg apart, a third reading was done. The average of the two closest readings was calculated and used for analysis.

With shoes and bulky clothing removed, height was measured to the nearest 0.1 cm with the Seca 213 Stadiometer, and weight was measured to the nearest 0.1 kg using the Seca 874 Digital Scale. Measurements were taken in duplicate, and an average was calculated. Body mass index-for-age z-scores were then calculated based on the World Health Organization child growth standards[158].

Statistical analyses

Associations between outdoor air pollution and retinal blood vessel diameter

Linear mixed-effect models with a random subject intercept (with a first order autoregressive correlation structure) were used to evaluate associations between $PM_{2.5}$ (as a continuous variable, in units of $\mu g/m^3$) or O_x (a continuous variable, in units of ppb) and within-person changes in CRAE or CRVE (continuous variables, in units of μm). We assessed associations between CRAE or CRVE with four different exposure lags: $PM_{2.5}$ or O_x on the day of the retinal image, 3-day mean (mean of $PM_{2.5}$ or O_x on the day of the retinal image and two

preceding days), 7-day mean, and 21-day mean. These time periods were selected to examine both acute and sub-chronic exposures. For each exposure-outcome relationship, we ran crude models, and models adjusted for an *a priori* list of potential confounders or predictors of retinal blood vessel diameter, including 7-day mean temperature (degrees Celsius) and humidity (%) (which may be correlated with seasonal differences in air pollution concentrations), body mass index-for-age z-score at the time of the retinal image, sex, age (years), highest level of maternal education (high school or less/ community or technical college/ university), and time of day of outcome assessment (≤11:00 AM or >11:00 AM). We also explored whether associations between $PM_{2.5}$ and retinal vessel diameter were modified by concentrations of O_x by running models with an interaction term between $PM_{2.5}$ and O_x (as continuous variables using the same exposure lag for both air pollutants), while adjusting for the same set of covariates identified above. A p-value less than 0.05 for the interaction term was interpreted as evidence of effect modification (on the additive scale). We explored whether including a fixed effect for school was necessary to account for potential clustering within schools, but it did not improve model fit based on the minimum Akaike Information Criterion (AIC) so was not included in the final models. We also explored potential non-linear relationships between continuous covariates and CRAE or CRVE using spline terms, but as splines did not improve model fit (based on the minimum AIC), final models included linear terms for all continuous covariates. Residual plots were generated to verify model assumptions. All estimates are expressed as a change in retinal arteriolar or venular diameter per 5 $\mu g/m^3$ increase $PM_{2.5}$ or 10 ppb increase in O_x, which reflect the approximate interquartile ranges of $PM_{2.5}$ and O_x.

Associations between outdoor air pollution and blood pressure

Linear mixed-effect models with a random subject intercept (and a first order autoregressive correlation structure) were used to evaluate associations between short-term and sub-chronic $PM_{2.5}$ or O_x (the same exposure lags described above) and systolic and diastolic blood pressure. Similar to analyses for retinal vessel diameter, crude models, adjusted models (including the same set of covariates identified above), and models with an interaction term between $PM_{2.5}$ and O_x were examined.

Sensitivity analyses

Several sensitivity analyses were conducted. First, analyses were repeated excluding retinal images or blood pressure measurements in which the relevant $PM_{2.5}$ exposure lags included imputed $PM_{2.5}$ values. Second, instead of evaluating associations between O_x and retinal blood vessel diameter and blood pressure, we looked at associations with each gas (O_3 or NO_2) individually. Third, we additionally adjusted our models for season (fall/winter/spring/summer).

All data cleaning and manipulation were conducted using Stata v.15 (StataCorp, College Station, TX), and all modelling was conducted using R (R-project.org).

Results

Study population

A description of the study population is presented in Table 1. A total of 71 children (median age of 8 years) enrolled in the study and high-quality retinal images were available for 64 of these children. Most participants (N=54, 76%) enrolled during the second year (2019-2020) of the study. The sample was predominantly Caucasian (N=64, 90%), there were a similar

number of boys and girls, and most mothers of participants had some post-secondary education. The majority of participants lived in households that used electricity (N=46, 65%) or natural gas (N=21, 30%) as their primary heating source, while few households used wood burning as their primary heating source (N=3, 4%). The use of woodstoves or wood fireplaces as a secondary source of heating was uncommon in this sample (N= 6, 8%), and 17 participants (24%) lived in households that used an air filter. The average (± standard deviation) body mass index-for age z-score was 0.7 ± 1.3, indicating body mass index of children was slightly higher than the age and sex-specific reference population. Mean (± standard deviation) systolic and diastolic blood pressure at baseline were 106 ± 7 and 63 ± 5 mm Hg, respectively, while mean (± standard deviation) CRAE and CRVE at baseline were 181.51 ± 11.88 and 260.34 ± 15.70 μm.

There was a total of 344 high quality retinal images and 432 blood pressure measurements. The median number of retinal images and blood pressure measurements per child was 6 but some children had as few as three measurements. The maximum number of retinal images was 6 per child, and for blood pressure the maximum number of measurements was 10 per child. Median time between retinal images and blood pressure measurements was 28 days (range: 20-63 days).

Table 1 Description of the study population

Socio-demographic characteristics	
Total enrolled participants, N	71
Participants with retinal images available[a], N	64
Date on study, n (%)	
September 2018-June 2019	17 (24)
September 2019-March 2020	54 (76)
Age (years) at baseline, median (range)	8 (4-12)
Girls, n (%)	33 (46)
Caucasian, n (%)	64 (90)
Highest level of maternal education complete, n (%)	
Graduated high school or less	11 (15)
Some or graduated community/technical college	15 (21)
Some or graduated university	45 (63)
Household characteristics	
Main heating source in home, n (%)	
Wood	3 (4)
Natural gas	21 (30)
Electricity	46 (65)
Oil	1 (1)
Use of a woodstove or wood fireplace in home as a secondary heating source[b], n (%)	6 (8)
Use of air filter in home, n (%)	17 (24)
Cardiovascular measures	
Central retinal arteriolar equivalent (μm), mean ± SD	181.51 ± 11.88
Central retinal venular equivalent (μm), mean ± SD	260.34 ± 15.70
Systolic blood pressure (mm Hg), mean ± SD	106 ± 7
Diastolic blood pressure (mm Hg), mean ± SD	63 ± 5
Body mass index-for-age z-score[c], mean ± SD	0.7 ± 1.3

[a] High-quality images were unavailable for some participants due to blinking, inability to sit still, and general discomfort with getting their eyes photographed

[b] Excludes participants in which a woodstove/wood fireplace is the main source of heating

[c] Body mass index-for-age-and-sex z-score calculated based on World Health Organization growth charts

Exposure characteristics

Distributions of daily mean outdoor $PM_{2.5}$ and O_x concentrations throughout the study are shown in Figure 1 and additional exposure characteristics are provided in Table S1 of the Supplementary Material. Overall, mean daily $PM_{2.5}$ ranged from <1 $\mu g/m^3$ to 32 $\mu g/m^3$ over the entire study period, and was slightly higher and more variable in the first year of the study (mean ± standard deviation: 9 ± 7 $\mu g/m^3$) than in the second year of the study (mean ± standard deviation: 6 ± 4 $\mu g/m^3$). Average $PM_{2.5}$ on the day of the retinal image was the same as the 3-day mean, 7-day mean, and 21-day mean concentrations (7 $\mu g/m^3$), although the standard deviation was slightly larger on the day of the retinal image (standard deviation: 6 $\mu g/m^3$) compared to the 3-day and 7-day means (standard deviation of 4 $\mu g/m^3$ for both lags), and the 21-day mean (standard deviation: 3 $\mu g/m^3$). O_x ranged from 3 ppb to 27 ppb over the entire study period, and was slightly higher and more variable during the first year of the study (mean ± standard deviation: 14 ± 6 ppb) compared to the second year of the study (mean ± standard deviation: 13 ± 5 ppb). Mean O_x for all exposure lags was 13 ppb, and the standard deviation was slightly larger on the day of the retinal image (6 ppb) compared to the 3-day, 7-day, and 21-day means (5 ppb). There was a moderate inverse correlation between $PM_{2.5}$ and O_x based on Pearson's correlation coefficient (r=-0.43).

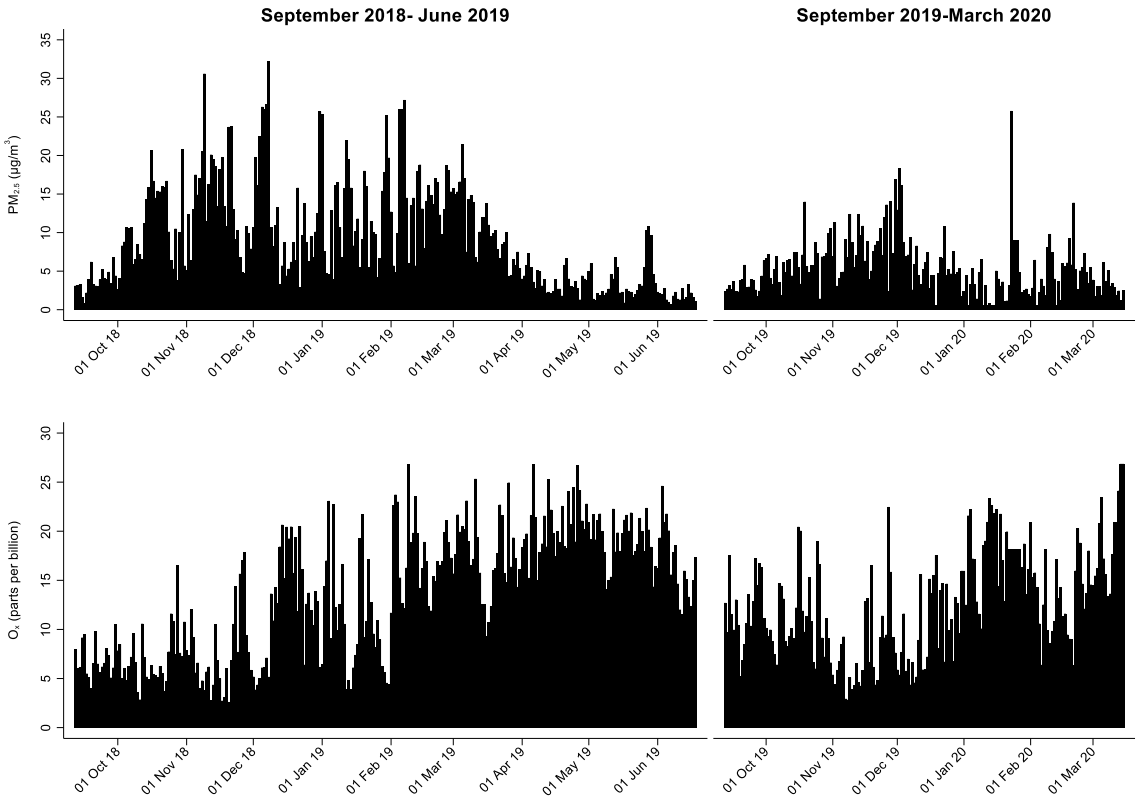

Figure 1 Distribution of daily mean ambient $PM_{2.5}$ ($\mu g/m^3$) and O_x (parts per billion) over the study duration

Associations between outdoor $PM_{2.5}$ or O_x and retinal blood vessel diameter

Associations between $PM_{2.5}$ or O_x from single-pollutant models and retinal arteriolar and venular diameter are presented in Figure 2 and Tables S2 and S3 of the Supplementary Material. In adjusted models, $PM_{2.5}$ was associated with a small increase in CRAE but 95% confidence intervals included the null. The strength of this association was largest for the 21-day exposure lag: a 5 $\mu g/m^3$ increase in 21-day mean $PM_{2.5}$ was associated with a 1.42 μm increase in CRAE (95 % CI: -0.47, 3.32). On the other hand, O_x was consistently associated with a reduction in CRAE and the strongest association was for the 7-day exposure lag: a 10 ppb increase in O_x was associated with a 2.63 μm decrease in CRAE (95% CI: -4.63, -0.63).

In general, positive association were observed between $PM_{2.5}$ and venular diameter and inverse associations were observed between O_x and venular diameter but the strength of these associations was small and 95% confidence intervals included the null in all adjusted models. There were no notable differences in associations between $PM_{2.5}$ and CRAE or CRVE when analyses excluded retinal images with imputed $PM_{2.5}$ (Table S4 of the Supplementary Material). In sensitivity analyses, estimated associations between O_3 and retinal blood vessel diameter were similar to that of O_x (Table S5 of the Supplementary Material), while NO_2 was positively associated with retinal arteriolar and venular diameter, but estimates were imprecise and all confidence intervals included the null (Table S6 of the Supplementary Material). When models were additionally adjusted for season, conclusions remain the same (Table S7 and S8 of the Supplementary Material).

Models including an interaction term between $PM_{2.5}$ and O_x suggested that O_x modified associations between outdoor $PM_{2.5}$ and retinal arteriolar diameter (p-values from interaction terms for same-day, 3-day mean, 7-day mean and 21-day mean exposures: 0.10, 0.04, 0.02, and

0.03, respectively). To visualize the associations between $PM_{2.5}$ and CRAE modified by O_x, we plotted predicted values of CRAE across a range of $PM_{2.5}$ concentrations (2-16 $\mu g/m^3$) stratified by O_x concentrations 1 standard deviation above or below the mean (Figure 3). This figure suggests that when O_x is low there is a weak positive association between $PM_{2.5}$ and CRAE, while when O_x concentrations are higher there is a weak inverse association between $PM_{2.5}$ and CRAE. These trends were more pronounced in the 3-day, 7-day, and 21-day lags compared to same-day exposure. Similar figures were generated to visualize how concentrations of $PM_{2.5}$ modified the associations between O_x and CRAE and suggest that a negative association between O_x and CRAE is only present when concentrations of $PM_{2.5}$ were high (i.e., 1 standard deviation above the mean) (Figure S2 of the Supplementary Material). There was no evidence of interaction between $PM_{2.5}$ and O_x for CRVE (p-values from interaction terms for same-day, 3-day mean, 7-day mean, and 21-day mean exposures: 0.52, 0.63, 0.14, and 0.83, respectively).

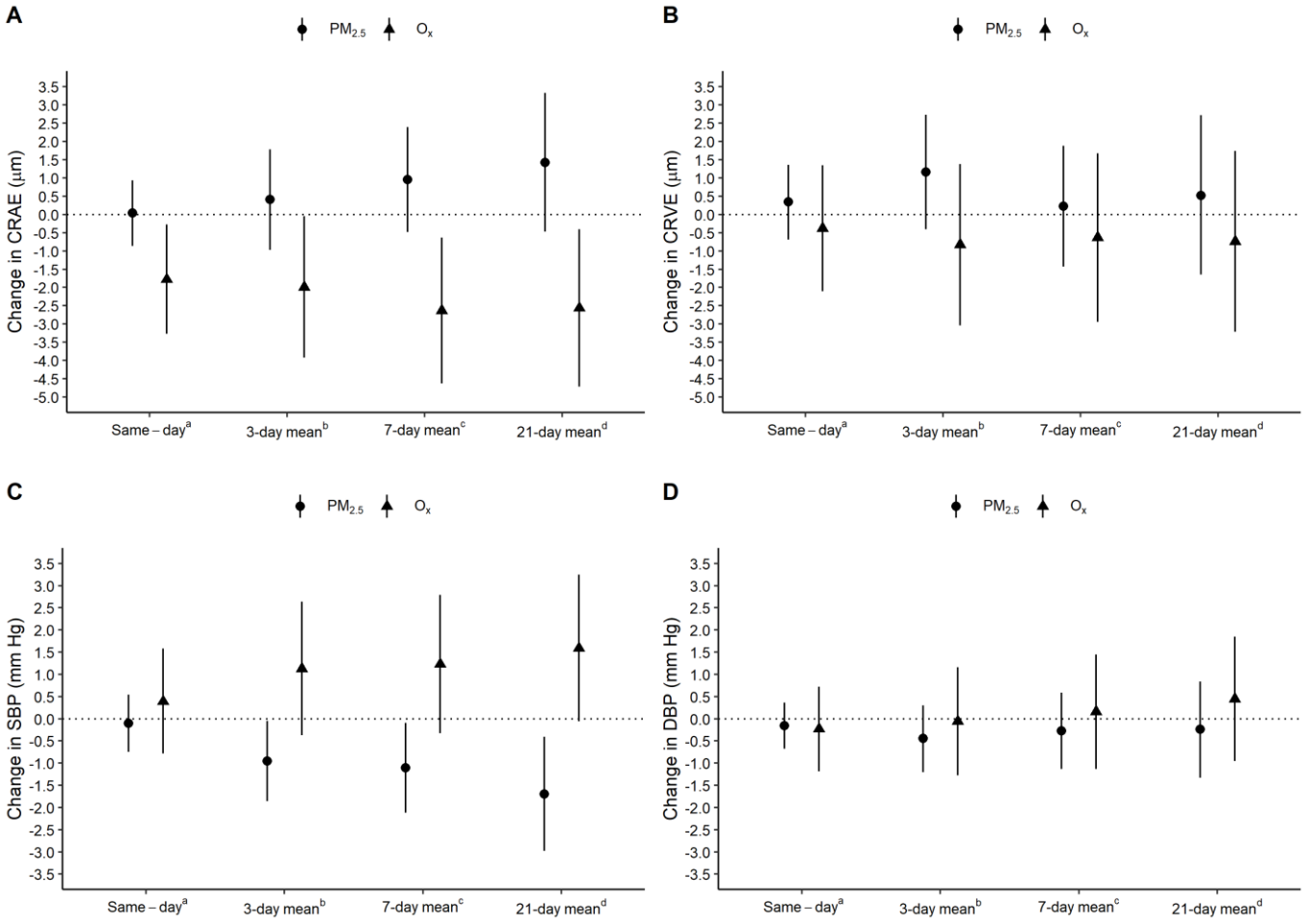

Figure 2 Estimated change (95% confidence interval) in (A) central retinal arteriolar diameter (CRAE, μm); (B) central retinal venular diameter (CRVE, μm); (C) systolic blood pressure (SBP, mm Hg) and; (D) diastolic blood pressure (DBP, mm Hg) per 5 $\mu g/m^3$ increase in $PM_{2.5}$ or 10 ppb increase in O_x. Models adjusted for 7-day mean temperature and humidity, body mass index-for-age z-score on the day of the retinal image, sex, age (years), maternal education (high school or less vs. community/technical college vs. university), and time of day of outcome assessment (≤11:00 AM vs. >11:00 AM).

[a] $PM_{2.5}$ or O_x on the same day as the outcome assessment

[b] Mean $PM_{2.5}$ or O_x on the day of the outcome assessment and two preceding days

[c] Mean $PM_{2.5}$ or O_x on the day of the outcome assessment and 6 preceding days

[d] Mean $PM_{2.5}$ or O_x on the day of the outcome assessment and 20 preceding days

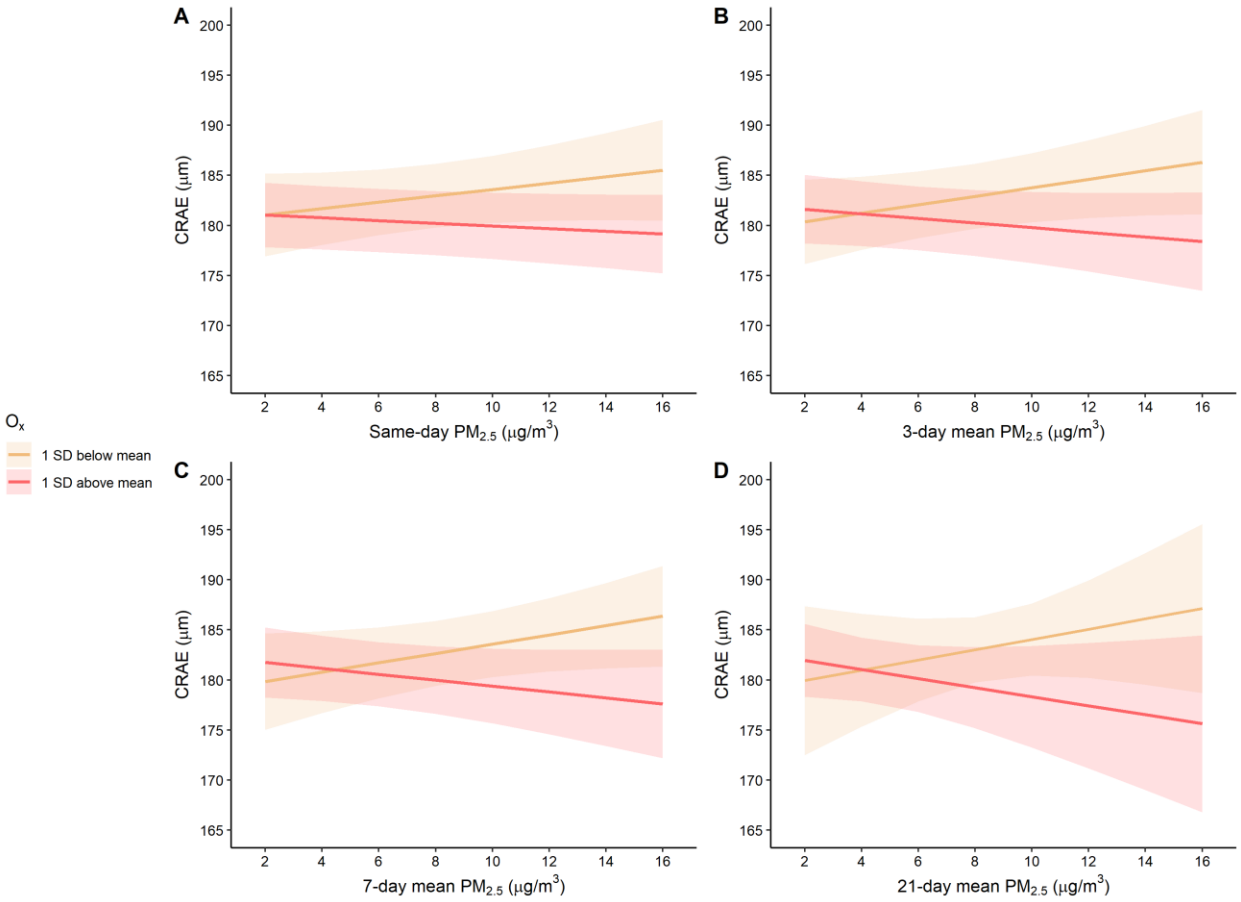

Figure 3 Predicted values and 95% confidence intervals for central retinal arteriolar equivalent (CRAE) at different concentrations of $PM_{2.5}$, stratified by O_x (1 standard deviation below and above mean O_x). Plots correspond to (A): Same-day exposure lag; (B): 3-day mean exposure lag; (C): 7-day mean exposure lag; (D): 21-day mean exposure lag.

Associations between outdoor $PM_{2.5}$ or O_x and blood pressure

Associations between outdoor $PM_{2.5}$ or O_x concentrations and blood pressure are presented in Figure 2 and Tables S2 and S3 of the Supplementary Material. In adjusted models, each 5 $\mu g/m^3$ increase in 3-day mean $PM_{2.5}$ was associated with a 0.95 mm Hg reduction in systolic blood pressure (95% CI: -1.86, -0.05), 7-day mean $PM_{2.5}$ was associated with a 1.11 mm Hg reduction in systolic blood pressure (95% CI: -2.12, -0.09), and 21-day mean $PM_{2.5}$ was associated with a 1.70 mm Hg reduction in systolic blood pressure (95% CI: -2.98, -0.41), but these associations were slightly attenuated and 95% confidence intervals included the null in sensitivity analyses excluding exams where $PM_{2.5}$ was imputed (Table S4 of the Supplementary Material). Conversely, positive associations were observed between O_x and systolic blood pressure, with the largest association detected for the 21-day exposure lag (estimated change per 10 ppb increase in 21-day mean O_x from an adjusted model: 1.59 [95% CI: -0.06, 3.25]), but confidence intervals included the null for all exposure lags. There were no clear associations between $PM_{2.5}$ or O_x and diastolic blood pressure. In sensitivity analyses, associations between O_3 and blood pressure were similar to those found for O_x and no clear relationship was observed between NO_2 and blood pressure (Tables S5 and S6 of the Supplementary Material). When models were additionally adjusted for season, conclusions are similar except the confidence intervals for associations between 3-day and 7-day mean $PM_{2.5}$ now include the null (Table S7 and S8 of the Supplementary Material).

There was evidence that 7-day mean O_x modified the associations between 7-day mean $PM_{2.5}$ and systolic blood pressure (p-value from interaction term: 0.04), but there was no evidence of a significant interaction for the same-day, 3-day mean, or 21-day mean exposures (p-values from interaction terms for same-day, 3-day mean, and 21-day mean exposures: 0.63, 0.26,

0.55). Figure S3 in the Supplementary Material suggests that an inverse relationship between 7-day mean $PM_{2.5}$ and systolic blood pressure is present when 7-day mean O_x concentrations are above average (i.e., 1 standard deviation above the mean), while there is no association when O_x concentrations are lower (i.e., 1 standard deviation below mean). O_x did not modify associations between $PM_{2.5}$ or diastolic blood pressure for any exposure lags (p-value for interaction term for same-day, 3-day mean, 7-day mean, and 21-day mean exposures: 0.57, 0.46, 0.51 and 0.61).

Discussion

Our findings suggest that outdoor air pollution in a region impacted by residential biomass burning has a measurable impact of the microvasculature of school-age children. Specifically, O_x was consistently associated with retinal arteriolar narrowing in single-pollutant models. Our findings also suggest that an important interaction may exist between outdoor concentrations of oxidant gases and $PM_{2.5}$, as $PM_{2.5}$ was only associated with arteriolar narrowing when O_x concentrations were elevated. We also found inverse associations between $PM_{2.5}$ and systolic blood pressure and evidence of effect modification by O_x for the 7-day exposure lag, while in single-pollutant models there were trends towards positive associations between O_x and systolic blood pressure. No clear associations between $PM_{2.5}$ or O_x and retinal venular diameter or diastolic blood pressure were observed.

Although this study did not conduct any source apportionment of $PM_{2.5}$, it is known that residential biomass burning affects air quality in this region of Canada. For example, Hong et al.[159] developed an algorithm that was applied to 23 communities in British Columbia, Canada, to identify smoky vs. non-smoky days, and classified 30% of days in Courtenay between 2014-2016 as smoky, making it the second smokiest community of the 23 studied. Moreover,

Weichenthal et al.[152] identified biomass burning as a major contributor to ambient $PM_{2.5}$ in Courtenay by measuring daily levoglucosan (a tracer of biomass burning) levels from January 2014-March 2015. Furthermore, traffic-related air pollution is very minimal in this region because it is a rural location on an island with a small population size, and there are no major industries in the area that would affect air quality.

The biological mechanisms underlying air pollution impacts on the microcirculation and blood pressure are thought to be related to oxidative stress, inflammation, and disturbances to the autonomic nervous system[2,160]. Inhaled particles can stimulate the generation of reactive oxygen species causing both pulmonary and systemic oxidative stress and inflammation which contributes to endothelial dysfunction and vasoconstiction[2]. Arteriolar narrowing may contribute to elevated blood pressure because arterioles are the main regulators of peripheral blood flow and are essential in the maintenance of blood pressure[161]. In addition, air pollution exposure may lead to an imbalance of the autonomic nervous system which favours sympathetic pathways, and can contribute to endothelial dysfunction, vasoconstriction, and elevated blood pressure[2].

In general, existing evidence from observational studies related to the associations between outdoor air pollution and blood pressure in children is inconsistent. For example, Yang et al.[162] found that short-term exposure to $PM_{2.5}$ was associated with very small increases in both systolic and diastolic blood pressure (<1 mm Hg increase in systolic and diastolic blood pressure per 10 $\mu g/m^3$ $PM_{2.5}$) in a large study of approximately 190,000 children in China, but a smaller study in the Netherlands found no clear associations between short-term PM_{10}, NO_2 or O_3 and systolic or diastolic blood pressure[163]. In another study in Belgium, consistent positive associations were detected between ultrafine particles and systolic blood pressure in children, but trends of an inverse association was observed for $PM_{2.5}$[164]. Inverse associations between systolic

blood pressure and short-term particulate matter[165,166] and ozone[167] have also been observed in adult populations. We are not sure why we observed inverse associations between air pollution and systolic blood pressure because our existing knowledge of physiological responses to air pollution generally would support positive associations[2]; however, these inconsistent findings highlight uncertainty in our current understanding of air pollution impacts on cardiovascular health. In this study, although we found limited evidence of effect modification by O_x for the associations between $PM_{2.5}$ and blood pressure, it still is possible that complex interactions between air pollutants exist and contribute to the heterogeneity of results observed between studies.

Regarding the retinal microvasculature, previous evidence in adults[146,147] and children[133] have observed arteriolar narrowing in response to $PM_{2.5}$ exposure. For example, Provost et al. found that same-day residential outdoor $PM_{2.5}$ was associated with a 0.62 μm decrease in retinal arteriolar diameter (95% CI: -1.12, -0.12) per 10 $\mu g/m^3$ increase in $PM_{2.5}$ in school-aged children in Belgium[133]. However, a second study by Luyten et al. found that the direction of associations between $PM_{2.5}$ and retinal arteriolar diameter in children was sensitive to the exposure lag that was selected[134]. Results for retinal venular diameter have been less conclusive but tend to suggest positive associations with air pollution[133,134]. To our knowledge, no studies to date have examined associations between O_x or O_3 and retinal blood vessel diameter but Luyten et al.[134] investigated the impact of NO_2 and did not find any clear associations.

The most interesting finding in our study is the interaction observed between $PM_{2.5}$ and O_x in models for retinal arteriolar diameter. Specifically, the direction of the association between $PM_{2.5}$ and arteriolar diameter was modified by concentrations of O_x, with weak positive associations observed at lower concentrations of O_x and inverse associations observed at higher

concentrations of O_x. Similarly, the inverse association between O_x and retinal arteriolar diameter was only observed when concentrations of $PM_{2.5}$ were high. This modifying role of O_x in $PM_{2.5}$ health effects has been observed previously for other outcomes. For example, Weichenthal et al.[23] found stronger associations between $PM_{2.5}$ and all-cause, cardiovascular, and respiratory mortality when concentrations of O_x were higher, while Lavigne et al.[22] observed similar results with short-term $PM_{2.5}$ and all-cause and cardiovascular mortality. Together, this evidence highlights the importance of considering O_x when evaluating the health impacts of $PM_{2.5}$ and also suggests possible co-benefits of regulatory interventions aimed at reducing outdoor air pollution (i.e. reducing O_x may also reduce the health impacts of $PM_{2.5}$ even if $PM_{2.5}$ mass concentrations remain unchanged).

Existing evidence suggests several possible mechanisms underlying the observed interaction between $PM_{2.5}$ and O_x. First, elevated ozone depletes antioxidants in the epithelial lining fluid of the respiratory tract[168], and this may lower our defenses against reactive oxygen species produced in response to $PM_{2.5}$ exposure, contributing to greater oxidative stress. In addition, ozone has been shown to increase the permeability of the lung epithelial barrier[46,169,170], which may contribute to greater absorption of particles into the systemic circulation and greater health impacts of $PM_{2.5}$. Lastly, oxidant gases can increase the toxicity of $PM_{2.5}$ through photochemical aging processes; for example, exposure to ozone has been shown to increase the oxidative potential of particles from both engine exhaust[171,172] and biomass burning[173].

There are several strengths of this study, including the repeated measures design that eliminates potential confounding by variables that do not change within individuals over a short time period, exposure information for multiple air pollutants, and the study setting that allowed us to evaluate air pollution primarily from residential biomass burning. However, this study also

had limitations. Foremost, this study is subject to non-differential, Berkson-type exposure measurement error because true personal $PM_{2.5}$ or O_x exposures may differ from outdoor concentrations. The result of Berkson measurement error is a reduction in precision without any systematic bias[174]. Another limitation is we are evaluating short-term changes in retinal blood vessel diameter but how this may impact future health is not clear. We (and others[175]) hypothesize that repeated short-term damage to microvascular structure can lead to chronic microvascular changes in later life, but there are no longitudinal studies demonstrating this. In addition, there is likely some classical measurement error in estimating arteriolar and venular diameter, but this is almost certainly non-differential with respect to outdoor air pollution concentrations.

Conclusion

In summary, these results suggest that short-term and sub-chronic exposures to air pollution impact the retinal microvasculature and blood pressure of children, and highlight the importance of considering potential interactions between air pollutants when evaluating cardiovascular health impacts. Given the small number of studies that have investigated the impact of outdoor air pollution on the retinal microvasculature or blood pressure in children, additional work is needed to confirm these findings.

3.3 Supplementary material

Table S1 $PM_{2.5}$ and O_x exposure characteristics

	Mean ± standard deviation	Median (range)
$PM_{2.5}$ ($\mu g/m^3$)		
Over the entire study duration (September 2018-March 2020)	8 ± 6	6 (<1- 32)
Year 1: September 2018-June 2019	9 ± 7	8 (<1- 32)
Year 2: September 2019-March 2020	6 ± 4	5 (<1- 26)
Same-day[a]	7 ± 6	6 (<1- 31)
3-day mean[b]	7 ± 4	6 (1- 26)
7-day mean[c]	7 ± 4	6 (2- 21)
21-day mean[d]	7 ± 3	5 (3- 17)
O_x (parts per billion)		
Over the entire study duration (September 2018-March 2020)	13 ± 6	13 (3- 27)
Year 1: September 2018-June 2019	14 ± 6	15 (3- 27)
Year 2: September 2019-March 2020	13 ± 5	12 (3- 27)
Same-day[a]	13 ± 6	13 (3- 27)
3-day mean[b]	13 ± 5	14 (4- 23)
7-day mean[c]	13 ± 5	13 (4- 22)
21-day mean[d]	13 ± 5	13 (6- 21)

[a] $PM_{2.5}$ or O_x on the day of the outcome assessment

[b] Mean $PM_{2.5}$ or O_x on the day of the outcome assessment and two preceding days

[b] Mean $PM_{2.5}$ or O_x on the day of the outcome assessment and 6 preceding days

[d] Mean $PM_{2.5}$ or O_x on the day of the outcome assessment and 20 preceding days

Table S2 Estimated change and 95% confidence interval in retinal blood vessel diameter (μm) and blood pressure (mm Hg) associated with 5 $\mu g/m^3$ increase in $PM_{2.5}$

	Crude	Adjusted[a]
Retinal Blood Vessel Diameter		
Central retinal arteriolar diameter		
Same-day $PM_{2.5}$[b]	-0.09 (-0.94, 0.76)	0.04 (-0.86, 0.93)
3-day mean $PM_{2.5}$[c]	0.20 (-1.03, 1.42)	0.41 (-0.97, 1.78)
7-day mean $PM_{2.5}$[d]	0.64 (-0.64, 1.93)	0.95 (-0.48, 2.39)
21-day mean $PM_{2.5}$[e]	0.94 (-0.63, 2.52)	1.42 (-0.47, 3.32)
Central retinal venular diameter		
Same-day $PM_{2.5}$[b]	0.49 (-0.49, 1.48)	0.34 (-0.69, 1.36)
3-day mean $PM_{2.5}$[c]	0.97 (-0.46, 2.41)	1.16 (-0.41, 2.73)
7-day mean $PM_{2.5}$[d]	0.27 (-1.25, 1.79)	0.22 (-1.43, 1.88)
21-day mean $PM_{2.5}$[e]	0.78 (-1.06, 2.63)	0.52 (-1.65, 2.71)
Blood Pressure		
Systolic blood pressure		
Same-day $PM_{2.5}$[b]	-0.14 (-0.73, 0.45)	-0.10 (-0.75, 0.54)
3-day mean $PM_{2.5}$[c]	-0.67 (-1.44, 0.10)	-0.95 (-1.86, -0.05)
7-day mean $PM_{2.5}$[d]	-0.76 (-1.61, 0.09)	-1.11 (-2.12, -0.09)
21-day mean $PM_{2.5}$[e]	-0.90 (-1.90, 0.10)	-1.70 (-2.98, -0.41)
Diastolic blood pressure		
Same-day $PM_{2.5}$[b]	-0.07 (-0.56, 0.41)	-0.16 (-0.68, 0.36)
3-day mean $PM_{2.5}$[c]	-0.23 (-0.87, 0.42)	-0.44 (-1.20, 0.30)
7-day mean $PM_{2.5}$[d]	-0.07 (-0.80, 0.65)	-0.27 (-1.13, 0.59)
21-day mean $PM_{2.5}$[e]	0.05 (-0.80, 0.89)	-0.24 (-1.33, 0.84)

N=344 measurements for retinal vessel diameter analyses, N=432 measurements for blood pressure analyses. 5 $\mu g/m^3$ is the approximate interquartile range of $PM_{2.5}$

[a] Adjusted for 7-day mean temperature and humidity, body mass index-for-age z-score on the day of the retinal image, sex, age (years), maternal education (high school or less vs. community/technical college vs. university), and time of day of outcome assessment (≤11:00 AM vs. >11:00 AM).

[b] $PM_{2.5}$ on the day of the outcome assessment

[c] Mean $PM_{2.5}$ on the day of the outcome assessment and two preceding days

[d] Mean $PM_{2.5}$ on the day of the outcome assessment and 6 preceding days

[e] Mean $PM_{2.5}$ on the day of the outcome assessment and 20 preceding days

Table S3 Estimated change and 95% confidence interval in retinal blood vessel diameter (μm) and blood pressure (mm Hg) associated with 10 ppb increase in O_x

	Crude	Adjusted[a]
Retinal Blood Vessel Diameter		
Central retinal arteriolar diameter		
Same-day O_x[b]	-1.10 (-2.48, 0.28)	-1.78 (-3.27, -0.28)
3-day mean O_x[c]	-0.97 (-2.66, 0.72)	-1.99 (-3.92, -0.05)
7-day mean O_x[d]	-1.59 (-3.41, 0.22)	-2.63 (-4.63, -0.63)
21-day mean O_x[e]	-1.88 (-3.93, 0.17)	-2.56 (-4.71, -0.41)
Central retinal venular diameter		
Same-day O_x[b]	-0.44 (-2.05, 1.16)	-0.38 (-2.10, 1.34)
3-day mean O_x[c]	-0.83 (-2.80, 1.13)	-0.83 (-3.04, 1.38)
7-day mean O_x[d]	-0.47 (-2.60, 1.66)	-0.63 (-2.94, 1.67)
21-day mean O_x[e]	-0.64 (-3.08, 1.79)	-0.74 (-3.21, 1.74)
Blood Pressure		
Systolic blood pressure		
Same-day O_x[b]	0.74 (-0.28, 1.77)	0.39 (-0.78, 1.58)
3-day mean O_x[c]	1.31 (0.10, 2.51)	1.13 (-0.37, 2.64)
7-day mean O_x[d]	1.51 (0.24, 2.78)	1.23 (-0.33, 2.79)
21-day mean O_x[e]	1.81 (0.39, 3.22)	1.59 (-0.06, 3.25)
Diastolic blood pressure		
Same-day O_x[b]	-0.26 (-1.10, 0.59)	-0.23 (-1.19, 0.72)
3-day mean O_x[c]	-0.16 (-1.16, 0.85)	-0.06 (-1.28, 1.16)
7-day mean O_x[d]	0.06 (-1.03, 1.14)	0.16 (-1.13, 1.45)
21-day mean O_x[e]	0.28 (-0.95, 1.52)	0.45 (-0.95, 1.85)

N=344 measurements for retinal vessel diameter analyses, N=432 measurements for blood pressure analyses. 10 ppb is the approximate interquartile range of O_x

[a] Adjusted for 7-day mean temperature and humidity, body mass index-for-age z-score on the day of the retinal image, sex, age (years), maternal education (high school or less vs. community/technical college vs. university), and time of day of outcome assessment (≤11:00 AM vs. >11:00 AM).

[b] O_x on the day of the outcome assessment

[c] Mean O_x on the day of the outcome assessment and two preceding days

[d] Mean O_x on the day of the outcome assessment and 6 preceding days

[e] Mean O_x on the day of the outcome assessment and 20 preceding days

Table S4 Estimated change and 95% confidence interval in retinal blood vessel diameter (μm) and blood pressure (mm Hg) associated with 5 $\mu g/m^3$ increase in $PM_{2.5}$, excluding days in which $PM_{2.5}$ was imputed

	N	Crude	Adjusted[a]
Retinal Blood Vessel Diameter			
Central retinal arteriolar equivalent			
Same-day $PM_{2.5}$[b]	276	-0.17 (-1.08, 0.74)	0.03 (-0.93, 0.99)
3-day mean $PM_{2.5}$[c]	268	0.02 (-1.26, 1.30)	0.45 (0.98, 1.89)
7-day mean $PM_{2.5}$[d]	254	0.46 (-0.94, 1.85)	0.97 (-0.62, 2.56)
21-day mean $PM_{2.5}$[e]	231	0.71 (-0.86, 2.29)	1.81 (-0.14, 3.76)
Central retinal venular equivalent			
Same-day $PM_{2.5}$[b]	276	0.31 (-0.72, 1.35)	0.13 (-0.92, 1.19)
3-day mean $PM_{2.5}$[c]	268	0.82 (-0.73, 2.36)	0.88 (-0.81, 2.57)
7-day mean $PM_{2.5}$[d]	254	0.82 (-1.01, 2.65)	1.00 (-1.06, 3.05)
21-day mean $PM_{2.5}$[e]	231	0.64 (-1.43, 2.72)	1.09 (-1.50, 3.67)
Blood Pressure			
Systolic blood pressure			
Same-day $PM_{2.5}$[b]	357	-0.17 (-0.79, 0.45)	-0.13 (-0.81, 0.54)
3-day mean $PM_{2.5}$[c]	349	-0.55 (-1.37, 0.26)	-0.73 (-1.69, 0.24)
7-day mean $PM_{2.5}$[d]	334	-0.71 (-1.63, 0.21)	-1.03 (-2.18, 0.11)
21-day mean $PM_{2.5}$[e]	313	-0.82 (-1.90, 0.26)	-1.43 (-2.87, 0.00)
Diastolic blood pressure			
Same-day $PM_{2.5}$[b]	357	-0.11 (-0.60, 0.38)	-0.22 (-0.75, 0.30)
3-day mean $PM_{2.5}$[c]	349	-0.21 (-0.86, 0.44)	-0.46 (-1.22, 0.31)
7-day mean $PM_{2.5}$[d]	334	-0.12 (-0.86, 0.61)	-0.45 (-1.36, 0.46)
21-day mean $PM_{2.5}$[e]	313	0.06 (-0.80, 0.92)	-0.23 (-1.39, 0.92)

5 $\mu g/m^3$ is the approximate interquartile range of $PM_{2.5}$

[a] Adjusted for 7-day mean temperature and humidity, body mass index-for-age z-score on the day of the retinal image, sex, age (years), maternal education (high school or less vs. community/technical college vs. university), and time of day of outcome assessment (≤11:00 AM vs. >11:00 AM).

[b] $PM_{2.5}$ on the day of the outcome assessment

[c] Mean $PM_{2.5}$ on the day of the outcome assessment and two preceding days

[d] Mean $PM_{2.5}$ on the day of the outcome assessment and 6 preceding days

[e] Mean $PM_{2.5}$ on the day of the outcome assessment and 20 preceding days

Table S5 Estimated change and 95% confidence interval in retinal blood vessel diameter (μm) and blood pressure (mm Hg) associated with 15 ppb increase in O_3

	Crude	Adjusted[a]
Retinal Blood Vessel Diameter		
Central retinal arteriolar diameter		
Same-day O_3[b]	-1.02 (-2.31, 0.27)	-1.61 (-3.01, -0.21)
3-day mean O_3[c]	-0.94 (-2.54, 0.66)	-1.89 (-3.74, -0.05)
7-day mean O_3[d]	-1.61 (-3.33, 0.12)	-2.57 (-4.48, -0.66)
21-day mean O_3[e]	-1.83 (-3.80, 0.14)	-2.45 (-4.53, -0.38)
Central retinal venular diameter		
Same-day O_3[b]	-0.54 (-2.04, 0.96)	-0.45 (-2.05, 1.16)
3-day mean O_3[c]	-0.92 (-2.78, 0.94)	-0.87 (-2.98, 1.24)
7-day mean O_3[d]	-0.60 (-2.63, 1.43)	-0.65 (-2.85, 1.55)
21-day mean O_3[e]	-0.76 (-3.10, 1.57)	-0.74 (-3.12, 1.64)
Blood Pressure		
Systolic blood pressure		
Same-day O_3[b]	0.65 (-0.32, 1.61)	0.35 (-0.76, 1.46)
3-day mean O_3[c]	1.22 (0.07, 2.36)	1.13 (-0.31, 2.58)
7-day mean O_3[d]	1.40 (0.18, 2.61)	1.19 (-0.32, 2.70)
21-day mean O_3[e]	1.71 (0.34, 3.07)	1.59 (-0.02, 3.19)
Diastolic blood pressure		
Same-day O_3[b]	-0.25 (-1.05, 0.54)	-0.24 (-1.13, 0.66)
3-day mean O_3[c]	-0.16 (-1.11, 0.79)	-0.06 (-1.23, 1.11)
7-day mean O_3[d]	0.03 (-1.00, 1.07)	0.15 (-1.10, 1.39)
21-day mean O_3[e]	0.24 (-0.94, 1.43)	0.42 (-0.94, 1.79)

N=344 measurements for retinal vessel diameter analyses, N=432 measurements for blood pressure analyses. 15 ppb is the approximate interquartile range of O_3

[a] Adjusted for 7-day mean temperature and humidity, body mass index-for-age z-score on the day of the retinal image, sex, age (years), maternal education (high school or less vs. community/technical college vs. university), and time of day of outcome assessment (≤11:00 AM vs. >11:00 AM).

[b] O_3 on the day of the outcome assessment

[c] Mean O_3 on the day of the outcome assessment and two preceding days

[d] Mean O_3 on the day of the outcome assessment and 6 preceding days

[e] Mean O_3 on the day of the outcome assessment and 20 preceding days

Table S6 Estimated change and 95% confidence interval in retinal blood vessel diameter (μm) and blood pressure (mm Hg) associated with 2 ppb increase in NO_2

	Crude	Adjusted[a]
Retinal Blood Vessel Diameter		
Central retinal arteriolar diameter		
Same-day NO_2[b]	0.34 (-0.56, 1.25)	0.37 (-0.71, 1.44)
3-day mean NO_2[c]	0.53 (-0.63, 1.70)	0.94 (-0.88, 2.77)
7-day mean NO_2[d]	1.17 (-0.11, 2.45)	2.80 (0.58, 5.02)
21-day mean NO_2[e]	0.77 (-0.81, 2.34)	1.40 (-1.31, 4.11)
Central retinal venular diameter		
Same-day NO_2[b]	1.08 (0.04, 2.13)	0.99 (-0.22, 2.21)
3-day mean NO_2[c]	1.29 (-0.06, 2.64)	1.48 (-0.60, 3.56)
7-day mean NO_2[d]	1.33 (-0.16, 2.83)	1.37 (-1.19, 3.93)
21-day mean NO_2[e]	1.47 (-0.36, 3.30)	1.23 (-1.87, 4.33)
Blood Pressure		
Systolic blood pressure		
Same-day NO_2[b]	0.08 (-0.56, 0.73)	0.04 (-0.76, 0.84)
3-day mean NO_2[c]	-0.21 (-1.03, 0.61)	-0.97 (-2.29, 0.34)
7-day mean NO_2[d]	0.06 (-0.89, 1.02)	-0.46 (-2.15, 1.22)
21-day mean NO_2[e]	-0.12 (-1.26, 1.02)	-1.36 (-3.33, 0.60)
Diastolic blood pressure		
Same-day NO_2[b]	0.18 (-0.35, 0.70)	0.20 (-0.44, 0.85)
3-day mean NO_2[c]	0.14 (-0.54, 0.83)	0.07 (-1.00, 1.13)
7-day mean NO_2[d]	0.15 (-0.65, 0.94)	0.05 (-1.33, 1.43)
21-day mean NO_2[e]	0.20 (-0.75, 1.15)	0.07 (-1.52, 1.66)

N=344 measurements for retinal vessel diameter analyses, N=432 measurements for blood pressure analyses. 2 ppb is the approximate interquartile range of NO_2

[a] Adjusted for 7-day mean temperature and humidity, body mass index-for-age z-score on the day of the retinal image, sex, age (years), maternal education (high school or less vs. community/technical college vs. university), and time of day of outcome assessment (≤11:00 AM vs. >11:00 AM).

[b] NO_2 on the day of the outcome assessment

[c] Mean NO_2 on the day of the outcome assessment and two preceding days

[d] Mean NO_2 on the day of the outcome assessment and 6 preceding days

[e] Mean NO_2 on the day of the outcome assessment and 20 preceding days

Table S7 Estimated change and 95% confidence interval in retinal blood vessel diameter (μm) and blood pressure (mm Hg) associated with 5 $\mu g/m^3$ increase in $PM_{2.5}$, in models additionally adjusted for season

	Adjusted[a]
Retinal Blood Vessel Diameter	
Central retinal arteriolar diameter	
Same-day $PM_{2.5}$[b]	0.05 (-0.92, 1.01)
3-day mean $PM_{2.5}$[c]	0.56 (-1.13, 2.26)
7-day mean $PM_{2.5}$[d]	1.33 (-0.40, 3.06)
21-day mean $PM_{2.5}$[e]	1.95 (-0.26, 4.15)
Central retinal venular diameter	
Same-day $PM_{2.5}$[b]	0.35 (-0.74, 1.44)
3-day mean $PM_{2.5}$[c]	1.53 (-0.40, 3.46)
7-day mean $PM_{2.5}$[d]	0.12 (-1.87, 2.11)
21-day mean $PM_{2.5}$[e]	0.41 (-2.13, 2.94)
Blood Pressure	
Systolic blood pressure	
Same-day $PM_{2.5}$[b]	0.04 (-0.64, 0.72)
3-day mean $PM_{2.5}$[c]	-0.84 (-1.86, 0.19)
7-day mean $PM_{2.5}$[d]	-0.95 (-2.11, 0.16)
21-day mean $PM_{2.5}$[e]	-1.62 (-3.03, -0.20)
Diastolic blood pressure	
Same-day $PM_{2.5}$[b]	-0.14 (-0.69, 0.41)
3-day mean $PM_{2.5}$[c]	-0.45 (-1.30, 0.39)
7-day mean $PM_{2.5}$[d]	-0.22 (-1.17, 0.72)
21-day mean $PM_{2.5}$[e]	-0.23 (-1.40, 0.94)

N=344 measurements for retinal vessel diameter analyses, N=432 measurements for blood pressure analyses. 5 $\mu g/m^3$ is the approximate interquartile range of $PM_{2.5}$

[a] Adjusted for 7-day mean temperature and humidity, body mass index-for-age z-score on the day of the retinal image, sex, age (years), maternal education (high school or less vs. community/technical college vs. university), and time of day of outcome assessment (≤11:00 AM vs. >11:00 AM), and season (September-November/December-February/March-May/June).

[b] $PM_{2.5}$ on the day of the outcome assessment

[c] Mean $PM_{2.5}$ on the day of the outcome assessment and two preceding days

[d] Mean $PM_{2.5}$ on the day of the outcome assessment and 6 preceding days

[e] Mean $PM_{2.5}$ on the day of the outcome assessment and 20 preceding days

Table S8 Estimated change and 95% confidence interval in retinal blood vessel diameter (μm) and blood pressure (mm Hg) associated with 10 ppb increase in O_x, in models additionally adjusted for season

	Adjusted[a]
Retinal Blood Vessel Diameter	
Central retinal arteriolar diameter	
Same-day O_x[b]	-2.05 (-3.71, -0.38)
3-day mean O_x[c]	-2.38 (-4.56, -0.20)
7-day mean O_x[d]	-3.58 (-5.94, -1.22)
21-day mean O_x[e]	-4.87 (-7.78, -1.96)
Central retinal venular diameter	
Same-day O_x[b]	-0.15 (-2.06, 1.76)
3-day mean O_x[c]	-0.53 (-3.02, 1.96)
7-day mean O_x[d]	-0.33 (-3.04, 2.39)
21-day mean O_x[e]	-0.83 (-4.19, 2.53)
Blood Pressure	
Systolic blood pressure	
Same-day O_x[b]	0.12 (-1.20, 1.44)
3-day mean O_x[c]	0.90 (-0.80, 2.60)
7-day mean O_x[d]	0.95 (-0.92, 2.81)
21-day mean O_x[e]	1.59 (-0.73, 3.91)
Diastolic blood pressure	
Same-day O_x[b]	-0.41 (-1.47, 0.65)
3-day mean O_x[c]	-0.22 (-1.58, 1.14)
7-day mean O_x[d]	0.03 (-1.48, 1.53)
21-day mean O_x[e]	0.49 (-1.40, 2.37)

N=344 measurements for retinal vessel diameter analyses, N=432 measurements for blood pressure analyses. 10 ppb is the approximate interquartile range of O_x

[a] Adjusted for 7-day mean temperature and humidity, body mass index-for-age z-score on the day of the retinal image, sex, age (years), maternal education (high school or less vs. community/technical college vs. university), and time of day of outcome assessment (≤11:00 AM vs. >11:00 AM), and season (September-November/December-February/March-May/June).

[b] O_x on the day of the outcome assessment

[c] Mean O_x on the day of the outcome assessment and two preceding days

[d] Mean O_x on the day of the outcome assessment and 6 preceding days

[e] Mean O_x on the day of the outcome assessment and 20 preceding days

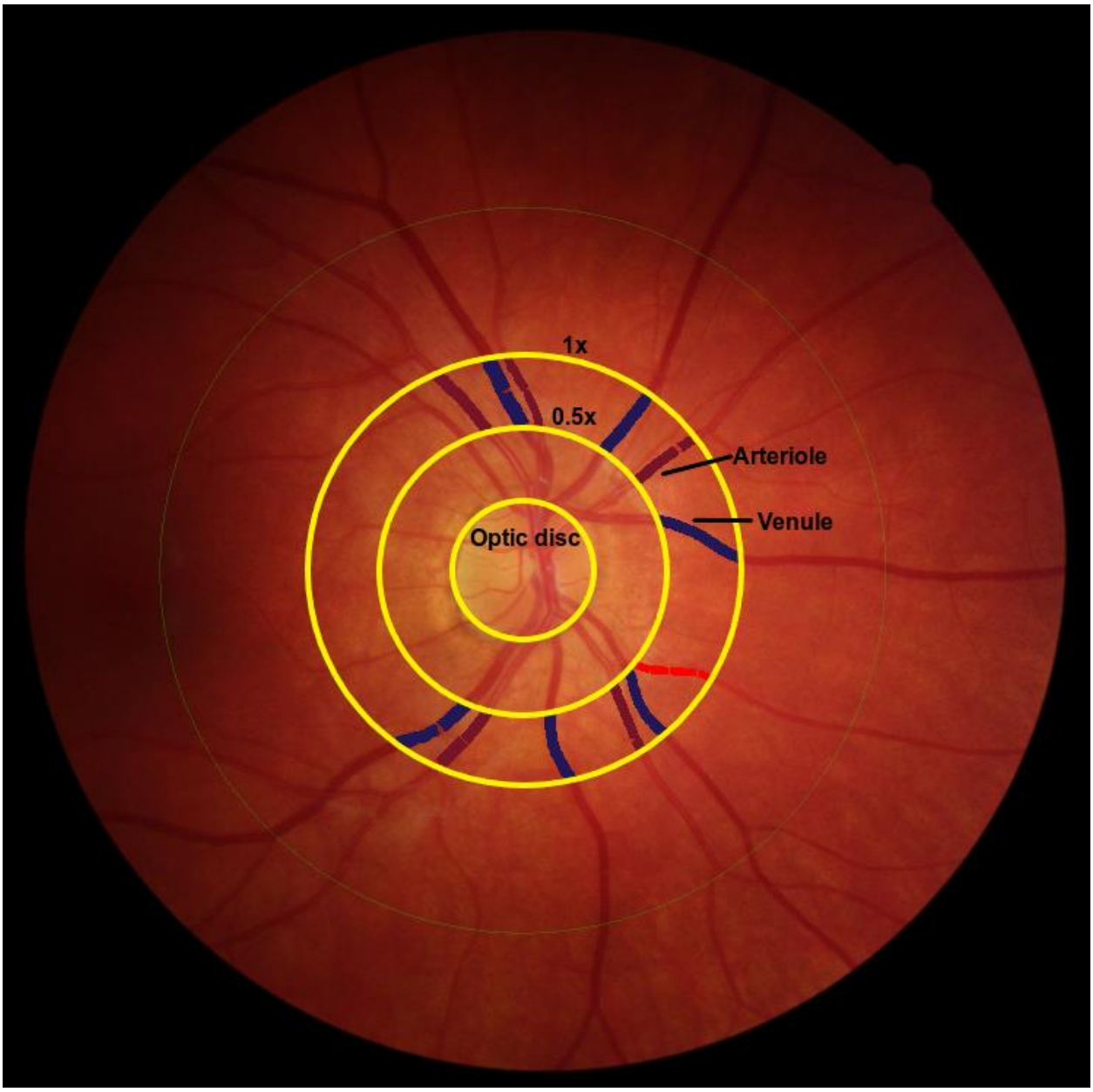

Figure S1 Central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) calculated within an area equal to 0.5-1 times the disc diameter from the optic disc margin. Arterioles are identified in red and venules in blue.

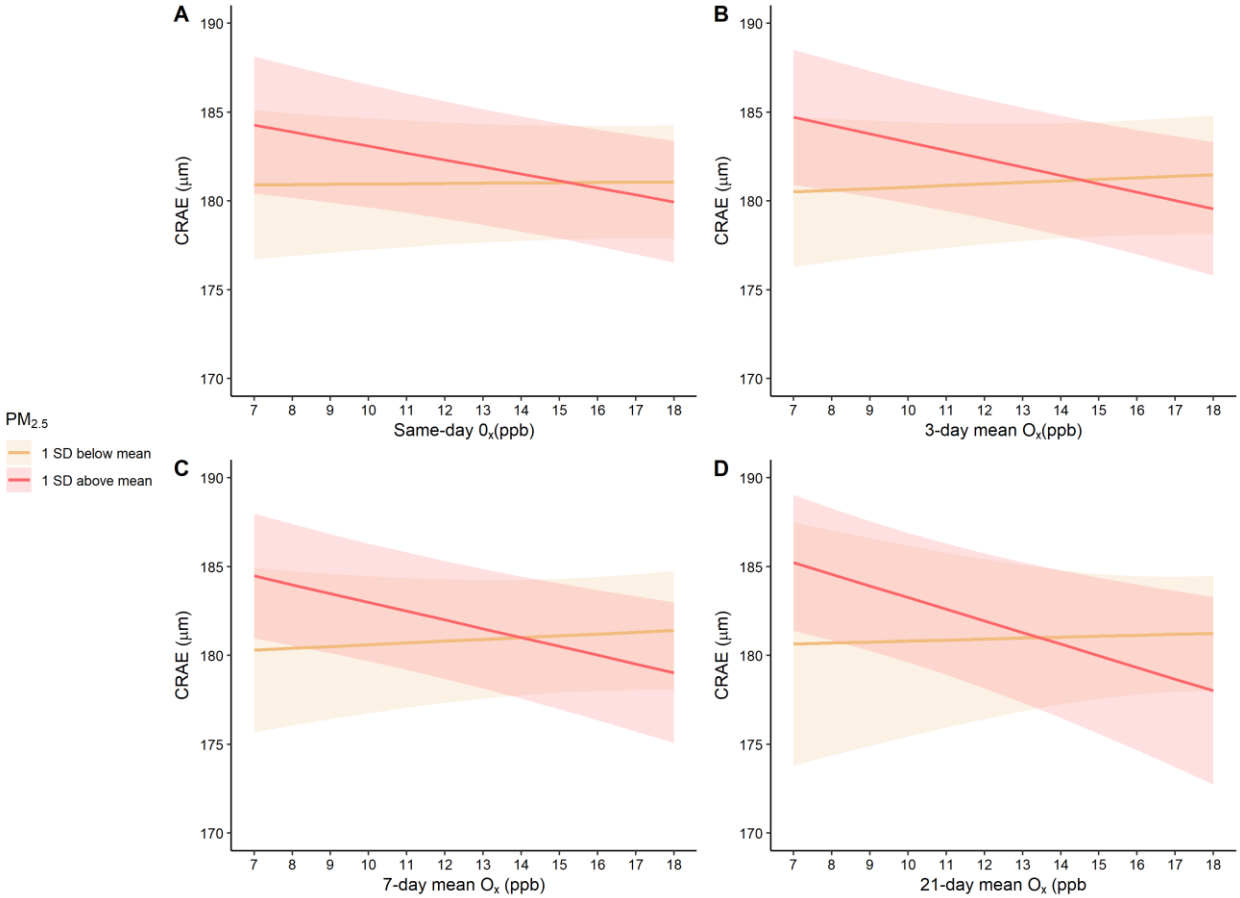

Figure S2 Predicted values and 95% CIs for central retinal arteriolar equivalent (CRAE) at different concentrations of O_x (7-18 ppb), stratified by $PM_{2.5}$ (1 standard deviation below and above mean $PM_{2.5}$ concentrations). Plots correspond to (A): Same-day exposure lag; (B): 3-day mean exposure lag; (C): 7-day mean exposure lag; (D): 21-day mean exposure lag.

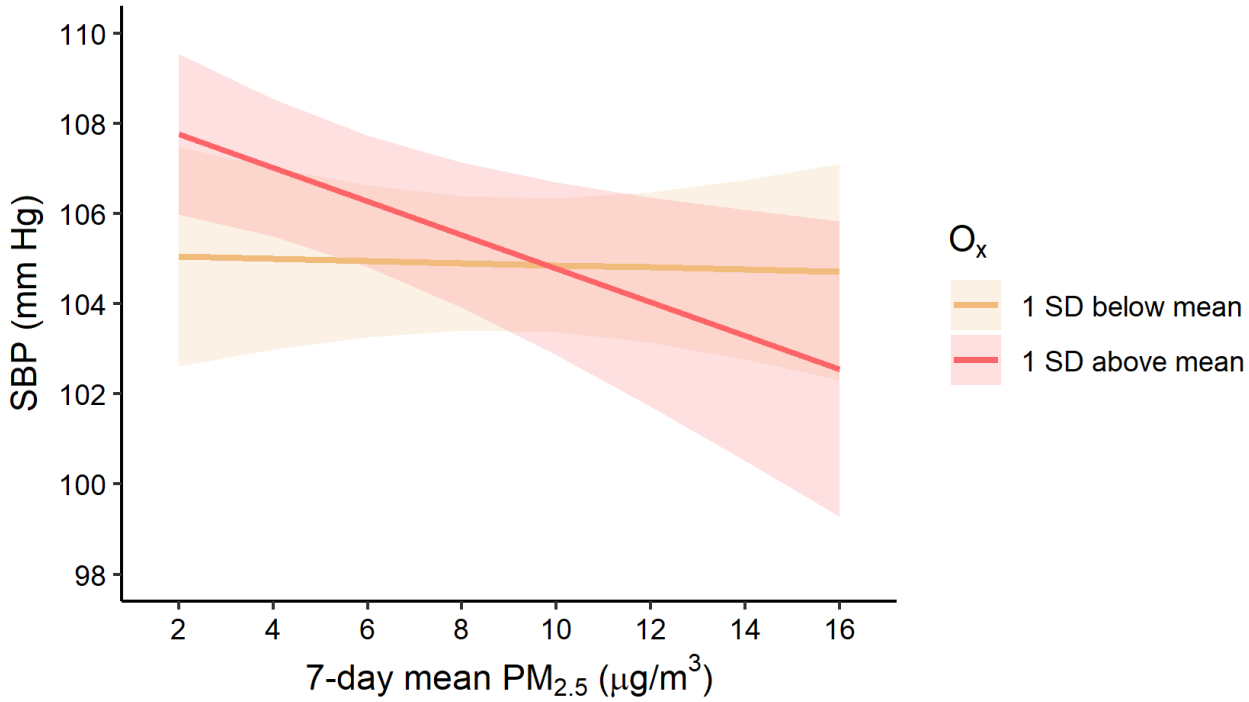

Figure S3 Predicted values and 95% CIs for systolic blood pressure at different concentrations of 7-day mean $PM_{2.5}$, stratified by 7-day mean O_x (1 standard deviation below and above 7-day mean O_x concentrations).

CHAPTER 4: Manuscript 2

4.1 Preface

While Manuscript 1 concentrates on a specific source of ambient air pollution (residential biomass burning) and child cardiovascular health in Canada, the second manuscript of this thesis focuses on acute respiratory effects of ambient air pollution among Canadian children. Here we investigate whether associations between short-term $PM_{2.5}$ or O_x and acute respiratory outcomes are modified by specific constituents in $PM_{2.5}$ (metals and sulfur) or particle oxidative potential. We address this question using a large case-crossover study of approximately 10,500 children from 34 cities in Canada, where daily estimates of ambient $PM_{2.5}$ mass and O_x concentrations were available, as well as city-specific monthly estimates of $PM_{2.5}$ constituents and oxidative potential metrics.

This manuscript was peer-reviewed and published in the *American Journal of Respiratory and Critical Care Medicine*.

Citation: Korsiak J, Lavigne E, You H, Pollitt K, Kulka R, Hatzopoulou M, Evans G, Burnett RT, Weichenthal S. Air Pollution and Pediatric Respiratory Hospitalizations: Effect Modification by Particle Constituents and Oxidative Potential. *American Journal of Respiratory and Critical Care Medicine* 2022; in press.

4.2 Air pollution and pediatric respiratory hospitalizations: effect modification by particle constituents and oxidative potential

Abstract

Rationale: Outdoor particulate and gaseous air pollutants impair respiratory health in children and these associations may be influenced by particle composition.

Objectives: To examine whether associations between short-term variations in fine particulate air pollution, oxidant gases, and respiratory hospitalizations in children are modified by particle constituents (metals, sulfur) or oxidative potential.

Methods: We conducted a case-crossover study of 10,500 children (0-17 years of age) across Canada. Daily fine particle mass concentrations and oxidant gases (nitrogen dioxide, ozone) were collected from ground monitors. Monthly estimates of fine particle constituents (metals, sulfur) and oxidative potential were also measured. Conditional logistic regression models were used to estimate associations between air pollutants and respiratory hospitalizations, above and below median values for particle constituents and oxidative potential.

Measurements and Main Results: Lag-1 fine particulate matter mass concentrations were not associated with respiratory hospitalizations (odds ratio and 95% confidence interval per 10 $\mu g/m^3$ increase in fine particulate matter: 1.004 [0.955, 1.056]) in analyses ignoring particle constituents and oxidative potential. However, when models were examined above/below median metals, sulfur, and oxidative potential, positive associations were observed above the median. For example, the odds ratio and 95% confidence interval per 10 $\mu g/m^3$ increase in fine particulate matter was 1.084 [1.007, 1.167] when copper was above the median, and 0.970 [0.929, 1.014] when copper was below the median. Similar trends were observed for oxidant gases.

Conclusions: Stronger associations were observed between outdoor fine particles, oxidant gases, and respiratory hospitalizations in children when metals, sulfur and particle oxidative potential were elevated.

Introduction

Exposure to ambient (outdoor) air pollution has a detrimental impact on respiratory health worldwide[9], and children are particularly vulnerable to the adverse impacts of air pollution[121]. Notably, exposure to ambient air pollution has been demonstrated to increase the risk of childhood asthma[135,176,177] and respiratory infections[139,178,179]. Gaseous and particulate pollutants, including ozone (O_3), nitrogen dioxide (NO_2), and fine particulate matter ($PM_{2.5}$), can impair respiratory health through the shared mechanism of inducing oxidative stress[8].

Although considerable evidence supports an impact of O_3, NO_2 and $PM_{2.5}$ on respiratory health, heterogeneity in health impacts have been observed[140,141]. When considering $PM_{2.5}$ exposure, spatial and temporal differences in $PM_{2.5}$ composition may explain variability in health effects[140]. Traditional mass-based measures of $PM_{2.5}$ treat all particles as equally toxic and do not account for differences in particle composition and toxicity, which is a limitation given that $PM_{2.5}$ is a mixture of harmful and relatively harmless constituents that vary in space and time. Measuring properties of $PM_{2.5}$ beyond mass concentration may help identify what specific sources/components of $PM_{2.5}$ are most harmful to health and can help inform more efficient regulatory measures.

Transition metals present in $PM_{2.5}$ are known to cause oxidative stress[180], so it is plausible that $PM_{2.5}$ mass concentration may be more strongly associated with adverse health outcomes when the metal content in $PM_{2.5}$ is higher. Similarly, sulfate, another common constituent found in $PM_{2.5}$, may influence the toxicity of particles because it facilitates the dissolution of metals, and metal solubility is an important determinant of particle oxidative potential[50]. Additionally, metrics of particle oxidative potential, which can be measured through several a-cellular assays including the ascorbic acid (OP^{AA}), glutathione (OP^{GSH}) and

dithiothreitol (OP^{DTT}) assay, may also be useful to incorporate into epidemiological air pollution studies. Recently, studies of adverse birth outcomes[181] and acute cardiovascular[15] and respiratory[63] events found the health impacts of $PM_{2.5}$ were stronger when OP^{GSH} was higher[15,63,181].

Regarding oxidant gases, co-exposure to other pollutants has been hypothesized as a possible source of heterogeneity in observed health impacts[141], but to our knowledge no studies have explored whether $PM_{2.5}$ constituents or particle oxidative potential modify the acute health effects of oxidant gases. It is plausible that the health impacts of oxidant gases may be greater when individuals are simultaneously exposed to particles that are more likely to cause oxidative stress, such as when the metal or sulfate content is high or when measures of particle oxidative potential are greater.

In this case-crossover study across 34 cities in Canada, we investigate whether associations between short-term outdoor $PM_{2.5}$ mass concentrations or oxidant gases and acute respiratory outcomes in children are modified by $PM_{2.5}$ metal and sulfur content (as a proxy for sulfate) or oxidative potential.

Methods

Study design and population

This is a time-stratified case-crossover study design[182,183] across 34 Canadian cities (listed in the Supplementary Material). This data source has been used for a different study investigating associations between $PM_{2.5}$ and acute cardiovascular events in adults[15] and there is no overlap with the results reported in this manuscript. Cases include children 0-17 years of age hospitalized from June 2016-December 2017 with a discharge diagnosis of any respiratory

disease identified using the International Classification of Disease-10th revision codes (ICD J00-J99), and who lived within 5 km of a daily air pollutant monitoring site. The study was restricted to this time period because monthly estimates of $PM_{2.5}$ constituents and metals (described below) were only measured during this time. For all provinces and territories except Quebec, cases were identified using the Discharge Abstract Database (DAD) maintained by the Canadian Institute for Health Information, while hospitalization information for Quebec were obtained from the Quebec Ministry of Health and Social Services through MED-ÉCHO. Patient sex, age and 6-digit residential postal code at the time of hospital admissions were also obtained through these data sources.

With the time-stratified case-crossover design, referent periods are selected on the same day of the week as the emergency department visit during that month and year[182] (see the Supplementary Material for additional details of this study design). Ethics approval for this study was obtained through a data sharing agreement between Health Canada and the Canadian Institute for Health Information.

Daily air pollution and meteorological data

The primary exposures were daily mean outdoor $PM_{2.5}$ mass concentration ($\mu g/m^3$), and the redox-weighted oxidant capacity of outdoor NO_2 and O_3 (O_x, ppb). O_x was calculated as a weighted average of NO_2 and O_3, with weights equivalent to the respective redox potentials using the formula $O_x=[(1.07\times NO_2) + (2.075 \times O_3)]/3.145)$[44,154]. Concentrations of daily air pollutants were obtained from fixed-site monitoring stations operated by the National Air Pollution Surveillance network maintained by Environment Canada. Daily mean temperature data (°C) were obtained from the closest weather stations operated by Environment and Climate Change Canada.

Monthly estimates of $PM_{2.5}$ metals and sulfur content, and particle oxidative potential

Integrated two-week $PM_{2.5}$ samples were collected at each study location each month between June 2016-December 2017. Gravimetric analyses were first performed, then the $PM_{2.5}$ filters were analysed for monthly estimates of sulfur (S) and transition metal content and oxidative potential. We *a prior* included copper (Cu), iron (Fe), nickel (Ni), manganese (Mn) and zinc (Zn) in our analyses because previous evidence suggests these metals are most strongly associated with particle oxidative potential[47,50]. Monthly estimates of sulfur and transition metals were expressed as mass proportions of $PM_{2.5}$ (i.e., Mass proportion= $\left(\frac{metal\ or\ sulfur\ mass}{2-week\ integrated\ PM_{2.5} mass}\right) x\ 100$). Three metrics of particle oxidative potential were measured: ascorbate (OP^{AA}), glutathione (OP^{GSH}), and dithiothreitol (OP^{DTT}) oxidative potential. All oxidative potential values are expressed in the units of pmol/min/μg. Therefore, each monitoring site each month was assigned an estimate of $PM_{2.5}$ metals and sulfur content and particle oxidative potential. Additional details on these methods are provided in the Supplementary Material.

Statistical analyses

Conditional logistic regression was used to estimate associations between lag-1 $PM_{2.5}$ or O_x and hospitalizations for respiratory diseases, where lag-1 refers to air pollution measured the day before a hospitalization. Models were adjusted for lag-1 temperature, and adjusted for each co-exposure (e.g., estimates for lag-1 O_x were adjusted for lag-1 $PM_{2.5}$ and visa versa). Our primary analysis considers lag-1 exposures because model fit (based on the minimum Akaike information criterion [AIC]) was better than other exposure lags, including lag-0 (same-day) and three-day mean (mean of lags 0-2) exposures (AICs presented in Table S1 of the Supplementary

Material). However, other exposure lags were considered in sensitivity analyses. A cluster variance estimator was used to account for within-city clustering.

To evaluate whether the associations between lag-1 $PM_{2.5}$ or O_x and respiratory hospitalizations were modified by monthly estimates of particle oxidative potential, metal or sulfur content, analyses were performed above and below the median level of metals, sulfur and particle oxidative potential. Said another way, we 1) calculated the median value of sulfur and metal content and particle oxidative potential from the monthly estimates available from each monitoring site, 2) labelled each month-site combination as above or below the median sulfur, metal or oxidative potential value, and 3) evaluated associations between lag-1 $PM_{2.5}$ or O_x and respiratory hospitalizations separately, by those who were above the median metal/sulfur/oxidative potential value vs. those who were below the median metal/sulfur/oxidative potential value. To formally test effect modification, we included an interaction term between lag-1 $PM_{2.5}$ or O_x and an indicator variable reflecting above/below the median metal/sulfur content or oxidative potential, and a p-value of <0.05 for the interaction term was used as evidence of effect modification (on the multiplicative scale). As additional sensitivity analyses, we explored whether findings were similar in the warm (May-September) and cold (October-April) seasons because seasonal trends in short-term air pollution health impacts are commonly observed[184–187] and particle toxicity/metal concentrations might vary by seasons[188], and performed the analyses separately by sex. All odds ratios (ORs) reflect a 10-unit increase in $PM_{2.5}$ or O_x. Additional details of the statistical analyses are included in the Supplementary Material.

Results

In total, 10,534 children were hospitalized for respiratory diseases. The median age was 5 years (interquartile range: 3-10 years), and there were more boys than girls (6,029 boys and 4,505 girls). Descriptive statistics for daily mean air pollutants ($PM_{2.5}$, NO_2, O_3, O_x), monthly estimates of $PM_{2.5}$ constituents (Cu, Fe, Ni, Mn, Zn, S) and particle oxidative potential (OP^{GSH}, OP^{AA}, OP^{DTT}) over the entire study duration are shown in Table 1. As expected in Canada, concentrations of daily air pollutants were low (mean ± standard deviation $PM_{2.5}$ ($\mu g/m^3$): 7.33 ± 6.38; NO_2 (ppb): 9.13 ± 6.33; O_3 (ppb): 22.76 ± 8.37; O_x (ppb): 18.12 ± 4.90). Descriptive statistics separated by the warm (May-September) and cold (October-April) seasons are shown in Table S2. There were several differences in $PM_{2.5}$ constituents and oxidative potential metrics between the warm and cold seasons; for example, Fe was considerably higher in the warm season than the cold season (median [IQR] Fe in the warm seasons: 105.2 [73.1- 164.1] ng/m^3: cold season: 67.9 [33.0- 111.2] ng/m^3). Distributions of mass proportions for Cu, Fe, Ni, Mn, Zn and S in monthly $PM_{2.5}$ are shown in Table S3, and the relationship between daily temperature and hospital admissions is shown in Figure S1.

Table 1: Descriptive statistics of daily and monthly air pollution data (July 2016-December 2017)

	Percentiles				
	5th	**25th**	**50th**	**75th**	**95th**
Daily air pollutants and temperature data					
$PM_{2.5}$ ($\mu g/m^3$)	1.9	3.9	6.1	9.0	16.6
O_3 (ppb)	8.9	17	22.5	28.7	36.3
NO_2 (ppb)	2.0	4.6	7.6	11.7	21.9
O_x (ppb)	10.3	14.8	18	21.5	26.2
Temperature (°C)	-16.6	-2.4	5.3	14.3	21.3
Monthly average data					
$PM_{2.5}$ ($\mu g/m^3$)	3.4	5.2	6.8	9	14.1
OP^{GSH} (pmol/min/μg)	1.1	2.1	3.1	4.3	7.6
OP^{AA} (pmol/min/μg)	1.5	2.2	2.8	3.5	4.7
OP^{DTT} (pmol/min/μg)	1.8	5.9	10.1	16.6	26.2
Cu (ng/m^3)	0.5	1	1.9	4.4	9.4
Fe (ng/m^3)	20.3	43.0	85.5	129.2	202.3
Ni (ng/m^3)	0.1	0.1	0.2	0.4	2.3
Mn (ng/m^3)	0.6	1.3	2.8	4.2	7.5
Zn (ng/m^3)	2.2	4.3	7.2	15.5	46.6
S (ng/m^3)	97.6	160.2	242.4	312.8	487.8

Note: $PM_{2.5}$, fine particulate matter; O_3, ozone; NO_2, nitrogen dioxide; O_x, weighted oxidant capacity of NO_2 and O_3; OP^{GSH}, glutathione oxidative potential; OP^{AA}, ascorbate oxidative potential; OP^{DTT}, dithiothreitol oxidative potential; Cu, copper; Fe, iron; Ni, nickel; Mn, manganese; Zn, zinc; S, sulfur

Figure 1 shows the correlation between monthly estimates of $PM_{2.5}$ mass, constituents and oxidative potential over the entire study duration. Constituents were positively correlated with one another: Spearman correlation coefficients ranged from 0.30 (between S and Fe) to 0.86 (between Mn and Fe). Relatively weak (positive and negative) correlations were observed between metals and particle oxidative potential, with the strongest correlation observed between Cu and OP^{GSH} (r=0.33). Correlations in the warm and cold season separately are shown in Figures S2 and S3 of the Supplementary Material. Correlations are generally similar in the warm and cold seasons, except for OP^{DTT}: in the warm season, weak positive correlations were observed between OP^{DTT} and constituents (r ranging from 0.21 to 0.33), while in the cold season, weak negative correlations were observed (r ranging from -0.20 to -0.09).

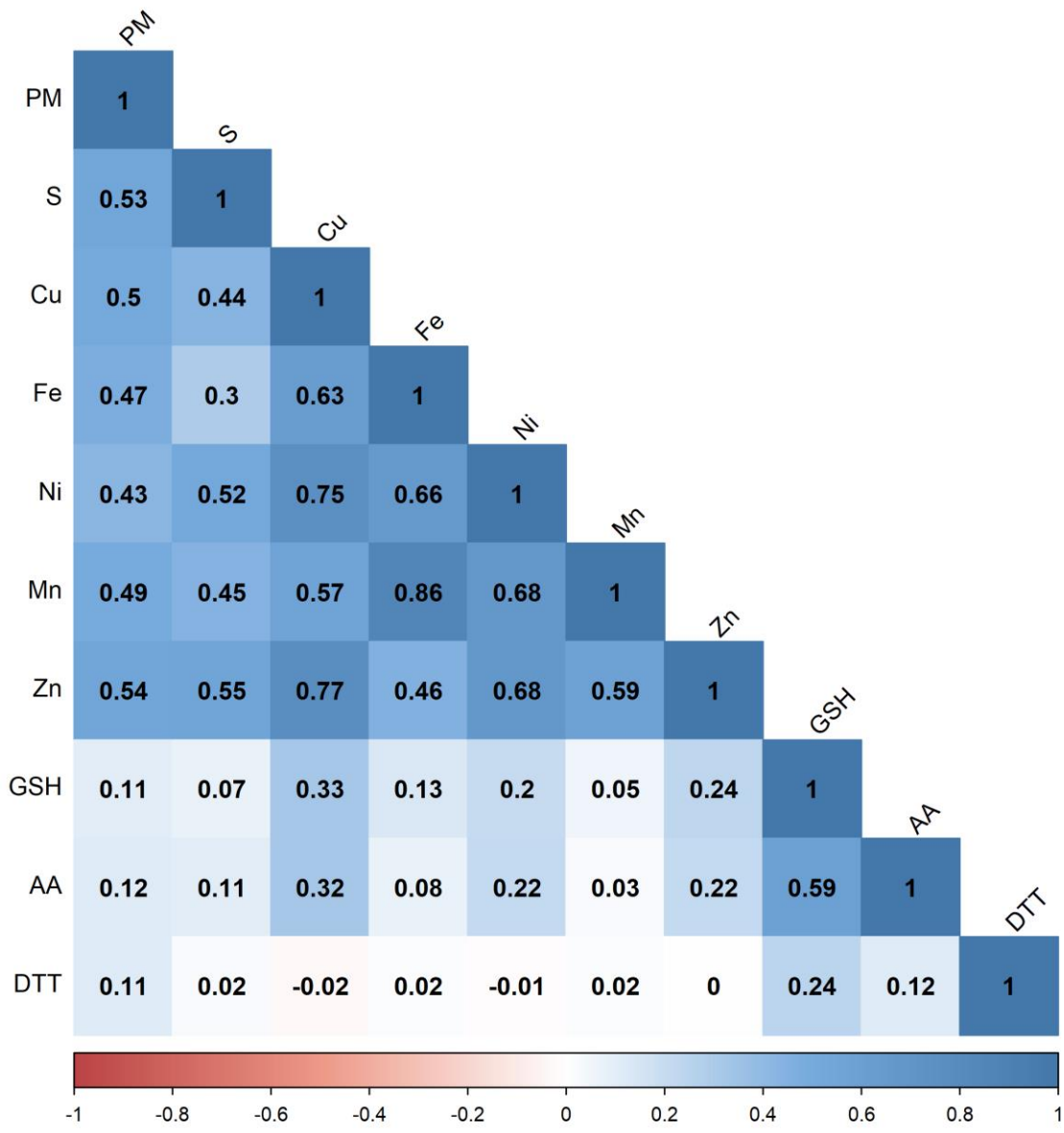

Figure 1 Spearman correlation coefficients between monthly mean $PM_{2.5}$ mass concentration (PM, μg/m^3), constituents (Cu, Fe, Ni, Mn, Zn, S, ng/m^3) and oxidative potential (OP^{GSH}, OP^{AA}, OP^{DTT}, pmol/min/μg) in Canada from 2016-2017

Associations between lag-1 $PM_{2.5}$ and respiratory hospitalizations are shown in Figure 2 and Table S4. Overall, lag-1 $PM_{2.5}$ was not associated with respiratory hospitalizations (OR and 95% confidence interval per 10 $\mu g/m^3$ increase in $PM_{2.5}$: 1.004 [0.955, 1.056]). However, when analyses were performed above and below median metals, S and oxidative potential, positive associations were observed and the 95% CIs excluded the null when Cu, Ni, Zn, and OP^{GSH} were above the median, while no clear associations were observed below the median. For example, the OR and 95% CI when Cu was above the median was 1.084 [1.007, 1.167], and 0.970 [0.929, 1.014] when Cu was below the median. When an interaction term between lag-1 $PM_{2.5}$ and an indicator variable for $PM_{2.5}$ constituents and oxidative potential metrics (above/below the median) were included in the models, p-values for the interaction terms were <0.05 for all metals and OP^{GSH}, indicating that metals and OP^{GSH} modified the associations between lag-1 $PM_{2.5}$ and respiratory hospitalizations (Table S4). No significant effect modification by S, OP^{AA} or OP^{DTT} was observed (interaction p-values between lag-1 $PM_{2.5}$ and S: 0.331; OP^{AA}: 0.435; and OP^{DTT}: 0.995).

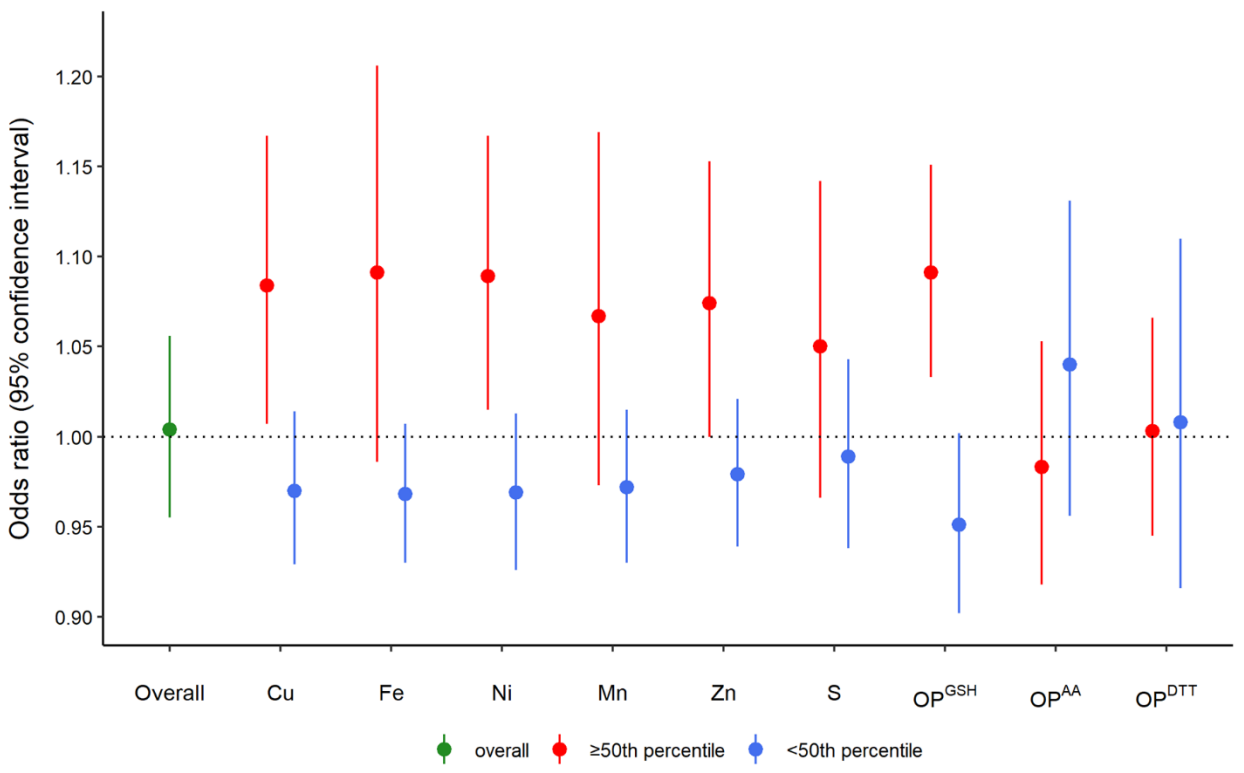

Figure 2 Odds ratios (95% confidence intervals) for associations between lag-1 $PM_{2.5}$ (per 10 $\mu g/m^3$) and respiratory hospitalizations in children, overall and across strata (above/below the median) of monthly particle constituents (Cu, Fe, Ni, Mn, Zn, S) and oxidative potential (OP^{GSH}, OP^{AA}, OP^{DTT})

Associations between lag-1 O_x and respiratory hospitalizations are shown in Figure 3 and Table S5. Overall, lag-1 O_x was positively associated with respiratory hospitalizations (OR and 95% CI per 10 ppb increase in O_x: 1.088 [1.005, 1.177]). When analyses were stratified above/below median constituents and oxidative potential, associations were stronger and the confidence intervals excluded the null when Cu, Fe, Ni, Zn, S and OP^{GSH} were above the median, while weaker associations were observed below the median. For example, the OR and 95% CI when Cu was above the median was 1.125 [1.028, 1.232], and 1.055 [0.962, 1.157] when Cu was below the median. For OP^{AA} and OP^{DTT}, associations were stronger and the 95% CIs excluded the null when OP^{AA} and OP^{DTT} were below the median, while no associations were observed above the median. When an interaction term between lag-1 O_x and an indicator variable for $PM_{2.5}$ constituents and oxidative potential metrics (above or below the median) were included in the models, significant effect modification was observed for OP^{AA} only (p-value for interaction term between lag-1 O_x and OP^{AA}: 0.015).

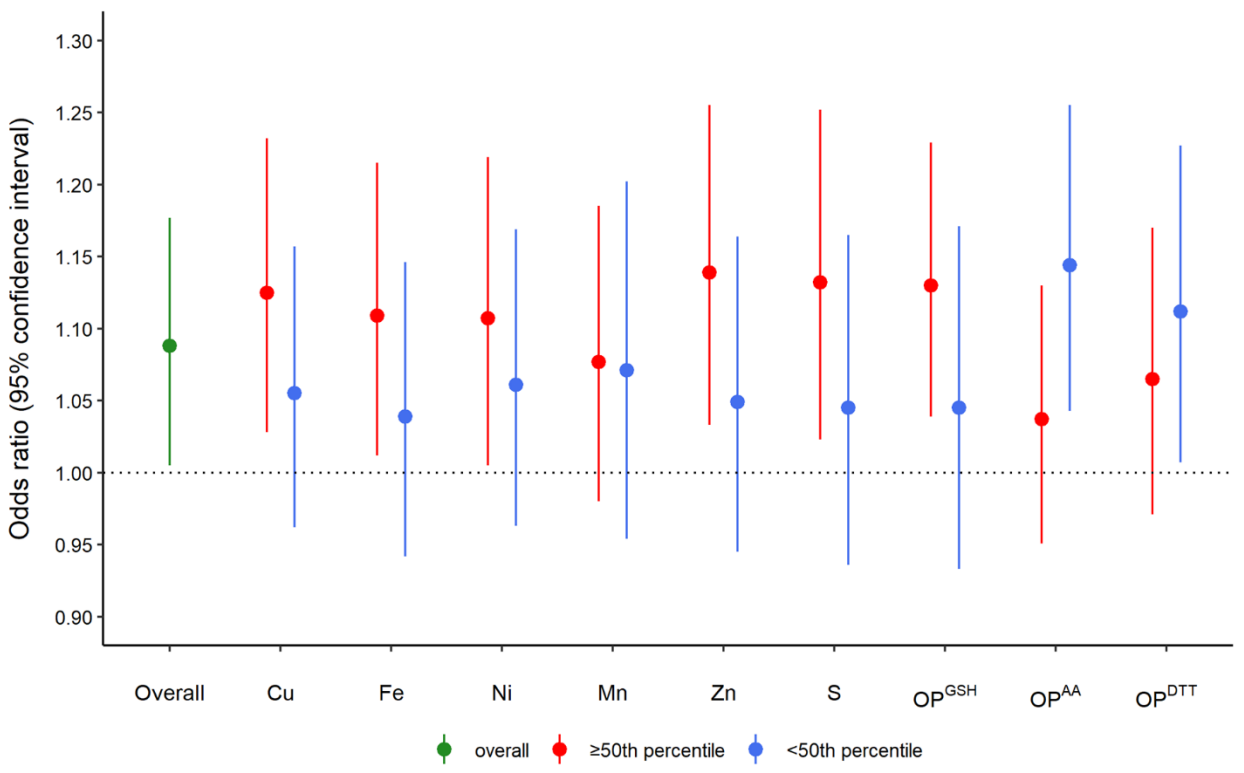

Figure 3 Odds ratios (95% confidence intervals) for associations between lag-1 O_x (per 10 ppb) and respiratory hospitalizations in children, overall and across strata (above/below the median) of monthly particle constituents (Cu, Fe, Ni, Mn, Zn, S) and oxidative potential (OP^{GSH}, OP^{AA}, OP^{DTT})

In the analyses performed in the warm and cold season separately, there were no overall associations between lag-1 $PM_{2.5}$ and respiratory hospitalizations (OR and 95% CI per 10 $\mu g/m^3$ increase in lag-1 $PM_{2.5}$ in the warm season: 1.003 [0.936, 1.075]; cold season: 1.039 [0.961, 1.123], Figure 4 and Table S6). However, effect modification by metals, S and oxidative potential was more pronounced in the warm season compared to the cold season. In the warm season, stronger associations were observed between lag-1 $PM_{2.5}$ and respiratory hospitalizations when all metals, S and OP^{GSH} were above the median compared to below the median (p-value for the interaction term between lag-1 $PM_{2.5}$ and metals, S and OP^{GSH} were <0.05). In the cold season, the strength of associations between lag-1 $PM_{2.5}$ and respiratory hospitalizations were still stronger when all metals and OP^{GSH} were above the median compared to below the median, but the confidence intervals around the estimated association included the null and no significant effect modification was observed. Moreover, S was not an important modifier in the cold season (OR and 95% CI when S is above the median: 1.032 [0.931, 1.146]; S below the median: 1.047 [0.949, 1.155]).

The OR and 95% CI per 10 ppb increase in O_x was 1.196 [1.075, 1.331] in the warm season and 1.112 [1.026, 1.206] in the cold season (Figure 4, Table S7). Due to the non-collapsibility of the odds ratio (i.e., when the overall OR does not equal a weighted average of subgroup ORs[189,190]), the estimated OR in both the warm and cold season are greater than the OR in all seasons combined. When the analyses were stratified by metals, S and oxidative potential in the warm season, stronger associations were observed when Ni and Zn were above the median compared to below the median (OR and 95% CI when Ni was above the median: 1.210 [1.078, 1.359]; Ni below the median: 1.152 [0.974, 1.363]; Zn above the median: 1.274 [1.091, 1.488], Zn below the median: 1.108 [0.972, 1.264]; p-value for interaction terms <0.05). In the cold

season, no significant effect modification by $PM_{2.5}$ constituents or oxidative potential were observed.

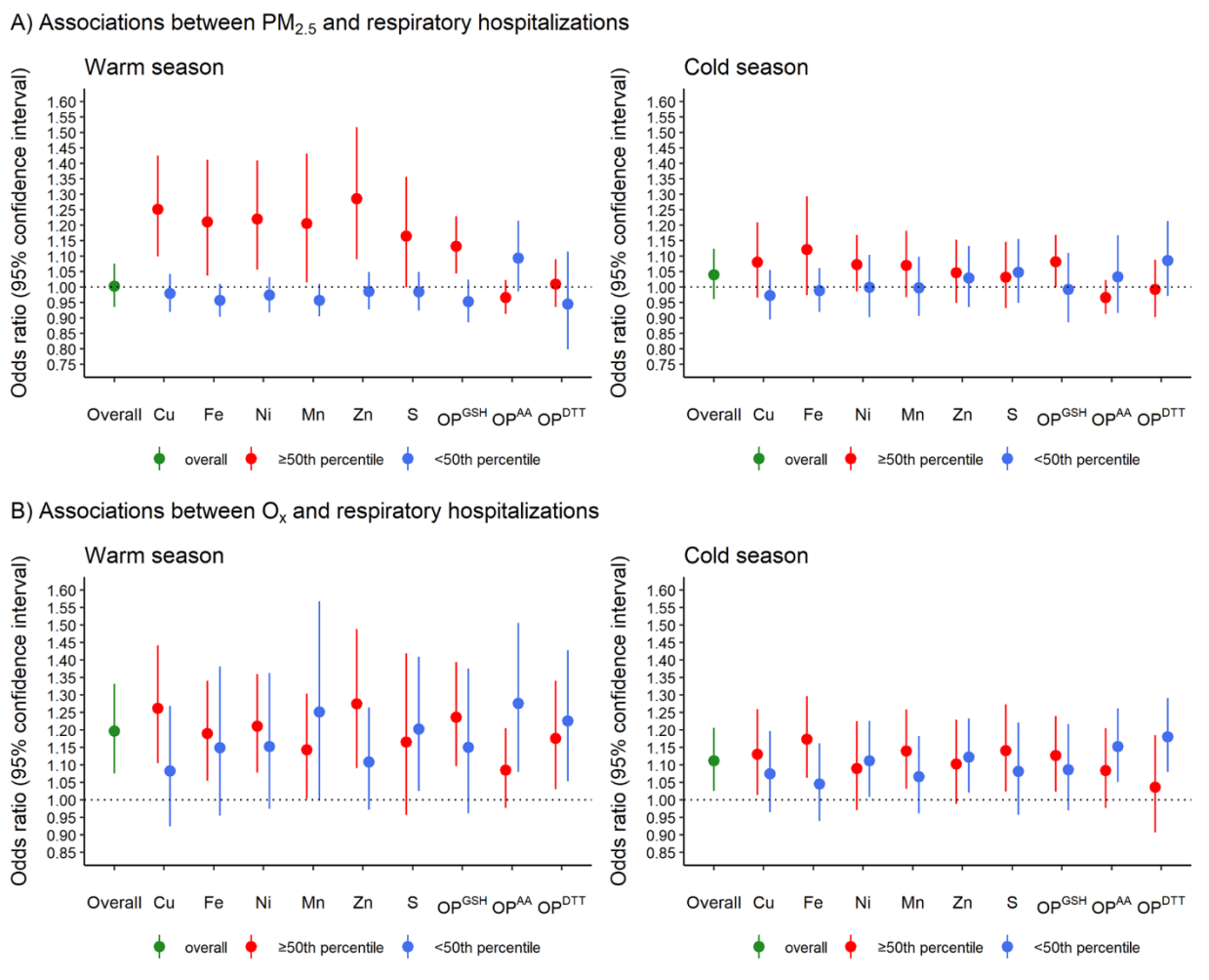

Figure 4 Odds ratios (95% confidence intervals) for associations between lag-1 A) $PM_{2.5}$ (per 10 $\mu g/m^3$), or B) O_x (per 10 ppb) and respiratory hospitalizations in children in the warm (May-September) and cold (October-April) seasons, overall and across strata (above/below the median) of monthly particle constituents (Cu, Fe, Ni, Mn, Zn, S) and oxidative potential (OP^{GSH}, OP^{AA}, OP^{DTT})

Sex-stratified analyses are presented in Tables S8 and S9. Effect modification by metals, S and oxidative potential for the associations between $PM_{2.5}$ and respiratory hospitalizations was more common among girls than boys (p-value <0.05 for the interaction term between lag-1 $PM_{2.5}$ and above/below median Cu, Fe, Ni, Mn and Zn among girls; <0.05 for Ni and OP^{GSH} among boys). No significant effect modification was observed for the associations between O_x and respiratory hospitalizations among boys or girls (Table S9).

Associations between lag-0 and 3-day mean exposures and respiratory hospitalizations are shown in Tables S10-S13 of the Supplementary Material. Generally, associations are slightly weaker and effect modification was less frequent, but overall, a similar pattern of stronger associations when $PM_{2.5}$ constituents or oxidative potential was above the median emerges (particularly for 3-day mean exposures, Tables S11 and S13).

Discussion

Although Canada has some of the cleanest air in the world[10,11], health impacts of air pollution are still observed[12,13]. Increasing evidence suggests that the health effects of $PM_{2.5}$ vary depending on the source and chemical composition of particles and traditional mass-based measures are unable to account for these potential differences in particle toxicity[20]. In this case-crossover study, we examined associations between short-term (lag-1) outdoor $PM_{2.5}$ mass concentrations and oxidant gas concentrations and respiratory hospitalizations in children across strata of monthly average $PM_{2.5}$ constituents and oxidative potential in a setting with remarkably low air pollution concentrations. Without accounting for spatial and temporal differences in particle oxidative potential, metals or sulfur, lag-1 $PM_{2.5}$ was not associated with respiratory hospitalizations. However, when the analyses were stratified by monthly estimates of particle oxidative potential, metals, and sulfur, lag-1 $PM_{2.5}$ was positively associated with respiratory

hospitalizations only when monthly average $PM_{2.5}$ metals/sulfur and oxidative potential were elevated. Similarly, stronger associations were also observed between lag-1 O_x and respiratory hospitalizations when monthly average $PM_{2.5}$ metals/sulfur and oxidative potential were higher, and effect modification was generally more pronounced in the warm months compared to the cold months.

A pertinent question from the results of this study is whether similar trends would emerge in highly polluted settings, or if effect modification by $PM_{2.5}$ constituents and oxidative potential is more important in low exposure settings. The answer to this question remains elusive because to our knowledge, no existing studies have investigated whether associations between ambient air pollution and adverse health outcomes are modified by $PM_{2.5}$ constituents/oxidative potential in highly polluted regions of the world, and this is an important gap in knowledge.

Our study supports previous evidence that found stronger associations between short-term $PM_{2.5}$ and respiratory hospitalizations when OP^{GSH} was higher[63]. However, an important strength of our current study compared to the previous study is that oxidative potential was measured prospectively on a monthly basis to account for temporal differences in oxidative potential[64], while previously only long-term estimates were available. Regardless, the findings from both studies support the idea that OP^{GSH} is an important modifier of $PM_{2.5}$ health effects and this finding has also been observed in studies of preterm birth[181] and acute cardiovascular events[15,154]. In addition to considering whether particle oxidative potential modifies $PM_{2.5}$ health effects, several studies have evaluated the direct associations between measures of particles oxidative potential and respiratory health outcomes. For example, two time-series study found that short-term OP^{DTT} was associated with emergency department visits for respiratory diseases[59,68], while another time-series study did not observe consistent associations between

OP^{AA} or OP^{GSH} and respiratory mortality[60]. In children specifically, long-term OP^{DTT} has been associated with an increased risk of asthma and rhinitis, and decreased lung function[61], and short-term OP^{GSH} (but not OP^{AA}) has been associated with airway inflammation[62].

Assays to measure oxidative potential are sensitive to different components of $PM_{2.5}$; for example, OP^{AA} and OP^{GSH} are sensitive to metal components, while OP^{DTT} is sensitive to metals as well as organic species from biomass burning[47]. Evidence of modification was more apparent by OP^{GSH} than OP^{AA} and OP^{DTT} in this study, and previous evidence suggests that OP^{GSH} and OP^{DTT} are most related with health outcomes[47]. However, there is currently no consensus as to which a-cellular test is the best, but instead it is recommended to use various assays to potentially provide complimentary information about particle toxicity[47,191].

Transition metals in $PM_{2.5}$ originate from a variety of different sources including coal and oil combustion, industrial emissions, traffic sources, and road dust resuspension[48]. Short-term exposure to metals in ambient particulate matter have previously been associated with respiratory health outcomes in children, including positive associations between Ni, Fe, barium, and vanadium and airway inflammation[53,54], and Zn, Cu, Fe and respiratory hospitalizations[55,56]. To our knowledge, no studies have specifically looked at whether metals modify the respiratory health impacts of $PM_{2.5}$ in children, but effect modification by metals for acute cardiovascular events in men has been observed[15].

We also observed stronger associations between $PM_{2.5}$ and respiratory hospitalizations when sulfur (used as a proxy for sulfate) was higher, although the 95% CI included the null. Sulfate itself is not particularly toxic, but sulfate increases aerosol acidity and facilitates metal dissolution, and soluble metals are more bioavailable than insoluble metals and more likely to cause to oxidative stress[48,50,192,193]. Therefore, when the sulfur content in $PM_{2.5}$ is higher, the

toxicity of $PM_{2.5}$ may be greater. Recently, we found stronger associations between $PM_{2.5}$ mass and cardiovascular hospitalizations in men when both sulfur and metals were elevated[15]. Although sample size constraints did not allow us to investigate whether the combined impact of sulfur and metals modified the associations between $PM_{2.5}$ and respiratory hospitalizations, it is possible that the slightly stronger association we observed when sulfur was elevated may be attributed to a higher fraction of soluble metals present in the $PM_{2.5}$.

There was some evidence of effect modification by metals, sulfur and oxidative potential for the associations between O_x and respiratory hospitalizations. Over the entire study duration, the strength of association between O_x and respiratory outcomes was stronger when metals, sulfur and OP^{GSH} were higher, but effect modification was only statistically significant in the warm season. To our knowledge, no other studies have investigated whether particle oxidative potential or $PM_{2.5}$ constituents modify associations between O_x and any health outcomes, but several studies of all-cause, cardiovascular and respiratory mortality have observed interactions between $PM_{2.5}$ mass concentration and oxidant gases[22,23]. Both gaseous and particulate air pollution contribute to the generation of reactive oxygen species and oxidative stress, so it is biologically plausible that the health impacts of O_x may be greater in regions/times when the composition of $PM_{2.5}$ has a greater capacity to cause oxidative stress.

Regarding more pronounced effect modification by particle constituents and oxidative potential in the warm season compared to the cold season, seasonal/temporal trends in short-term air pollution health impacts have been observed in many other studies[184–187], likely due to differences in particle composition between seasons. In this study, we observed differences in $PM_{2.5}$ constituents and oxidative potential between the warm and cold season. In addition, people also spend more time outside in the warm months so ambient air pollution exposure is a better

proxy for personal exposure than during the winter months, and statistical power to detect significant effect modification is improved when exposure measurement error is minimized.

An important implication of our findings suggesting the health impacts of O_x are greater when certain $PM_{2.5}$ constituents or oxidative potential are higher is that regulatory measures that target $PM_{2.5}$ constituents/oxidative potential may have considerable co-benefits in also reducing O_x health impacts, even if O_x remains unchanged. Ozone (a component of O_x) is challenging to regulate because unlike other air pollutants, ozone is not directly emitted but is formed when volatile organic compounds and nitrous oxides released from a wide range of sources (e.g., automobiles, oil and gas production, biomass burning, power plants, disinfectants, paints/paint strippers, aerosol sprays etc.) react with sunlight in the atmosphere. Moreover, because temperature is a strong driver of ozone formation, ozone is also expected to increase into the future with climate change[37] and may become increasingly difficult to regulate. Therefore, policies that target $PM_{2.5}$ constituents/oxidative potential may be efficient in reducing the health impacts of both $PM_{2.5}$ and O_x. However, as no other studies have investigated effect modification by $PM_{2.5}$ constituents or oxidative potential for the associations between O_x and respiratory hospitalizations, replication in other studies is needed to support these findings.

This study had a number of important strengths including prospective measures of monthly $PM_{2.5}$ constituents and oxidative potential metrics across Canada and the time-stratified case crossover design that prevents confounding by covariates that are time-invariant (e.g., sex) as well as some time-dependent covariates (day of week, season, year)[182]. However, several limitations should be mentioned. First, because metals were correlated and most followed the similar pattern of elevated risk at higher metal content, we are unable to identify which specific metals may be most harmful to health. In addition, we only looked at hospitalization admissions

(not emergency room visits) so only captured the more severe cases of respiratory conditions. Furthermore, Berkson-type exposure measurement error is present because true personal $PM_{2.5}$ or O_x exposures may differ from ambient concentrations, which would reduce the precision of the estimates[174]. In addition, monthly mean oxidative potential metrics and $PM_{2.5}$ constituents were based on two-week integrated samples, but it is possible that measurement error may be present if the two-week sample was not representative of the entire month. This could potentially lead to individuals being misclassified in respect to their assignment of above or below median monthly $PM_{2.5}$ constituents/oxidative potential, which would diminish the magnitude of observed effect modification across strata[174].

In summary, our results suggest that the strength of associations between respiratory hospitalizations in children and short-term exposure to outdoor $PM_{2.5}$ mass concentrations and O_x are influenced by the metal and sulfur content of $PM_{2.5}$ and particle oxidative potential. These findings provide further support for efforts targeting specific sources of $PM_{2.5}$ with high metal/sulfur content and oxidative potential as opposed to regulations targeting only $PM_{2.5}$ mass. Additional work is needed, both in different populations and with different health outcomes, to evaluate whether similar trends emerge.

4.3 Supplementary material

Supplementary Methods

1. List of Canadian cities where the study took place

Athabasca Valley, Brandon, Calgary, Courtenay, Duncan, Edmonton, Fort Mackay, Fort McMurray, Fredericton, Halifax, Hamilton, Kamloops, Kelowna, London, Montreal, Mt. Pearl, Nanaimo, Ottawa, Prince Albert, Prince George, Quebec, Quesnel, Red Deer, Regina, Saint John, Saskatoon, St. Albert, St. John's, Swift Current, Victoria, Whitehorse, Windsor, Winnipeg, and Yellowknife.

2. Additional details on the time-stratified case-crossover study design

This was a time-stratified case-crossover study. With the time-stratified case-crossover design, referent periods are selected on the same day of the week as the emergency department visit during that month and year[182]**;** for example, if an emergency department visit occurred on Monday June 13, 2016, then referent periods were all other Mondays in June 2016 (June 6, June 20, June 27). This study design is advantageous in that factors that are time-invariant (e.g., sex/gender) or do not vary within subjects over short periods of time (e.g., age, body mass index) are controlled for by design[182]. Moreover, time-dependent covariates such as season, day of week, and year are also adjusted for by design because the referent times are matched to the index date with respect to these covariates (i.e., the referent periods are selected as the same day of the week, month and year as the index date)[182]. This is in contrast to time-series studies (another study design frequently used to evaluate short-term effects of environmental exposures), where time-dependent covariates are adjusted for by modelling, and is a major advantage of the case-crossover design over the time-series design.

3. Additional details on $PM_{2.5}$ sample collection for monthly estimates of metals, sulfur, and oxidative potential

Integrated two-week $PM_{2.5}$ samples were collected on Teflon filters using cascade impactors operating at a flow rate of 5 liters per minute at each study location each month between June 2016-December 2017. All monitors were located at the provincial monitoring sites (the same location where daily $PM_{2.5}$, NO_2 and O_3 were measured), except for the cities of Ottawa and Montreal, where the monitors were located at private residences located less than 3 km away from the provincial monitoring sites. Gravimetric analyses were first performed, then the $PM_{2.5}$ filters were analysed for monthly estimates of transition metal (copper, iron, nickel, manganese, zinc) and sulfur content using X-ray fluorescence (U.S. Environmental Protection Agency method IO-3.3), and particle oxidative potential.

Three metrics of particle oxidative potential were measured: ascorbate (OP^{AA}), glutathione (OP^{GSH}), and dithiothreitol (OP^{DTT}) oxidative potential. To measure particle oxidative potential, the 2-week $PM_{2.5}$ samples were extracted into High Performance Liquid Chromatography (HPLC) grade methanol by vortexing at 1800 revolutions per minute for 20 minutes and sonicating for 10 minutes. Decanted methanol was evaporated under a gentle flow of nitrogen. $PM_{2.5}$ samples were resuspended in ultrapure water containing 5% HPLC methanol to a storage concentration of 200 μg PM/mL. Resuspended $PM_{2.5}$ samples were analyzed in triplicate using the ascorbate (AA), glutathione (GSH) and dithiothreitol (DTT) assays.

OP^{AA} and OP^{GSH} were assessed using the acellular respiratory tract lining fluid (RTLF) oxidative potential assay, as previously described[62,194]. Briefly, $PM_{2.5}$ samples were incubated at a concentration of 75 μg/mL for 4 h at 37 °C with synthetic respiratory tract lining fluid (RTLF) containing 200 μM of each AA, GSH, and uric acid in an ultraviolet- visible plate reader

(Molecular Devices, Spectra Max 190) alongside positive controls (0.5 μM $Cu(NO_3)_2$, 0.02% H_2O_2) and blanks. AA depletion was calculated over the 4-h incubation period, and GSH depletion was measured using the glutathione-reductase enzyme recycling assay[195]. OP^{DTT} was assessed using a similar method described previously[196]. Briefly, resuspended $PM_{2.5}$ samples were incubated with 100 μM DTT in a 96-well plate alongside positive controls (0.5 μM $Cu(NO_3)_2$), blanks, and DTT standards (containing 0−100 μM DTT) for 35 min at 37°C, with constant shaking. After 5, 15, 25, and 35 minutes, the remaining DTT was measured by adding 1.0 mM 5,5′-dithiobis(2- nitrobenzoic acid) to each well and measuring absorbance at 412 nm. Samples were initially analyzed at a concentration of 50 μg/mL but if DTT depletion exceeded 25% after 35 min, the sample was re-analyzed at a lower concentration.

An important limitation of using Teflon filters to measure monthly estimates of monthly estimates of $PM_{2.5}$ constituents (metals and sulfur) is that volatile constituents (e.g., ammonium nitrate, organic material, etc.) are not retained well by Teflon filters. As such, $PM_{2.5}$ mass concentration estimated from two-week integrated samples (used as an estimate of monthly $PM_{2.5}$) will be systematically underestimated, and the mass proportion of $PM_{2.5}$ constituents will be systematically overestimated (because mass proportion of metals/sulfur = $\left(\frac{metal\ or\ sulfur\ mass}{2-week\ integrated\ PM_{2.5} mass}\right) x\ 100$)). However, because measurement error in estimating the mass proportion of metals/sulfur in monthly $PM_{2.5}$ was systematic and estimates of mass proportions were only used to rank individuals with respect to above/below median mass proportions (to perform stratified analyses), no bias in the associations between lag-1 $PM_{2.5}$ or O_x should result.

4. Additional details on statistical analyses

Our primary analyses focused on lag-1 exposures because model fit (based on the minimum Akaike information criterion [AIC]) was best compared to models using same-day (lag-0) and 3-day mean exposures (see Table S1 for AICs). However, as sensitivity analyses, we also ran the models using lag-0 and 3-day mean exposures.

Natural cubic splines with 1 knot were examined for temperature, but model fit (based on the minimum AIC) did not meaningfully improve so a linear term for temperature was used in all models. In addition, we *a priori* chose to categorize metals, sulfur and oxidative potential at the median values to ensure an adequate sample size in each group. To formally test effect modification by patient sex (male vs. female), an interaction term was included in the model between lag-1 O_x or $PM_{2.5}$ and an indicator variable for sex (1=male, 0=female), and a p-value <0.05 for the interaction term was interpreted as effect modification (on the multiplicative scale) by patient sex. The same approach was performed to evaluate effect modification by season (warm vs. cold).

Supplementary Tables

Table S1 Model fit (using the Akaike information criterion [AIC]) comparing different exposure lags[a]

Exposure lag	AIC
Lag 0 (same-day exposures)	29364.94
Lag 1	29358.97
Lag 2	29364.04
3-day mean (mean of lags 1-3)	29361.32

[a] Covariates in the model include linear terms of $PM_{2.5}$, O_x, and temperature. A lower AIC indicates better model fit.

Table S2 Descriptive statistics of daily and monthly air pollution data, by the warm (May-September) and cold (October-April) seasons

	Warm season May-September	**Cold season October-April**
Air pollutants and temperature data	**Median (Interquartile Range)**	**Median (Interquartile Range)**
Daily data		
$PM_{2.5}$ ($\mu g/m^3$)	5.7 (3.7-8.7)	6.2 (4.1-9.1)
O_3 (ppb)	24 (19.3-29.8)	21.6 (15.7-27.9)
NO_2 (ppb)	5.3 (3.5-7.8)	9.2 (5.9-14.0)
O_x (ppb)	17.8 (14.6-21.8)	18.1 (14.9-21.4)
Temperature (°C)	16.6 (13.3-19.7)	0.2 (-6.7, 5.2)
Monthly data		
$PM_{2.5}$ ($\mu g/m^3$)	6.8 (5.3-8.7)	6.9 (5.1-9.0)
OP^{GSH} (pmol/min/μg)	3.0 (1.9- 4.4)	3.1 (2.2-4.4)
OP^{AA} (pmol/min/μg)	2.7 (2.1-3.5)	2.8 (2.3-3.6)
OP^{DTT} (pmol/min/μg)	11.1 (6.7-18.0)	9.0 (5.6-15.4)
Cu (ng/m^3)	1.9 (1-5)	1.9 (1-4.3)
Fe (ng/m^3)	105.2 (73.1- 164.1)	67.9 (33.0- 111.2)
Ni (ng/m^3)	0.2 (0.1-0.5)	0.2 (0.1-0.4)
Mn (ng/m^3)	3.5 (2.1- 5.6)	2.4 (1.1-3.9)
Zn (ng/m^3)	5.7 (3.0- 15.6)	7.9 (4.9- 15.5)
S (ng/m^3)	219.9 (159.1-299.5)	252.2 (162.3- 317.1)

OP^{GSH}, glutathione oxidative potential; OP^{AA}, ascorbate oxidative potential; OP^{DTT}, dithiothreitol oxidative potential; Cu, copper; Fe, iron; Ni, nickel; Mn, manganese; Zn, zinc; S, sulfur

Table S3 Descriptive statistics for mass proportions (%) of constituents in integrated two-week measurements of $PM_{2.5}$ (Canada, 2016-2017)

	Overall	**Warm season May-September**	**Cold season October-April**
	Median (Interquartile Range)	**Median (Interquartile Range)**	**Median (Interquartile Range)**
Cu	0.03 (0.02-0.06)	0.03 (0.02-0.06)	0.029 (0.017-0.052)
Fe	1.18 (0.69-1.80)	1.58 (1.11- 2.12)	1.055 (0.561-1.552)
Ni	0.003 (0.002-0.006)	0.003 (0.002-0.007)	0.003 (0.002-0.005)
Mn	0.04 (0.02-0.06)	0.048 (0.032- 0.065)	0.031 (0.018-0.054)
Zn	0.11 (0.07-0.19)	0.077 (0.045-0.216)	0.123 (0.084-0.185)
S	3.58 (2.67- 4.63)	3.49 (2.45-4.86)	3.65 (2.72-4.50)

Cu, copper; Fe, iron; Ni, nickel; Mn, manganese; Zn, zinc; S, sulfur

Table S4 Association between lag-1 $PM_{2.5}$ and hospitalizations for respiratory diseases in children (<18 years of age), overall and across strata (above or below the median) of mass proportions of sulfur and metals in monthly $PM_{2.5}$, and particle oxidative potential

		N events	Odds ratio (95% confidence interval)	Interaction p-value[a]
Overall		10,534	1.004 (0.955, 1.056)	-
Cu	>50th percentile	5,242	1.084 (1.007, 1.167)	0.013
	≤50th percentile	5,292	0.970 (0.929, 1.014)	
Fe	>50th percentile	5,285	1.091 (0.986, 1.206)	0.019
	≤50th percentile	5,249	0.968 (0.930, 1.007)	
Ni	>50th percentile	5,321	1.089 (1.015, 1.167)	0.006
	≤50th percentile	5,213	0.969 (0.926, 1.013)	
Mn	>50th percentile	5,276	1.067 (0.973, 1.169)	0.041
	≤50th percentile	5,258	0.972 (0.930, 1.015)	
Zn	>50th percentile	5,330	1.074 (1.000, 1.153)	0.029
	≤50th percentile	5,204	0.979 (0.939, 1.021)	
S	>50th percentile	5,303	1.050 (0.966, 1.142)	0.331
	≤50th percentile	5,231	0.989 (0.938-1.043)	
OP^{GSH}	>50th percentile	5,295	1.091 (1.033, 1.151)	<0.001
	≤50th percentile	5,239	0.951 (0.902, 1.002)	
OP^{AA}	>50th percentile	5,282	0.983 (0.918, 1.053)	0.435
	≤50th percentile	5,252	1.040 (0.956, 1.131)	
OP^{DTT}	>50th percentile	5,228	1.003 (0.945, 1.066)	0.995
	≤50th percentile	5,306	1.008 (0.916, 1.110)	

Cu, copper; Fe, iron; Ni, nickel; Mn, manganese; Zn, zinc; S, sulfur; OP^{GSH}, glutathione oxidative potential; OP^{AA}, ascorbate oxidative potential; OP^{DTT}, dithiothreitol oxidative potential

[a] p-value for the interaction term between lag-1 $PM_{2.5}$ and an indicator variable (above/below median) of monthly metals, sulfur or particle oxidative potential

Table S5 Association between lag-1 O_x and hospitalizations for respiratory diseases in children (<18 years of age), overall and across strata (above or below the median) of mass proportions of sulfur and metals in monthly $PM_{2.5}$, and particle oxidative potential

		N events	Odds ratio (95% confidence interval)	Interaction p-value[a]
Overall		10,534	1.088 (1.005, 1.177)	-
Cu	>50th percentile	5,242	1.125 (1.028, 1.232)	0.279
	≤50th percentile	5,292	1.055 (0.962, 1.157)	
Fe	>50th percentile	5,285	1.109 (1.012, 1.215)	0.148
	≤50th percentile	5,249	1.039 (0.942, 1.146)	
Ni	>50th percentile	5,321	1.107 (1.005, 1.219)	0.515
	≤50th percentile	5,213	1.061 (0.963, 1.169)	
Mn	>50th percentile	5,276	1.077 (0.980, 1.185)	0.838
	≤50th percentile	5,258	1.071 (0.954, 1.202)	
Zn	>50th percentile	5,330	1.139 (1.033, 1.255)	0.269
	≤50th percentile	5,204	1.049 (0.945, 1.164)	
S	>50th percentile	5,303	1.132 (1.023, 1.252)	0.388
	≤50th percentile	5,231	1.045 (0.936, 1.165)	
OP^{GSH}	>50th percentile	5,295	1.130 (1.039, 1.229)	0.362
	≤50th percentile	5,239	1.045 (0.933, 1.171)	
OP^{AA}	>50th percentile	5,282	1.037 (0.951, 1.130)	0.015
	≤50th percentile	5,252	1.144 (1.043, 1.255)	
OP^{DTT}	>50th percentile	5,228	1.065 (0.971, 1.170)	0.494
	≤50th percentile	5,306	1.112 (1.007, 1.227)	

Cu, copper; Fe, iron; Ni, nickel; Mn, manganese; Zn, zinc; S, sulfur; OP^{GSH}, glutathione oxidative potential; OP^{AA}, ascorbate oxidative potential; OP^{DTT}, dithiothreitol oxidative potential

[a] p-value for the interaction term between lag-1 O_x and an indicator variable (above/below median) of monthly metals, sulfur or particle oxidative potential

Table S6 Association between lag-1 $PM_{2.5}$ and hospitalizations for respiratory diseases in children (<18 years of age), overall and across strata (above or below the median) of mass proportions of sulfur and metals in monthly $PM_{2.5}$, and particle oxidative potential, stratified by the warm (May-September) and cold (October-April) seasons

		Warm season			Cold season			
		N	**Odds ratio (95% Confidence Interval)**	**Interaction p-value[a]**	**N**	**Odds ratio (95% Confidence Interval)**	**Interaction p-value[a]**	**Interaction p-value for season[b]**
Overall		3,610	1.003 (0.936, 1.075)	-	6,924	1.039 (0.961, 1.123)	-	0.329
Cu	>50th percentile	1,744	1.251 (1.099, 1.425)	0.003	3,498	1.080 (0.965, 1.209)	0.180	0.972
	≤50th percentile	1,866	0.979 (0.920, 1.042)		3,426	0.972 (0.895, 1.055)		0.828
Fe	>50th percentile	2,558	1.210 (1.037, 1.412)	0.004	2,727	1.121 (0.973, 1.293)	0.120	0.758
	≤50th percentile	1,052	0.956 (0.904, 1.011)		4,197	0.988 (0.920, 1.061)		0.513
Ni	>50th percentile	2,026	1.220 (1.057, 1.409)	0.001	3,295	1.072 (0.985, 1.168)	0.190	0.727
	≤50th percentile	1,584	0.973 (0.918, 1.032)		3,629	0.999 (0.903, 1.104)		0.782
Mn	>50th percentile	2,377	1.205 (1.014, 1.431)	0.007	2,899	1.069 (0.967, 1.181)	0.339	0.876
	≤50th percentile	1,233	0.956 (0.905, 1.011)		4,025	0.997 (0.907, 1.097)		0.467
Zn	>50th percentile	1,460	1.285 (1.089, 1.517)	<0.001	3,870	1.046 (0.949, 1.152)	0.734	0.286
	≤50th percentile	2,150	0.986 (0.927, 1.049)		3,054	1.029 (0.935, 1.133)		0.643
S	>50th percentile	1,643	1.164 (0.998, 1.357)	0.034	3,660	1.032 (0.931, 1.146)	0.620	0.433
	≤50th percentile	1,967	0.984 (0.923, 1.049)		3,264	1.047 (0.949, 1.155)		0.248
OP^{GSH}	>50th percentile	1,761	1.132 (1.043, 1.229)	0.002	3,534	1.081 (1.000, 1.168)	0.194	0.720
	≤50th percentile	1,849	0.952 (0.885, 1.023)		3,390	0.992 (0.885, 1.111)		0.555
OP^{AA}	>50th percentile	1,654	0.966 (0.913, 1.022)	0.065	3,628	0.966 (0.913, 1.022)	0.721	0.134
	≤50th percentile	1,956	1.093 (0.985, 1.214)		3,296	1.033 (0.915, 1.167)		0.796
OP^{DTT}	>50th percentile	2,008	1.009 (0.935, 1.090)	0.285	3,220	0.992 (0.903, 1.088)	0.433	0.893
	≤50th percentile	1,602	0.944 (0.799, 1.114)		3,704	1.085 (0.971, 1.213)		0.034

Cu, copper; Fe, iron; Ni, nickel; Mn, manganese; Zn, zinc; S, sulfur; OP^{GSH}, glutathione oxidative potential; OP^{AA}, ascorbate oxidative potential; OP^{DTT}, dithiothreitol oxidative potential

[a] p-value for the interaction term between lag-1 $PM_{2.5}$ and an indicator variable (above/below median) of monthly metals, sulfur or particle oxidative potential

[b] p-value for the interaction term between lag-1 $PM_{2.5}$ and an indicator variable for season (1=warm, 0=cold), within strata of monthly metals, sulfur, or particle oxidative potential (above/below median)

Table S7 Association between lag-1 O_x and hospitalizations for respiratory diseases in children (<18 years of age), overall and across strata (above or below the median) of mass proportions of sulfur and metals in monthly $PM_{2.5}$, and particle oxidative potential, stratified by the warm (May-September) and cold (October-April) seasons

		Warm season			Cold season			
		N	**Odds ratio (95% Confidence Interval)**	**Interaction p-value[a]**	**N**	**Odds ratio (95% Confidence Interval)**	**Interaction p-value[a]**	**Interaction p-value for season[b]**
Overall		3,610	1.196 (1.075, 1.331)	-	6,924	1.112 (1.026, 1.206)	-	0.796
Cu	>50th percentile	1,744	1.262 (1.104, 1.442)	0.086	3,498	1.130 (1.014, 1.259)	0.955	0.855
	≤50th percentile	1,866	1.082 (0.924, 1.268)		3,426	1.074 (0.965, 1.196)		0.640
Fe	>50th percentile	2,558	1.189 (1.055, 1.340)	0.402	2,727	1.173 (1.063, 1.296)	0.151	0.091
	≤50th percentile	1,052	1.149 (0.955, 1.381)		4,197	1.045 (0.939, 1.162)		0.707
Ni	>50th percentile	2,026	1.210 (1.078, 1.359)	0.020	3,295	1.090 (0.971, 1.224)	0.466	0.683
	≤50th percentile	1,584	1.152 (0.974, 1.363)		3,629	1.112 (1.008, 1.226)		0.219
Mn	>50th percentile	2,377	1.143 (1.003, 1.303)	0.939	2,899	1.139 (1.031, 1.258)	0.594	0.100
	≤50th percentile	1,233	1.251 (0.999, 1.567)		4,025	1.066 (0.962, 1.182)		0.400
Zn	>50th percentile	1,460	1.274 (1.091, 1.488)	0.002	3,870	1.102 (0.988, 1.229)	0.727	0.227
	≤50th percentile	2,150	1.108 (0.972, 1.264)		3,054	1.122 (1.021, 1.233)		0.222
Sulfur	>50th percentile	1,643	1.165 (0.957, 1.418)	0.837	3,660	1.141 (1.023, 1.273)	0.318	0.648
	≤50th percentile	1,967	1.202 (1.025, 1.409)		3,264	1.081 (0.957, 1.221)		0.972
OP^{GSH}	>50th percentile	1,761	1.236 (1.096, 1.394)	0.111	3,534	1.127 (1.023, 1.240)	0.980	0.879
	≤50th percentile	1,849	1.150 (0.961, 1.376)		3,390	1.086 (0.970, 1.216)		0.593
OP^{AA}	>50th percentile	1,654	1.085 (0.977, 1.204)	0.201	3,628	1.084 (0.977, 1.204)	0.391	0.648
	≤50th percentile	1,956	1.275 (1.080, 1.506)		3,296	1.152 (1.051, 1.262)		0.831
OP^{DTT}	>50th percentile	2,008	1.175 (1.030, 1.341)	0.534	3,220	1.036 (0.907, 1.185)	0.178	0.559
	≤50th percentile	1,602	1.226 (1.053, 1.428)		3,704	1.180 (1.080, 1.290)		0.181

Cu, copper; Fe, iron; Ni, nickel; Mn, manganese; Zn, zinc; S, sulfur; OP^{GSH}, glutathione oxidative potential; OP^{AA}, ascorbate oxidative potential; OP^{DTT}, dithiothreitol oxidative potential

[a] p-value for the interaction term between lag-1 O_x and an indicator variable (above/below median) of monthly metals, sulfur or particle oxidative potential

[b] p-value for interaction term between lag-1 O_x and an indicator variable for season (1=warm, 0=cold), within strata of monthly metals, sulfur, or particle oxidative potential (above/below median)

Table S8 Association between lag-1 $PM_{2.5}$ and hospitalizations for respiratory diseases in children (<18 years of age), overall and across strata (above or below the median) of mass proportions of sulfur and metals in monthly $PM_{2.5}$, and particle oxidative potential, stratified by sex

		Girls			Boys			
		N	**Odds ratio (95% Confidence Interval)**	**Interaction p-value[a]**	**N**	**Odds ratio (95% Confidence Interval)**	**Interaction p-value[a]**	**Interaction p-value for sex[b]**
Overall		4,505	1.017 (0.968, 1.068)	-	6,029	0.994 (0.935, 1.057)	-	0.479
Cu	>50th percentile	2,177	1.102 (1.022, 1.188)	0.010	3,065	1.071 (0.975, 1.176)	0.056	0.680
	≤50th percentile	2,328	0.980 (0.932, 1.030)		2,964	0.963 (0.909, 1.020)		0.605
Fe	>50th percentile	2,217	1.126 (1.012, 1.254)	0.015	3,068	1.064 (0.941, 1.204)	0.147	0.455
	≤50th percentile	2,288	0.969 (0.916, 1.025)		2,961	0.966 (0.913, 1.022)		0.808
Ni	>50th percentile	2,200	1.104 (1.002, 1.217)	0.038	3,121	1.077 (0.978, 1.186)	0.027	0.931
	≤50th percentile	2,305	0.980 (0.933, 1.028)		2,908	0.960 (0.908, 1.014)		0.393
Mn	>50th percentile	2,227	1.106 (1.013, 1.208)	0.005	3,049	1.037 (0.928, 1.159)	0.255	0.297
	≤50th percentile	2,278	0.968 (0.919, 1.019)		2,980	0.973 (0.914, 1.036)		0.904
Zn	>50th percentile	2,261	1.109 (1.015, 1.212)	0.022	3,069	1.047 (0.958, 1.144)	0.250	0.299
	≤50th percentile	2,244	0.982 (0.935, 1.031)		2,960	0.977 (0.920, 1.037)		0.974
S	>50th percentile	2,258	1.019 (0.918, 1.131)	0.921	3,045	1.075 (0.978, 1.181)	0.128	0.307
	≤50th percentile	2,247	1.016 (0.968, 1.066)		2,984	0.970 (0.909, 1.034)		0.099
OP^{GSH}	>50th percentile	2,242	1.072 (0.997, 1.152)	0.111	3,053	1.106 (1.039, 1.177)	<0.001	0.464
	≤50th percentile	2,263	0.978 (0.920, 1.040)		2,976	0.930 (0.865, 1.000)		0.261
OP^{AA}	>50th percentile	2,231	0.994 (0.933, 1.059)	0.427	3,051	0.976 (0.897, 1.062)	0.548	0.591
	≤50th percentile	2,274	1.051 (0.972, 1.137)		2,978	1.027 (0.917, 1.152)		0.810
OP^{DTT}	>50th percentile	2,201	1.026 (0.973, 1.081)	0.552	3,027	0.987 (0.914, 1.066)	0.749	0.303
	≤50th percentile	2,304	0.995 (0.898, 1.104)		3,002	1.017 (0.901, 1.148)		0.681

Cu, copper; Fe, iron; Ni, nickel; Mn, manganese; Zn, zinc; S, sulfur; OP^{GSH}, glutathione oxidative potential; OP^{AA}, ascorbate oxidative potential; OP^{DTT}, dithiothreitol oxidative potential

[a] p-value for the interaction term between lag-1 $PM_{2.5}$ and an indicator variable (above/below median) of monthly metals, sulfur or particle oxidative potential

[b] p-value for the interaction term between lag-1 $PM_{2.5}$ and an indicator variable for sex (1=male, 0=female), within strata of monthly metals, sulfur, or particle oxidative potential (above/below median)

Table S9 Association between lag-1 O_x and hospitalizations for respiratory diseases in children (<18 years of age), overall and across strata (above or below the median) of mass proportions of sulfur and metals in monthly $PM_{2.5}$, and particle oxidative potential, stratified by sex

		Girls			Boys			
		N	**Odds ratio (95% Confidence Interval)**	**Interaction p-value[a]**	**N**	**Odds ratio (95% Confidence Interval)**	**Interaction p-value[a]**	**Interaction p-value for sex[b]**
Overall		4,505	1.070 (0.987, 1.159)	-	6,029	1.101 (0.994, 1.221)	-	0.450
Cu	>50th percentile	2,177	1.069 (0.970, 1.178)	0.931	3,065	1.169 (1.044, 1.309)	0.165	0.083
	≤50th percentile	2,328	1.070 (0.958, 1.196)		2,964	1.043 (0.910, 1.196)		0.848
Fe	>50th percentile	2,217	1.088 (0.952, 1.244)	0.391	3,068	1.125 (1.027, 1.232)	0.430	0.552
	≤50th percentile	2,288	1.008 (0.896, 1.132)		2,961	1.062 (0.906, 1.244)		0.652
Ni	>50th percentile	2,200	1.088 (0.960, 1.233)	0.678	3,121	1.120 (1.013, 1.239)	0.599	0.462
	≤50th percentile	2,305	1.043 (0.930, 1.169)		2,908	1.076 (0.931, 1.244)		0.670
Mn	>50th percentile	2,227	1.079 (0.967, 1.204)	0.495	3,049	1.077 (0.965, 1.201)	0.810	0.934
	≤50th percentile	2,278	1.022 (0.892, 1.172)		2,980	1.107 (0.942, 1.301)		0.424
Zn	>50th percentile	2,261	1.088 (0.986, 1.200)	0.837	3,069	1.178 (1.043, 1.331)	0.169	0.114
	≤50th percentile	2,244	1.063 (0.937, 1.205)		2,960	1.037 (0.903, 1.192)		0.895
Sulfur	>50th percentile	2,258	1.093 (0.973, 1.229)	0.658	3,045	1.162 (1.028, 1.313)	0.362	0.369
	≤50th percentile	2,247	1.045 (0.931, 1.171)		2,984	1.045 (0.906, 1.205)		0.786
OP^{GSH}	>50th percentile	2,242	1.093 (0.954, 1.252)	0.775	3,053	1.159 (1.066, 1.258)	0.355	0.425
	≤50th percentile	2,263	1.045 (0.901, 1.212)		2,976	1.047 (0.890, 1.232)		0.816
OP^{AA}	>50th percentile	2,231	1.011 (0.898, 1.138)	0.223	3,051	1.057 (0.961, 1.162)	0.163	0.446
	≤50th percentile	2,274	1.138 (1.012, 1.281)		2,978	1.146 (0.998, 1.316)		0.746
OP^{DTT}	>50th percentile	2,201	1.057 (0.947, 1.180)	0.755	3,027	1.073 (0.956, 1.204)	0.521	0.742
	≤50th percentile	2,304	1.079 (0.982, 1.186)		3,002	1.138 (0.982, 1.318)		0.437

Cu, copper; Fe, iron; Ni, nickel; Mn, manganese; Zn, zinc; S, sulfur; OP^{GSH}, glutathione oxidative potential; OP^{AA}, ascorbate oxidative potential; OP^{DTT}, dithiothreitol oxidative potential

[a] p-value for the interaction term between lag-1 O_x and monthly metals, sulfur or particle oxidative potential (above/below median)

[b] p-value for the interaction term between lag-1 O_x and an indicator variable for sex (1=male, 0=female), within strata of monthly metals, sulfur, or particle oxidative potential (above/below median)

Table S10 Association between lag-0 $PM_{2.5}$ and hospitalizations for respiratory diseases in children (<18 years of age), overall and across strata (above/below the median) of mass proportions of monthly sulfur and metals in $PM_{2.5}$, and particle oxidative potential

		N events	Odds ratio (95% confidence interval)	Interaction p-value[a]
Overall		10,410	0.985 (0.951, 1.021)	-
Cu	>50th percentile	5,191	1.038 (0.981, 1.100)	0.034
	≤50th percentile	5,219	0.963 (0.920, 1.008)	
Fe	>50th percentile	5,221	1.041 (0.960, 1.129)	0.088
	≤50th percentile	5,189	0.965 (0.921, 1.010)	
Ni	>50th percentile	5,253	1.066 (0.995, 1.141)	0.004
	≤50th percentile	5,157	0.957 (0.913, 1.002)	
Mn	>50th percentile	5,209	1.016 (0.948, 1.088)	0.127
	≤50th percentile	5,201	0.970 (0.924, 1.018)	
Zn	>50th percentile	5,274	1.014 (0.945, 1.087)	0.365
	≤50th percentile	5,136	0.975 (0.934, 1.017)	
S	>50th percentile	5,234	1.030 (0.945, 1.121)	0.263
	≤50th percentile	5,176	0.975 (0.937-1.013)	
OP^{GSH}	>50th percentile	5,233	1.023 (0.960, 1.091)	0.174
	≤50th percentile	5,177	0.964 (0.922, 1.008)	
OP^{AA}	>50th percentile	5,224	0.978 (0.918, 1.042)	0.805
	≤50th percentile	5,186	1.000 (0.921, 1.085)	
OP^{DTT}	>50th percentile	5,168	0.981 (0.943, 1.021)	0.826
	≤50th percentile	5,242	0.994 (0.916, 1.078)	

Cu, copper; Fe, iron; Ni, nickel; Mn, manganese; Zn, zinc; S, sulfur; OP^{GSH}, glutathione oxidative potential; OP^{AA}, ascorbate oxidative potential; OP^{DTT}, dithiothreitol oxidative potential

[a] p-value for the interaction term between lag-0 $PM_{2.5}$ and monthly metals, sulfur or particle oxidative potential (above/below median)

Table S11 Association between 3-day mean $PM_{2.5}$ and hospitalizations for respiratory diseases in children (<18 years of age), overall and across strata (above/below the median) of monthly mass proportion of sulfur and metals in $PM_{2.5}$, and particle oxidative potential

		N events	Odds ratio (95% confidence interval)	Interaction p-value[a]
Overall		10,300	0.981 (0.937, 1.027)	-
Cu	>50th percentile	5,160	1.072 (0.979, 1.173)	0.014
	≤50th percentile	5,140	0.952 (0.920, 0.985)	
Fe	>50th percentile	5,185	1.101 (0.970, 1.251)	0.011
	≤50th percentile	5,115	0.942 (0.910, 0.975)	
Ni	>50th percentile	5,199	1.102 (1.015, 1.196)	0.001
	≤50th percentile	5,101	0.942 (0.909, 0.976)	
Mn	>50th percentile	5,160	1.074 (0.970, 1.189)	0.013
	≤50th percentile	5,140	0.948 (0.910, 0.987)	
Zn	>50th percentile	5,212	1.043 (0.933, 1.166)	0.189
	≤50th percentile	5,088	0.966 (0.934, 0.997)	
S	>50th percentile	5,194	1.018 (0.904, 1.147)	0.588
	≤50th percentile	5,106	0.972 (0.931, 1.014)	
OP^{GSH}	>50th percentile	5,173	1.064 (0.978, 1.156)	0.023
	≤50th percentile	5,127	0.939 (0.895, 0.985)	
OP^{AA}	>50th percentile	5,160	0.974 (0.907, 1.045)	0.828
	≤50th percentile	5,140	0.994 (0.898, 1.101)	
OP^{DTT}	>50th percentile	5,113	0.977 (0.933, 1.023)	0.908
	≤50th percentile	5,187	0.986 (0.876, 1.109)	

Cu, copper; Fe, iron; Ni, nickel; Mn, manganese; Zn, zinc; S, sulfur; OP^{GSH}, glutathione oxidative potential; OP^{AA}, ascorbate oxidative potential; OP^{DTT}, dithiothreitol oxidative potential

[a] p-value for the interaction term between 3-day mean $PM_{2.5}$ and monthly metals, sulfur or particle oxidative potential (above/below median)

Table S12 Association between lag-0 O_x and hospitalizations for respiratory diseases in children (<18 years of age), overall and across strata (above/below the median) of mass proportions of monthly sulfur and metals in $PM_{2.5}$, and particle oxidative potential

		N events	Odds ratio (95% confidence interval)	Interaction p-value[a]
Overall		10,410	1.030 (0.961, 1.104)	-
Cu	>50th percentile	5,191	1.050 (0.972, 1.134)	0.509
	≤50th percentile	5,219	1.013 (0.925, 1.109)	
Fe	>50th percentile	5,221	1.037 (0.944, 1.140)	0.650
	≤50th percentile	5,189	1.011 (0.935, 1.093)	
Ni	>50th percentile	5,253	1.002 (0.924, 1.086)	0.277
	≤50th percentile	5,157	1.051 (0.973, 1.136)	
Mn	>50th percentile	5,209	0.986 (0.893, 1.090)	0.478
	≤50th percentile	5,201	1.052 (0.950, 1.167)	
Zn	>50th percentile	5,274	1.047 (0.961, 1.139)	0.619
	≤50th percentile	5,136	1.019 (0.928, 1.119)	
S	>50th percentile	5,234	0.987 (0.898, 1.085)	0.107
	≤50th percentile	5,176	1.073 (0.976, 1.178)	
OP^{GSH}	>50th percentile	5,233	1.053 (0.969, 1.145)	0.590
	≤50th percentile	5,177	1.005 (0.902, 1.120)	
OP^{AA}	>50th percentile	5,224	1.004 (0.922, 1.093)	0.438
	≤50th percentile	5,186	1.061 (0.962, 1.169)	
OP^{DTT}	>50th percentile	5,168	1.054 (0.954, 1.164)	0.465
	≤50th percentile	5,242	1.006 (0.903, 1.120)	

Cu, copper; Fe, iron; Ni, nickel; Mn, manganese; Zn, zinc; S, sulfur; OP^{GSH}, glutathione oxidative potential; OP^{AA}, ascorbate oxidative potential; OP^{DTT}, dithiothreitol oxidative potential

[a] p-value for the interaction term between lag-0 O_x and monthly metals, sulfur or particle oxidative potential (above/below median)

Table S13 Association between 3-day mean O_x and hospitalizations for respiratory diseases in children (<18 years of age), overall and across strata (above/below the median) of monthly mass proportions of sulfur and metals in $PM_{2.5}$, and particle oxidative potential

		N events	Odds ratio (95% confidence interval)	Interaction p-value[a]
Overall		10,300	1.061 (0.999, 1.128)	-
Cu	>50th percentile	5,160	1.091 (1.014, 1.174)	0.283
	≤50th percentile	5,140	1.037 (0.964, 1.115)	
Fe	>50th percentile	5,185	1.072 (0.987, 1.163)	0.141
	≤50th percentile	5,115	1.025 (0.958, 1.096)	
Ni	>50th percentile	5,199	1.066 (0.986, 1.152)	0.640
	≤50th percentile	5,101	1.047 (0.979, 1.120)	
Mn	>50th percentile	5,160	1.016 (0.931, 1.108)	0.486
	≤50th percentile	5,140	1.076 (0.978, 1.184)	
Zn	>50th percentile	5,212	1.091 (1.010, 1.178)	0.380
	≤50th percentile	5,088	1.040 (0.962, 1.125)	
S	>50th percentile	5,194	1.085 (1.002, 1.176)	0.395
	≤50th percentile	5,106	1.036 (0.960, 1.118)	
OP^{GSH}	>50th percentile	5,173	1.099 (1.024, 1.179)	0.256
	≤50th percentile	5,127	1.022 (0.929, 1.124)	
OP^{AA}	>50th percentile	5,160	1.036 (0.965, 1.113)	0.280
	≤50th percentile	5,140	1.091 (1.003, 1.187)	
OP^{DTT}	>50th percentile	5,113	1.095 (1.004, 1.194)	0.374
	≤50th percentile	5,187	1.030 (0.937, 1.131)	

Cu, copper; Fe, iron; Ni, nickel; Mn, manganese; Zn, zinc; S, sulfur; OP^{GSH}, glutathione oxidative potential; OP^{AA}, ascorbate oxidative potential; OP^{DTT}, dithiothreitol oxidative potential

[a] p-value for the interaction term between 3-day mean O_x and monthly metals, sulfur or particle oxidative potential (above/below median)

Supplementary Figures

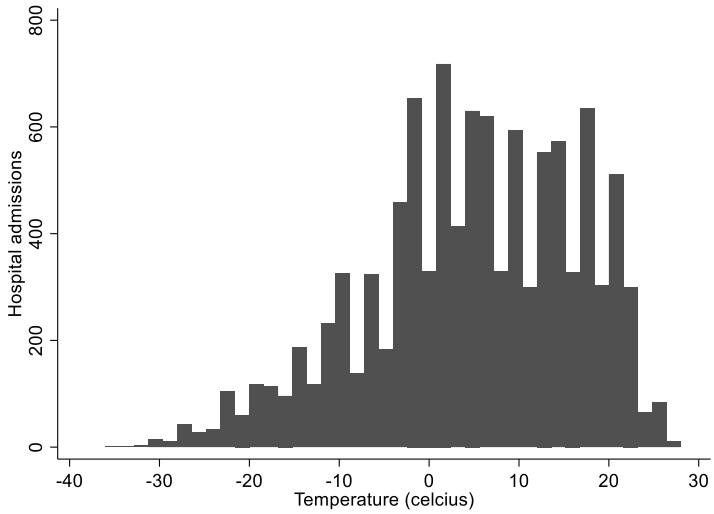

Figure S1 Frequency of hospital admissions for respiratory diseases among children (<18 years of age) in the study, by daily temperature (degrees Celsius)

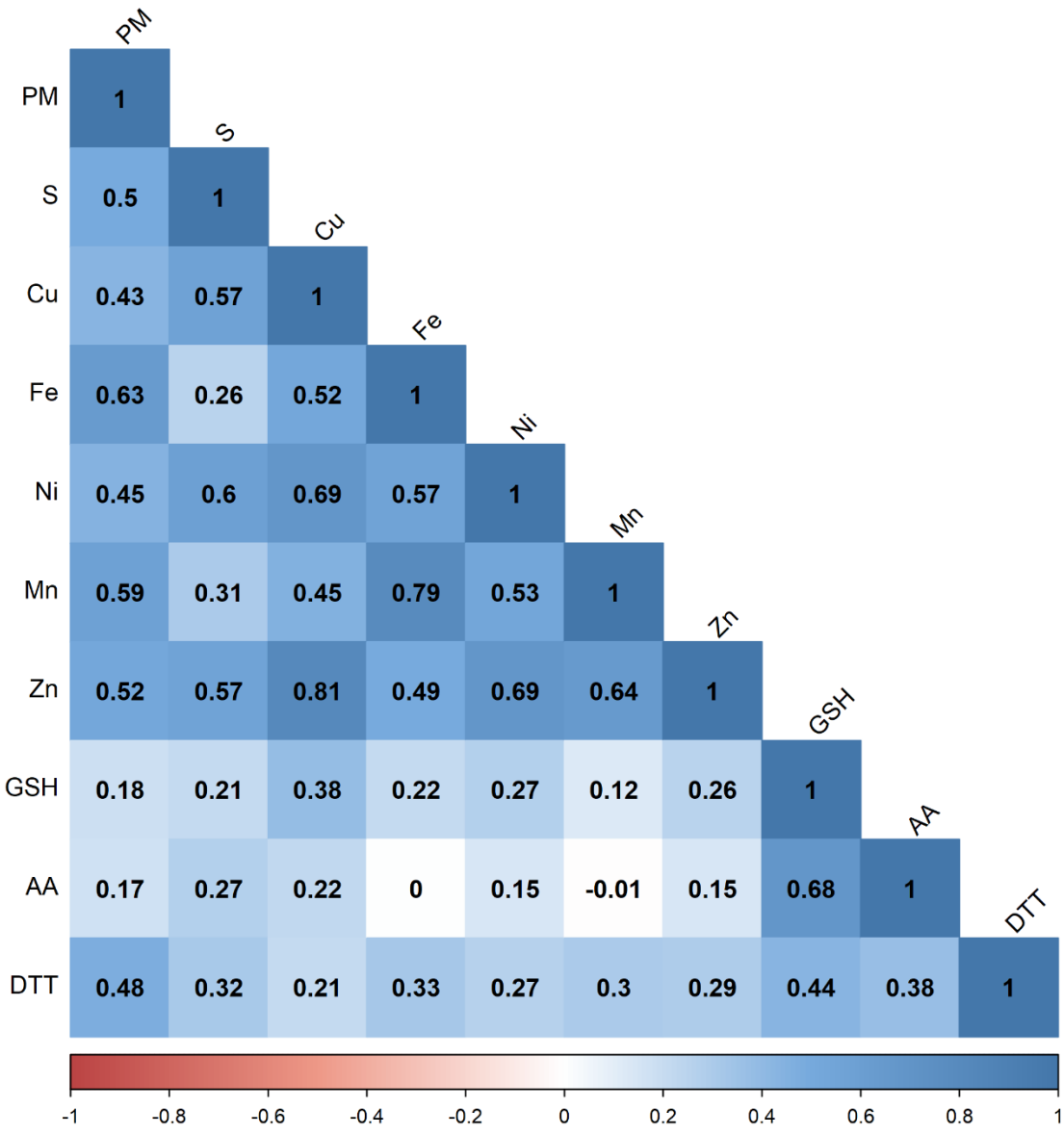

Figure S2 Spearman correlation coefficients between monthly mean $PM_{2.5}$ mass concentration (PM, μg/m^3), constituents (Cu, Fe, Ni, Mn, Zn, S, ng/m^3) and oxidative potential (OP^{GSH}, OP^{AA}, OP^{DTT}, pmol/min/μg) in Canada from 2016-2017, during the warm season (May-September)

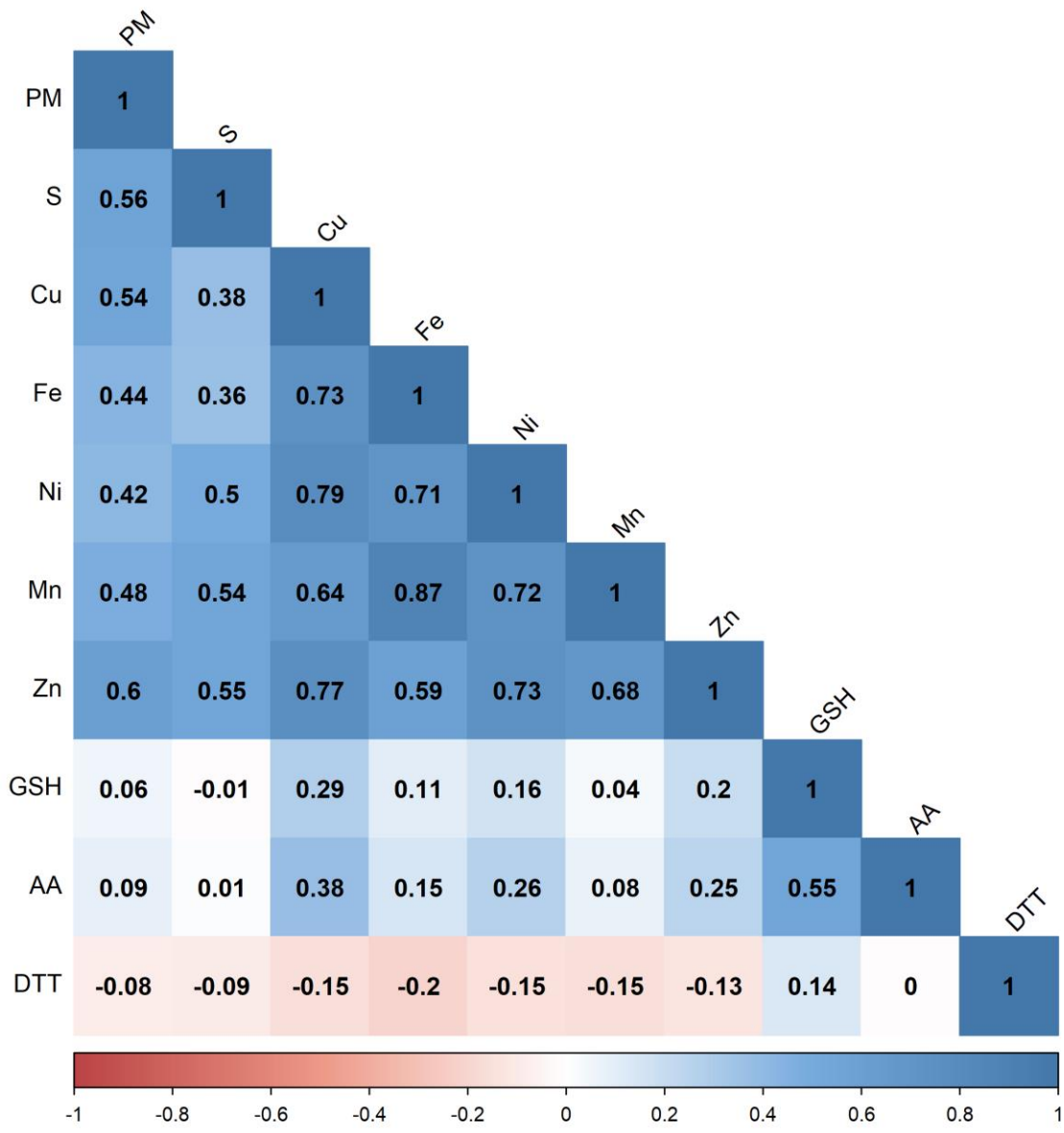

Figure S3 Spearman correlation coefficients between monthly mean $PM_{2.5}$ mass concentration (PM, μg/m^3), constituents (Cu, Fe, Ni, Mn, Zn, S, ng/m^3) and oxidative potential (OP^{GSH}, OP^{AA}, OP^{DTT}, pmol/min/μg) in Canada from 2016-2017, during the cold season (October-April)

CHAPTER 5: Manuscript 3

5.1 Preface

In Manuscript 3, we investigate the chronic health impacts of wildfires, another major source of pollution in Canada. Specifically, we assess whether wildfire exposure based on residential proximity is associated with several cancer outcomes in the 1996 Canadian Census Health and Environment Cohort. Although air pollution is a major component of wildfire exposure and the general unifying theme of this overall dissertation, we conceptualized the health risks of wildfires encompassing more than just air pollution; for example, wildfires are known to contaminate aquatic, terrestrial and indoor environments, which may pose important health risks to humans. Our surrogate measure of exposure based on residential proximity aimed to capture pollutant mixtures released by wildfires, given that we were interested in the mixture in its entirety and not just traditional air pollutants. This manuscript has been peer-reviewed and published in the *Lancet Planetary Health.*

Citation: Korsiak J, Pinault L, Christidis T, Burnett RT, Abrahamowicz M, Weichenthal S. Long-term exposure to wildfires and cancer incidence in Canada: a population-based observational cohort study. *Lancet Planetary Health* 2022;6(5): E400-E409. https://doi.org/10.1016/S2542-5196(22)00067-5

5.2 Long-term exposure to wildfires and cancer incidence in Canada: A population-based cohort study

Abstract

Background: Wildfires emit many carcinogenic pollutants that contaminate air, water, terrestrial and indoor environments. However, little is currently known about the relationship between exposure to wildfires and cancer risk.

Methods: We conducted a population-based cohort study of over two million Canadians followed for cancer incidence over 20 years (approximately 34 million person-years). Exposures to wildfires were assigned based on area burned within a 20 or 50 km radius of residential locations and updated for annual residential mobility. Multivariable Cox proportional hazards models were used to estimate associations between exposure to wildfires and specific cancers associated with carcinogenic compounds released by wildfires including lung and brain cancer, non-Hodgkin lymphoma, multiple myeloma, and leukemia, adjusted for many personal and neighbourhood-level covariates.

Findings: Wildfire exposure was consistently associated with slightly increased incidence of lung cancer and brain tumors. For example, cohort members experiencing a wildfire within 50 km of residential locations in the past ten years had a 4·9% (adjusted HR= 1.049, 95% CI: 1.028-1.071) relatively higher incidence of lung cancer than unexposed populations, and a 10% (adjusted HR= 1.100, 95% CI: 1.026-1.179) relatively higher incidence of brain tumours. Similar associations were observed for the 20 km buffer size. Wildfires were not associated with hematological cancers in this study, and concentration-response trends were not readily apparent when area burned was modelled as a continuous variable.

Interpretations: Long-term exposure to wildfires may increase the risk of lung cancer and brain tumors. Further work is needed to develop long-term estimates of wildfire exposures that capture the complex mixture of environmental pollutants released during these events.

Introduction

With the changing climate, wildfires are predicted to become more prevalent, severe, and longer in duration in the future[83–86] and are increasingly recognized as a population health problem[78,79]. Wildfires emit a complex mixture of harmful pollutants into the environment, including well-known impacts on outdoor air quality as well as contamination of water[197–199], soil/terrestrial environments[200–202], and indoor environments[203,204]. Importantly, many of the pollutants emitted by wildfires are known human carcinogens, including polycyclic aromatic hydrocarbons, benzene, formaldehyde, phenols, and heavy metals, thus suggesting that exposures to wildfires may increase cancer risk in humans. However, little is known about the long-term health impacts of wildfires[78,89] including their potential impact on cancer risk.

This is an important question for several reasons. In North America, wildfires typically occur in similar regions each year; consequently, people living in nearby communities may be exposed to carcinogenic wildfire pollutants on a chronic basis. Moreover, although some pollutants return to normal levels shortly after the fire has stopped burning (e.g., fine particulate air pollution, $PM_{2.5}$), other chemicals may persist in the environment for long periods of time, including heavy metals[100] and polycyclic aromatic hydrocarbons[101]. As such, exposure to harmful environmental pollutants may continue beyond the period of active burning through multiple routes of exposure.

The aim of this study was to characterize the relationship between residential exposure to wildfires and the incidence of several cancer outcomes in a national, population-based cohort in Canada. We *a priori* selected specific cancer types including lung and brain cancer, non-Hodgkin lymphoma, multiple myeloma, and leukemia, based on evidence linking known wildfire pollutants to these types of cancers. Our primary exposure variable is defined as area burned

within a given radius of residential locations. This surrogate measure of exposure aims to capture pollutant mixtures released by wildfires as we are interested in the mixture in its entirety and not just traditional air pollutants. To our knowledge, this is the first study in the world to investigate how long-term residential exposure to wildfires may impact cancer risk.

Methods

Cohort description

This observational cohort study included a subset of participants in the 1996 Canadian Census Health and Environment Cohort (CanCHEC). The 1996 CanCHEC has been described in detail elsewhere[205,206]. Briefly, this is a population-based cohort that follows approximately 3.6 million individuals for mortality and cancer outcomes from 1996-2015. Annual residential postal codes (from 1986-2015) were available through linkage to tax records and were assigned geographic coordinates based on the nearest block face, dissemination block, or centroid of a dissemination area[207]. Postal codes were used to assign wildfire exposures (as a time-varying exposure, described below) and to extract neighbourhood-level covariates.

We excluded subjects from cities with populations >1.5 million people to improve computational efficiency and to limit potential residual confounding due to differences among people who live in urban versus rural locations. Consistent with other analyses of the CanCHEC databases[12,208,209], we also excluded subjects who immigrated to Canada during the ten years before census day and subjects <25 and ≥90 years of age at baseline.

Outcomes

The outcomes of this study were the incidence of lung cancer, brain tumors, non-Hodgkin lymphoma, multiple myeloma, and leukemia. These outcomes were selected *a priori* based on existing evidence related to known carcinogens (and associated cancer types) emitted by

wildfires (additional details in the appendix, additional methods 1). Other cancer outcomes were not examined. The CanCHEC is linked to the Canadian Cancer Registry, which reports cancer incidence from January 1st 1992 to December 31st 2015, except for the province of Quebec where data are available to December 31st, 2010. Outcomes were identified using the International Classification of Diseases for Oncology (ICD-O) typography and morphology codes (codes are listed in the Supplementary Material, additional methods 2). Individuals with a cancer diagnosis from 1992-1995 were excluded.

Wildfire exposure assessment

Wildfire exposures from 1986-2015 were assigned using the National Burned Area Composite (NBAC)[210,211]. The NBAC is a Geographic Information Systems (GIS) database and system that generates composite maps of burned area polygons for all of Canada's forests on an annual basis, indicating where and when a fire has occurred, and an estimate of the total area burned. The NBAC was developed jointly by the Canadian Centre for Mapping and Earth Observation and the Canadian Forest Service of Natural Resource Canada and relies on three different sources to map area burned: the Canadian National Fire Database (CNFDB), the Multi-Acquisition Fire Mapping System (MAFiMS), and the Hotspot and Normalized Difference Vegetation Index Differencing Synergy (HANDS) algorithm. Burned areas reported by all three sources are stored in the NBAC spatial data warehouse, and the NBAC then applies user-defined decision rules to select the best source of data for each fire to be used as the final NBAC product. Generally, the NBAC selects polygons generated through MAFiMS when available, followed by agency polygons, then HANDS polygons[211]. Additional details are provided in the Supplementary Material (additional methods 3).

Using these GIS surfaces, we calculated the total area of forest burned (in hectares) within a 20 km and 50 km radius of all residential six-character postal code representative locations, for each year between 1986-2015 (i.e., a time-varying exposure; see Figure S1). We estimated area burned within two different radii to evaluate the sensitivity of our results to the selection of buffer size.

To capture long-term exposures to wildfires, we calculated three-year, five-year, and ten-year moving averages of area burned with a one-year lag. For example, for the 20 km radius, the three-year, five-year, and ten-year moving averages were based off average hectares burned within 20 km of residential location from 1993-1995, 1991-1995, and 1986-1995, respectively. These calculations were done for each year of follow-up, and for each of the two radii.

Statistical analyses

Multivariable Cox proportional hazards models were used to estimate associations between exposure to wildfires (as defined below) and the incidence of lung cancer, brain cancer, non-Hodgkin lymphoma, multiple myeloma, and leukemia. We considered each outcome separately. Time-to-event was calculated as the duration between Census Day (time 0) and a diagnosis of a particular cancer. Subjects who had no relevant diagnosis during their follow-up were right-censored at death, loss to follow-up, or the administrative end of follow-up (December 31, 2010 for the province of Quebec, and December 31, 2015 for the rest of Canada). Cox models were stratified by baseline age (five-year groups), sex, and immigrant status, and adjusted for a range of personal covariates (marital status, income adequacy quintile, education, labour force status, occupation, Indigenous status, visible minority status, baseline age centered at the median of each 5-year strata) and neighbourhood-level covariates (population size, urban

form, regional airshed, and the Canadian Marginalization Index[212] (details in the Supplementary Material, additional methods 4).

As a first analysis, we dichotomized the individual values of the three, five and ten-year moving averages of area burned within a 20 or 50 km radius as ever/never exposed to wildfires within the past three, five or ten years. Next, we examined three levels of exposure: (i) never exposed to wildfires and two exposed groups (i.e., (ii) 'low exposure' and (iii) 'high exposure') separated at the median of the respective moving average of area burned within each buffer size. Adjusted hazard ratios (95% confidence intervals) were then estimated for each of the two exposed groups, relative to the unexposed category. Finally, we examined continuous exposures. To reduce bias that may result when modelling continuous exposures with many zeros (i.e., cohort members who were never exposed)[213,214], we included in the model both a binary variable (reflecting ever/never exposure in the past three, five or ten years) and a continuous exposure (reflecting the three, five or ten-year moving averages of area burned). For exposed person-years, the continuous variable was centered at the median area burned, while for unexposed person-years, the continuous variable was kept at a value of zero[213]. In this model, the coefficient for the binary term compares risk between those never exposed to wildfires and those with a median level of exposure while the estimate for the continuous term reflects the quantitative effect of increasing exposure among those exposed. In two alternative preliminary analyses, we modelled the continuous exposure term in this model as a linear term or with cubic B splines with 1 interior knot. However, because model fit did not meaningfully improve with flexible modelling (based on the minimum Akaike information criterion), using the parsimony principle, final models included only a linear term for the continuous exposure. For all models, the proportional

hazards assumption was checked through graphical diagnostics based on weighted Schoenfeld residuals.

Sensitivity analyses

Several sensitivity analyses were performed using models with three categories of wildfire exposure (unexposed, low exposure, high exposure). We evaluated effect modification by sex (on the multiplicative scale) by performing analyses stratified by sex and included an interaction term between sex and exposure categories (where $p<0.05$ was interpreted as evidence of effect modification); removed values of area burned $\geq 95^{th}$ percentile; adjusted for ambient $PM_{2.5}$ (as a three-year moving average with a one-year lag); and lagged the exposures by three years instead of one year (for example, the three-year moving average in 1996 was based on average area burned from 1991-1993). In addition, we repeated the lung cancer analyses using six categories of exposure (unexposed and exposed person-years grouped by quintiles) to further explore non-linear trends, and estimated associations between lung cancer and the cumulative frequency of fires in a moving 10-year window (with a 1-year lag), where the cumulative frequency of fires was modelled both as a continuous variable and a categorical variable (zero, one to three, four to six, and seven to ten fires). Lastly, data on smoking status, an important predictor of lung cancer, was not available in the CanCHEC database. We applied an indirect adjustment method to mathematically adjust the lung cancer HRs for unmeasured confounders[215] (details on the sensitivity analyses are provided in the Supplementary Material, additional methods 5 and 6).

The CanCHEC dataset was created under the authority of the Statistics Act and approved by the Executive Management Board at Statistics Canada (reference: 045-2015). This study was also approved by the McGill Faculty of Medicine Research Ethics Board (reference: A02-M09-

20B). All statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary NC) at the Statistics Canada Research Data Centre located at McGill University.

Role of the funding source

The funders were not involved in the study design, data collection, data analysis, data interpretation, writing, or decision to submit this manuscript

Results

Our analyses included over two million subjects followed for a median of 20 years, for a total of 34 million person-years (Table 1, Table S1). There were some differences in baseline covariates between those ever exposed to a wildfire within a 50 km radius of their residential location from 1986-2015 to those never exposed; for example, exposed populations were less likely to live in a census metropolitan area or census agglomeration and were more likely to live in western Canada than unexposed individuals (Table S2). A flow chart describing exclusions from the main cohort to those included in this analysis is shown in the appendix (Figure S2). Figure 1 shows the total area of forest burned in Canada from 1986-2015 and highlights the fact that wildfires tend to occur in similar areas each year. The person-year distribution of area burned within a 20 and 50 km radius of residential locations based on three-year, five-year and ten-year moving averages with a one-year lag is right-skewed, with most person-years unexposed to wildfires (Table S3).

Table 1 Cohort characteristics at baseline

Persons, N	2,040,995
Total person-years[a], N	34,022,680
Years of follow-up, median (interquartile range)	20 (15-20)
Age (years), median (range)	45 (25-89)
Female sex, n (%)	1,047,730 (51)
Marital status, n (%)	
Never married or common law	217,470 (11)
Common-law	179,370 (9)
Married	1,376,180 (67)
Separated	48,510 (2)
Divorced	100,420 (5)
Widowed	119,045 (6)
Income adequacy quintile, n (%)	
1 (lowest)	373,490 (18)
2	404,750 (20)
3	417,405 (20)
4	421,965 (21)
5 (highest)	423,385 (21)
Highest level of education, n (%)	
Less than high school graduation	714,060 (35)
High school graduate with or without trade certificate	728,495 (36)
Post-secondary non-university degree	356,670 (17)
University degree	241,765 (12)
Labour force status, n (%)	
Employed	1,252,175 (61)
Unemployed	116,160 (6)
Not in labour force	672,660 (33)
Occupational class, n (%)	
Management	131,225 (7)
Professional	210,155 (10)
Skilled, technical or supervisory	451,795 (22)
Semi-skilled	474,395 (23)
Unskilled	157,720 (8)
Not applicable	615,710 (30)
Indigenous, n (%)	123,270 (6)
Visible minority, n (%)	45,205 (2)
Immigrant, n (%)	224,545 (11)

All values have been randomly rounded to the nearest five to conform to institutional confidentiality requirements. Percentages based off total number of persons

[a] Includes person-years with at least one non-missing three-year, five-year, or ten-year moving average exposure

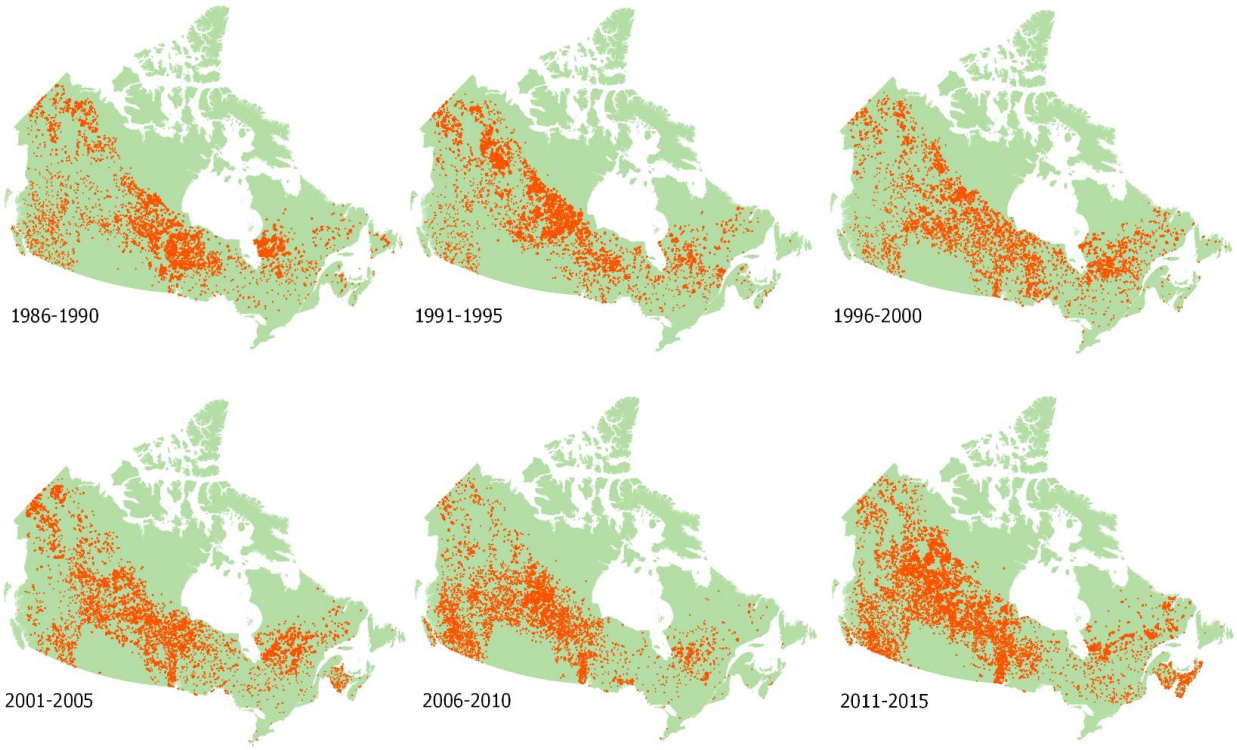

Figure 1 Area of forest burned (in orange) in Canada from 1986-2015

There were approximately 43,000 incident lung cancer events, 3,700 brain cancer events, 12,000 cases of non-Hodgkin lymphoma, 3,900 cases of multiple myeloma, and 7,700 cases of leukemia (Table S4). The adjusted hazard ratios and 95% confidence intervals for cancer outcomes comparing ever/never exposure to wildfires in the past three, five or ten-years is shown in Figure 2 and the appendix (Table S4). Small risk increases were consistently observed for associations between wildfires and lung cancer, with the strongest association observed between any exposure to wildfires in a 50 km radius of residential location in the past five years (HR and 95% CI: 1.061 [1.038-1.083]). Positive associations were also observed between wildfires and brain tumor incidence, with the strongest association observed between any exposure to wildfires in a 50 km radius of residential location in the past ten years (HR and 95% CI: 1.100 [1.026-1.179]).

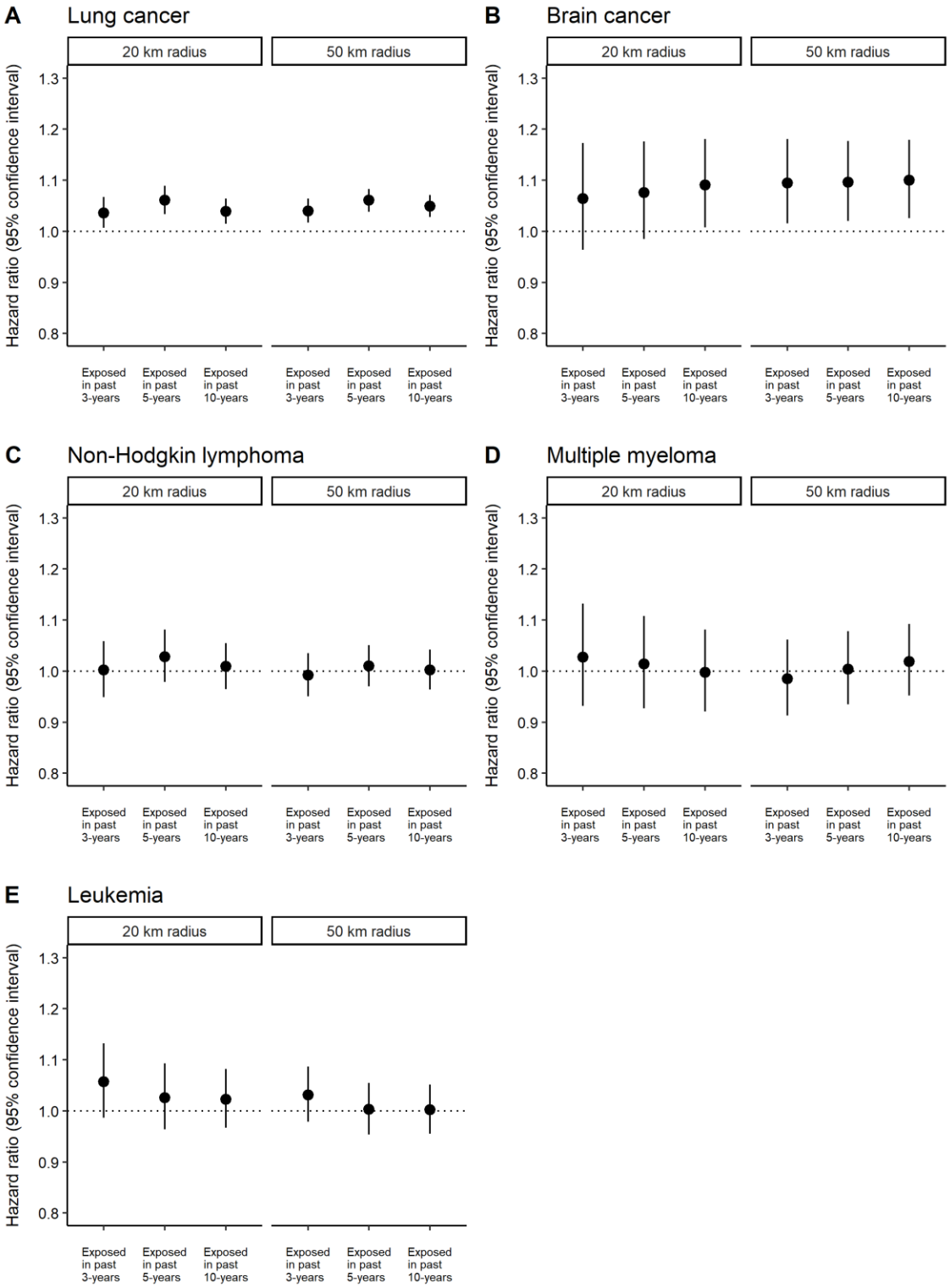

Figure 2 The adjusted associations between any exposure to wildfires in the past three, five or ten years within a 20 km or 50 km radius of residential location in reference to the unexposed group and the incidence of (A) lung cancer; (B) brain cancer; (C) non-Hodgkin lymphoma; (D) multiple myeloma, and; (E) leukemia

The adjusted hazard ratios and 95% confidence intervals for cancer outcomes comparing categories of area burned ('low exposure' and 'high exposure') to the unexposed group are shown in Figure 3 and the appendix (Table S5). As with the dichotomous exposure models, positive associations were consistently observed between wildfire exposure and lung and brain cancer. For lung cancer, the strongest association was observed in the low exposure category of the five-year moving average within the 50 km buffer (HR and 95% CI compared to unexposed: 1.074 [1.047-1.101]). For brain cancer, the risk was elevated in both categories of exposure compared to the unexposed group when exposure was based on a ten-year moving average of area burned within a 50 km radius (low exposure: HR= 1.096 [1.012-1.187]; high exposure: HR=1.105 [1.009-1.210]), and the strongest association was observed among the low exposure category of the ten-year moving average of area burned within a 20 km radius of residential location (HR and 95% CI: 1.144 [1.038-1.259]).

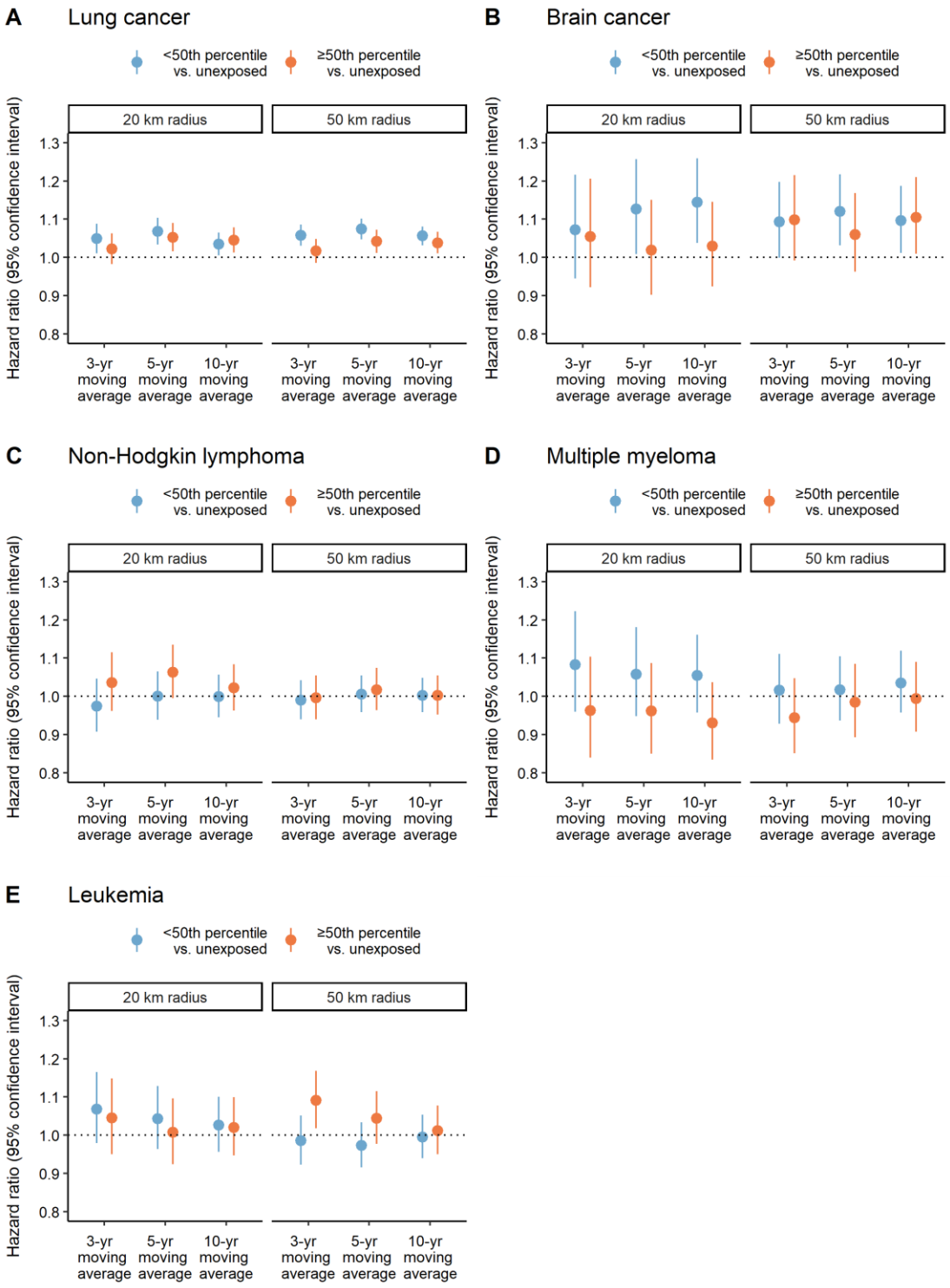

Figure 3 The adjusted associations between categories of area burned ('low exposure' and high exposure', separated at the median distribution of the three, five and ten-year moving average of area burned within a 20 km or 50 km radius) in reference to the unexposed group and the incidence of (A) lung cancer; (B) brain cancer; (C) non-Hodgkin lymphoma; (D) multiple myeloma, and; (E) leukemia

There was some evidence of effect modification (on the multiplicative scale) for lung cancer analyses. For example, when exposure was estimated in a 20 km radius, associations were generally stronger in the less exposed category of the three, five or ten-year moving average among women than men, while the opposite was found in the more exposed category (Table S6). When exposures were estimated in a 50 km radius, associations were typically stronger among men than women for both exposure categories (Table S6). Results were similar when exposures $\geq 95^{th}$ percentile were excluded (Table S7), after additional adjustment for ambient $PM_{2.5}$ (Table S8), and when moving averages were lagged three years (instead of one year) (Table S9). When the lung cancer estimates were indirectly adjusted for missing covariates, most hazard ratios were attenuated slightly, and in some instances, the confidence intervals now included the null (Table S10). When the moving averages were categorized into six groups for lung cancer analyses (an unexposed category and quintiles of exposure, where quintile one reflects lowest exposure and quintile five reflects highest exposure), increased lung cancer risk was generally observed for quintiles one through three compared to the unexposed group, while the HRs and 95% CIs included the null for the fourth and fifth quintile (Table S11). When we considered associations between lung cancer and the cumulative frequency of fires in a ten-year moving window, the adjusted hazard ratio and 95% CI for exposure to one to three fires, four to six fires, and seven to ten fires within a 20 km radius in reference to zero fires were 1.043 (1.017-1.069), 1.071 (1.012-1.132) and 1.055 (0.963-1.156), respectively, while a more apparent dose-response trend was observed in the 50 km radius (HR and 95% CI for one to three fires: 1.055 [1.031-1.079]; four to six fires: 1.067 [1.029-1.106]; seven to ten fires: 1.080 [1.031-1.131]) (Table S12).

When the models included both a dichotomous exposure term (reflecting whether the moving average was zero vs. greater than zero) and a continuous exposure variable (centered at the median among exposed person-years), the HR and 95% for the continuous exposure term included the null for all models (Table S13), indicating that among those with exposure greater than zero, there was no evidence of a clear association between area of forest burned and the risk of any cancers. On the other hand, the dichotomous exposure terms, which compares risk between those unexposed to wildfires vs. those exposed to the median area burned, were greater than one and excluded the null for both lung and brain cancer models. Together, this evidence suggests that exposure to wildfires may be associated with an increased lung cancer and brain tumour risk, but a clear concentration-response relationship was not apparent in terms of "area burned" within a given buffer distance surrounding residences. Wildfires were not associated with hematological cancers in this study (Figures 2 and 3, Tables S4-S9, S13).

Discussion

In the past half century, the total area of forest burned in Canada has increased[82] and projections at a global scale indicate greater fire activity into the future with the changing climate[84,85]. We conducted the first ever cohort study of long-term residential exposure to wildfires and cancer incidence including more than two million adults followed for a median of 20 years with the size and locations of wildfires identified across Canada back to 1986. In doing so, we noted several interesting results.

First, compared to cohort members never exposed to wildfires, exposed populations displayed consistent elevations in the incidence of both lung cancer and brain tumors. Risks were similar between low/high-exposure groups (and sometimes larger in low-exposed groups) in the

categorical analyses. However, no clear associations were observed for the continuous term in models including both a dichotomous term (describing risk in median-exposed populations compared to never exposed groups) and a continuous variable (describing the change in risk with increased area burned among the exposed). We suspect that several factors may have contributed to this result. First, the area burned measure was likely impacted by exposure measurement error, and while the methods used to compile these data were likely adequate in identifying the presence/absence of fires and their location, estimates of total area burned may be less accurate/precise. Moreover, as environmental concentrations of pollutants emitted from wildfires depend on a range of different factors including vegetation type and fire characteristics[216], and because other external factors such as wind patterns play an important role in determining where pollutants travel and deposit, a larger area burned may not directly translate into higher risk. In short, our surrogate measure of area burned within a given buffer is likely a reasonable indicator of whether exposure occurred but may not be ideally suited to accurately quantifying cumulative exposure gradients for environmental carcinogens over a continuous scale.

Wildfires are traditionally associated with elevated smoke and air pollution concentrations and outdoor air pollution is carcinogenic to humans[102], with some evidence suggesting elevated lung cancer risk attributed to biomass burning sources in particular[217]. However, there are several different ways in which people living near wildfires may be exposed to carcinogenic pollutants; for example, emerging evidence indicates that wildfires can contaminate soil and terrestrial environments, water, and indoor environments. Specifically, high concentrations of environmentally persistent free radicals have been found in charcoal samples that remained stable for at least five years after fire events[201]. Moreover, many heavy metals sequestered in soils and vegetation become more mobile and bioavailable following wildfires

due to increased soil erosion and ash dispersal[202]. Heavy metals can then be deposited in nearby bodies of water and contaminate watersheds[197], and may also accumulate in fish living in the affected watersources[218], which may be a potential health concern if consumed by humans. Similarly, wildfires are a significant source of polycyclic aromatic hydrocarbons to both terrestrial and aquatic ecosystems[219]. In addition, violations of exposure limits for nitrates, disinfection by-products, and arsenic in surface and groundwater have been observed in wildfire-affected areas[198]. Widespread drinking water distribution network contamination was also discovered following several fires in California, where concentrations of benzene and other volatile organic compounds (at least partially from the melting of plastic water pipes) were found to be above exposure limits[199].

Moreover, there is also a concern that wildfire-derived pollutants may be retained in indoor environments for long periods of time, but few studies have examined this question. One study reported detectable levels of char in wipe samples collected from homes three to eight months after a major wildfire event in New Mexico[204]. In another study conducted in the wildfire season in Oregon, indoor concentrations of gas-phase PAHs were higher than outdoor concentrations[203], suggesting that once these pollutants enter the home they may persist for long periods of time. On the other hand, two studies found limited retention of heavy metals and PAHs in house dust collected one to two years after a major wildfire event in Fort McMurray, Canada[220,221]. Further work is needed to measure persistent chemicals after wildfires to better understand the long-term impacts on human health. This information will be particularly helpful in determining why some cancers were associated with residential proximity to wildfires (i.e., lung and brain cancer) and some were not (i.e., hematological cancers).

This study had several important strengths including a detailed assessment of wildfire locations across Canada back to 1986, application of this exposure information in a large population-based cohort with exposures updated over time for residential mobility, and detailed adjustment for a number of personal and neighbourhood-level covariates. However, it is important to recognize several limitations. First, as noted above, exposure measurement error likely impacted our estimates of area burned within various buffers around residential locations. For example, there are likely spatial errors in the methods used to identify wildfire perimeters and area burned and six-character postal code centroids are imperfect measures of residential home addresses. Furthermore, the chemical composition of wildfire emissions is affected by numerous factors (e.g., climate, burn conditions, fuel type)[216], and this likely also contributes to variability in the toxicity of emitted pollutants and subsequent health effects. One additional limitation in our approach to assign exposures to wildfires based on residential proximity is that we may not capture pollutants from wildfires that travel long distances. However, we expect that individuals living near wildfires that occur regularly in the same area are more consistently exposed to local wildfire pollutants than pollutants transported over long distances from remote fires. In addition, although we conceptualize the pathway from wildfire exposure to cancer risk primarily through exposure to environmental pollutants, other pathways may also play a role (e.g., wildfires are inherently stressful events and psychological stress may have a role in cancer etiology[222]) and this study is unable to disentangle these different mechanisms. Moreover, this study focused on a small number of specific cancer types, and we acknowledge that other types of cancer may be associated with wildfires. For example, arsenic is a known risk factor of bladder cancer[223], while some evidence supports an association between air pollution breast

cancer[224,225], and future studies may wish to explore other chronic health outcomes. Lastly, we cannot rule out residual confounding by covariates that were not measured in this study.

In summary, this study provides the first epidemiological data that suggests long-term exposure to wildfires may be associated with an elevated risk of lung cancer and brain tumors. These findings are relevant on a global scale given the anticipated impacts of climate change on wildfire frequency and severity. However, in light of the study limitations, and because this is the first epidemiological study investigating associations between wildfires and cancer risk, we emphasize that a causal effect cannot be ascertained from this single study. Further work is needed to refine exposure metrics used in estimating the chronic health impacts of wildfires as well as replication in different geographic locations and populations.

5.3 Supplementary material

Additional Methods

1. Rationale for studying association between wildfire exposure and lung cancer, malignant brain tumors, non-Hodgkin lymphoma, multiple myeloma, and leukemia

We explored the association between wildfire exposure and 5 cancer outcomes selected *a priori*, based on evidence that specific pollutants emitted from wildfires contribute to these types of cancers. For example, particulate matter less than 2.5 μm in diameter ($PM_{2.5}$) is considered a causal agent for the development of lung cancer[102]. Epidemiological research has demonstrated that biomass burning sources of particulate matter may have a greater impact on respiratory health than particulate matter emitted from other sources[103], while toxicological studies have also shown that PM from wildfires is more toxic to lungs than PM collected from normal ambient air[104,105]. Wildfires also emit many ultrafine particles (less than 0.1 μm) which are able to pass the blood-brain barrier[106] and have recently been associated with increased risk of brain tumours in a large Canadian study[107]. Wildfires are also a significant source of human exposure to benzene[108], and benzene is classified as a group 1 carcinogen (carcinogenic to humans) because it causes acute myeloid leukemia[109], a common type of leukemia in adults. Positive associations have also been observed between benzene and non-Hodgkin lymphoma, leukemia, multiple myeloma, lung cancer and brain cancer[109,110]. Although most evidence pertaining to the ability of benzene to cause cancer in humans is from occupational cohorts[109], some evidence also supports the carcinogenicity of long-term, low-dose exposure to ambient benzene[110–112]. In addition, there is sufficient evidence in humans that 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD; a dioxin released from wildfires, among other sources) is carcinogenic and generally positive associations have been found between TCDD and lung cancer and non-Hodgkin lymphoma[113]. There is also

strong evidence that 1-3 butadiene and formaldehyde, both group 1 carcinogens resulting from incomplete combustion, cause tumors of the hematopoietic and lymphoid tissues[114,115]. Heavy metals, including arsenic, lead, cadmium, mercury and aluminum, are able to pass the blood-brain barrier[116] and have been implicated in the development of brain cancer, although evidence is limited[117]. Several heavy metals are also established causes of lung cancer[118].

In addition, we also considered the literature surrounding cancer risk in firefighters, and evidence from a large meta-analysis provides some evidence of an association between firefighting and brain cancer, non-Hodgkin lymphoma, multiple myeloma, and leukemia[119]. Regarding cancer risk among wildland firefighters in particular, the literature is scarce but some evidence supports an association with lung cancer[120]. However, firefighters are very different than the general population (i.e., much healthier), and different pathways beyond environmental pollutants/chemical exposures are likely involved in explaining the elevated cancer risk among firefighters (e.g., working patterns/shift work, psychological stress, etc.), so we did not rely too heavily on this literature when selecting the outcomes for this study.

Although we acknowledge that other types of cancers may also be associated with wildfire exposure, we based our decision to only study lung, brain and several blood cancers based off the strongest biological evidence suggesting that specific wildfire pollutants cause these types of cancers. Future studies may wish to consider other types of cancers. For example, arsenic is a known risk factor of bladder cancer[223], while some evidence supports an association between air pollution breast cancer[224,225].

2. ICD-O Codes (3rd revision) for Cancer Outcomes

Cancer Outcome	ICD-O codes
Lung Cancer (typography codes used)	C33-C34
Malignant neoplasms of the brain (typography codes used)	C71
Non-Hodgkin Lymphoma (morphology codes used)	9590–9597, 9670–9719, 9724–9729, 9735, 9737, 9738; 9811–9818, 9823, 9827, 9837 all sites except C42.0, .1, .4
Multiple myeloma (morphology codes used)	9731, 9732, 9734
Leukemia (morphology codes used)	9733, 9742, 9800–9801, 9805–9809, 9820, 9826, 9831–9836, 9840, 9860–9861, 9863, 9865–9867, 9869–9876, 9891, 9895–9898, 9910, 9911, 9920, 9930–9931, 9940, 9945–9946, 9948, 9963–9964; 9811–9818, 9823, 9827, 9837 sites C42.0,.1,.4. only

3. Additional details on wildfire exposure assessment

Wildfire exposures from 1986-2015 were assigned using the National Burned Area Composite (NBAC)[210,211]; a geographic information systems (GIS) database that relies on three different sources to map area burned: the Canadian National Fire Database (CNFDB), the Multi-Acquisition Fire Mapping System (MAFiMS), and the Hotspot and Normalized Difference Vegetation Index Differencing Synergy (HANDS) algorithm.

The CNFDB is maintained by the Canadian Wildland Fire Information System of Natural Resources Canada[226], and includes information on fire perimeters (polygon data) and fire locations (point data) submitted by provincial, territorial and Parks Canada fire management agencies on a yearly basis. These agencies map fire activity through different sources including ground-based and airborne global positioning system (GPS) surveys and remote sensing, and variation in mapping methods (both within a single agency over time, and between agencies) can affect the quality of polygon delineation, resulting in uncertainty in burned area estimates[211].

When more precise delineation of burned area is required, maps from Landsat (satellite) imagery processed through the Multi-Acquisition Fire Mapping System (MAFiMS) can be used. Details of this process are described elsewhere[211], but briefly, pre and post-burn Landstat images are downloaded and processed with MAFiMS to detect and map burned events, and are then extracted as vector polygons.

The third source contributing to the NBAC is from the Hotspot and Normalized Difference Vegetation Index Differencing Synergy (HANDS) algorithm[227], which Natural Resources Canada uses to generate national fire maps of fires ≥250 hectares on a yearly basis. Satellite data on hotspots detected during a period of interest, a pre-and-post-burn vegetation

index, and vegetation cover are used in the algorithm to map burned pixels, which can then be incorporated into the NBAC[211].

Burned areas reported by all three sources are stored in the NBAC spatial data warehouse, and the NBAC then applies user-defined decision rules to select the best source of data for each fire to be used as the final NBAC product. Generally, the NBAC selects polygons generated through MAFiMS when available, followed by agency polygons, then HANDS polygons[211].

4. Details on covariates

The models were stratified by baseline age (5-year categories), sex and immigrant status, and adjusted for a wide range of personal and neighbourhood-level covariates. Personal covariates were recorded through self-report at baseline, while neighbourhood-level covariates were time-varying. Models were adjusted for the following personal baseline covariates: marital status (never married or common law/common-law/married/separated/divorced/widowed), income adequacy quintile (1=lowest, 5=highest), highest level of education (less than high school graduation/high school graduate with or without trade certificate/postsecondary non-university degree/university degree), labour force status (employed/ unemployed/ not in labour force), occupation class (management/professional/skilled, technical and supervisory/semi-skilled/unskilled/not applicable), Indigenous status (yes/no) and visible minority status (yes/no). Models were also adjusted for age centered at the median of each 5-year strata to account for possible residual confounding within 5-year aga strata.

We also adjusted for several neighbourhood-level variables that were assigned to subjects using residential 6-digit postal codes and data from the closest census year (the census is collected every five years). Neighbourhood-level variables include population size (categorized as census metropolitan areas or census agglomerations (CMA/CA) 500,000-1,499,999/100,000-499,999/30,000-99,999/10,000-29,999/ non-CMA/CA), urban form (active urban core/ transit-reliant suburb/car-reliant suburb/exurban/non-CMA/CA)[228], regional airshed (Western Canada/Prairies/West Central/East Central/South Atlantic/ Northern Canada)[229] , and the Canadian Marginalization Index (CAN-Marg)[212]. CAN-Marg is an indicator of neighbourhood-level socioeconomic status and consists of four domains of marginalization: material deprivation, residential instability, dependency, and ethnic concentration. These indicators are continuous

scores but all four domains are categorized into quintiles to account for non-linear relationships with mortality and other outcomes[12].

Finally, annual estimates of outdoor $PM_{2.5}$ concentrations were assigned to residential postal codes at a spatial resolution of approximately 1 km x 1 km. Methods on how these estimates were derived are described in detail elsewhere[230,231]. $PM_{2.5}$ exposures was assigned using a 3-year moving average with a 1-year lag (updated annually for residential mobility) for consistency with other CanCHEC studies[12,232,233]. We did not include $PM_{2.5}$ in the primary analysis (it was only adjusted for in a sensitivity analysis) because $PM_{2.5}$ is part of the broader contaminant mixture released by wildfires and thus is on the causal pathway between exposure to wildfires and cancer outcomes.

5. Rationale for sensitivity analyses

The rationale for performing each sensitivity analysis is provided in the below table:

Sensitivity analysis	**Rationale for performing this sensitivity analysis**
Models stratified by sex	Biological factors that differ by sex (e.g., body size, hormones, etc.) may contribute to variability in wildfire health effects
Deleted values of area burned $\geq 95^{th}$ percentile	These records may be attributed to measurement error or rare, extreme events
Adjusted the models for ambient $PM_{2.5}$	We did not include $PM_{2.5}$ in the primary analysis because $PM_{2.5}$ is part of the broader contaminant mixture released by wildfires and thus is on the causal pathway between exposure to wildfires and cancer outcomes; however, adjusting for it may account for other sources of $PM_{2.5}$ (e.g., traffic, industry).
Exposures lagged 3 years (instead of 1 year)	To account for uncertainty in identifying the appropriate lag time between wildfire exposure and cancer risk
Lung cancer analyses using 6 categories of exposure	To further explore non-linear trends
Exposure modelled as cumulative number of fires in a moving 10-year window for lung cancer analyses	To further explore how repeated wildfire events may contribute to lung cancer risk
Indirect adjustment for smoking	To evaluate the extent to which confounding by smoking status and body mass index (not measured in our study) may influence the lung cancer results

6. Indirect adjustment for missing confounders

Smoking status is not available in the CanCHEC database and may be an important confounding factor for lung cancer analyses given the strength of association between smoking and lung cancer. Although adjusting for many socioeconomic and demographic covariates may help mitigate residual confounding by smoking, we also applied an indirect adjustment method to mathematically adjust the lung cancer HRs for unmeasured confounding variables (including both smoking and body mass index)[215]. This method has been described in detail[215] and validated[234] elsewhere and applied in several previous studies[13,107,235,236]. Briefly, this method entails estimating the multivariable associations between (i) the covariates included in our survival models and (ii) covariates we indirectly adjust for (never, former or current smoker; body mass index 25-29.9, 30-34.9, 35-39.9, or ≥40 kg/m^2) using a representative auxiliary dataset. We obtained these associations through linking our wildfire exposures to the 2001, 2003, 2005 and 2007 cycles of the Canadian Community Health Survey (CCHS), which has the same target population as the CanCHEC (the Canadian population) and collects information on smoking and body mass index, in addition to most other covariates we adjusted for in our study[237]. In addition to these multivariable associations, the sensitivity analysis also requires obtaining the associations between the missing covariates (smoking and body mass index) and lung cancer from the literature[238,239].

Supplementary figures

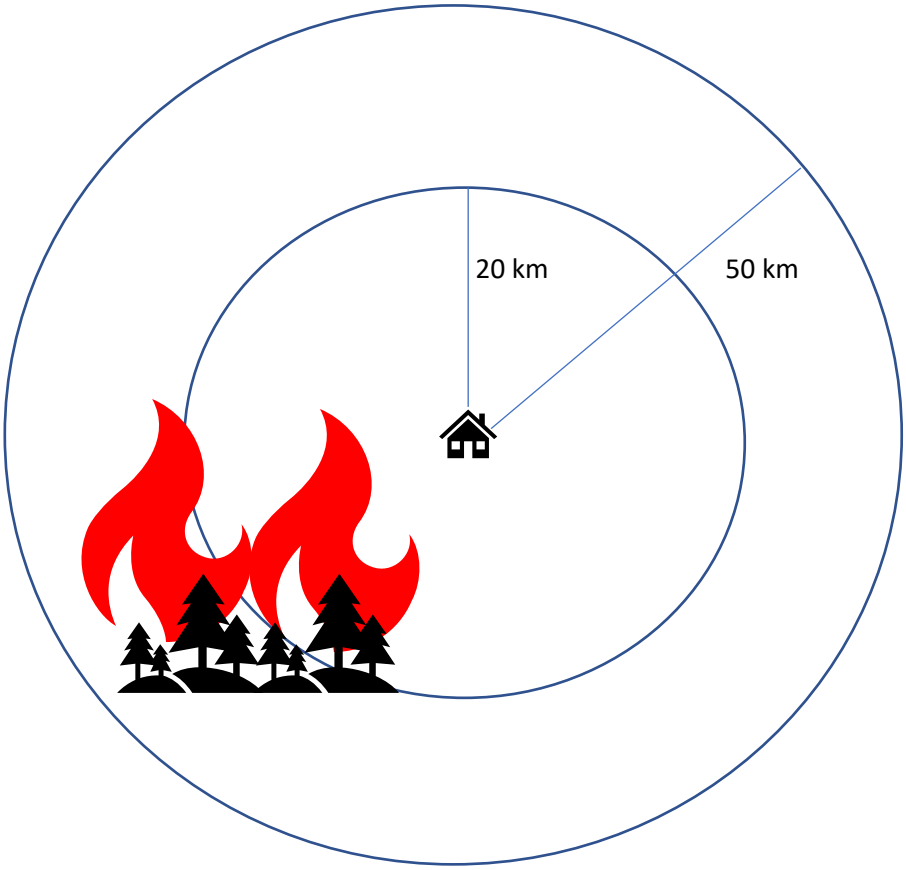

Figure S1 Total area burned (in the units of hectares) within a 20 km and 50 km radius of each residential location (based on a point estimate assigned to 6-digit postal codes) was calculated each year. Total area burned is therefore a time-varying exposure, assigned to each person-year and dependent on where the individual lived each year and where fires occurred.

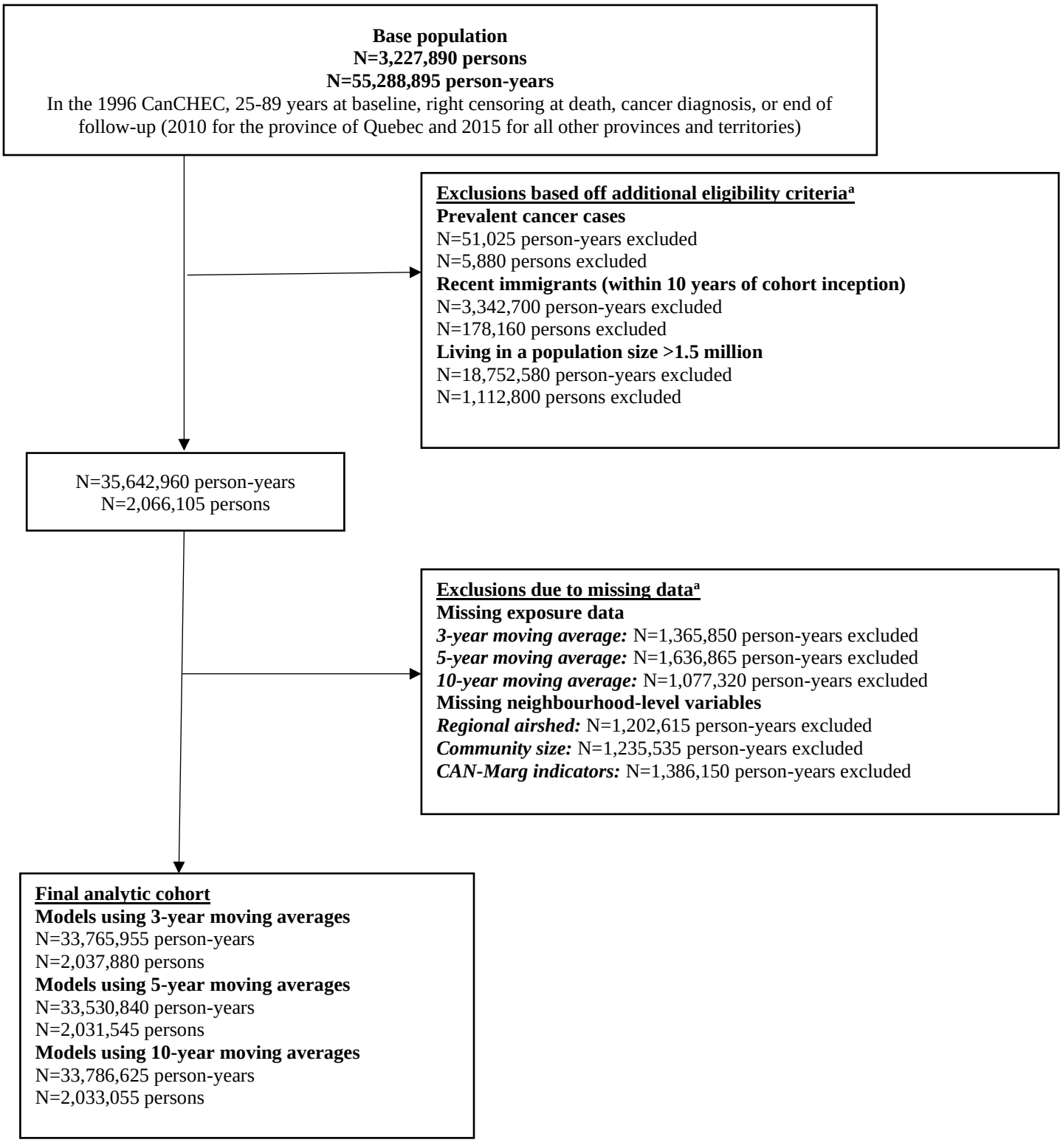

Figure S2 Exclusion of persons and person-years
Counts have been rounded to the nearest 5 to conform with institutional confidentiality requirements
[a] Reasons for exclusions are not mutually exclusive.

Supplementary Tables

Table S1 Neighbourhood-level variables at baseline

Persons, N	2,040,995
Census metropolitan area or census agglomeration (CMA/CA) population size, n (%)	
500,000-1,499,999	452,795 (22)
100,000-499,999	477,325 (23)
30,000-99,999	258,745 (13)
10,000-29,999	106,600 (5)
Non-CMA/CA	745,530 (37)
Urban form, n (%)	
Urban core	115,435 (6)
Transit-reliant suburb	72,335 (3)
Car-reliant suburb	531,075 (26)
Exurban	101,755 (5)
Non-CMA/CA	1,220,395 (60)
CAN-Marg[d]: Material deprivation, n (%)	
1 (lowest)	643,285 (32)
2	637,640 (31)
3	449,165 (22)
4	223,905 (11)
5 (highest)	86,995 (4)
CAN-Marg[d]: Residential instability, n (%)	
1 (lowest)	450,975 (22)
2	538,795 (26)
3	491,205 (24)
4	335,455 (17)
5 (highest)	224,565 (11)
CAN-Marg[d]: Dependency, n (%)	
1 (lowest)	330,430 (16)
2	385,005 (19)

3	401,005 (20)
4	467,030 (23)
5 (highest)	457,520 (22)
CAN-Marg[d]: Ethnic concentration, n (%)	
1 (lowest)	326,105 (16)
2	295,735 (15)
3	315,600 (15)
4	469,305 (23)
5 (highest)	634,245 (31)
Regional airshed, n (%)	
Western Canada	189,430 (10)
Prairies	373,105 (18)
West Central	187,315 (9)
South Atlantic	289,435 (14)
East Central	961,190 (47)
Northern Canada	40,520 (2)

[a] All values have been randomly rounded to the nearest five to conform to institutional confidentiality requirements
[b] Includes person-years with at least one non-missing three-year, five-year, or ten-year moving average exposure
[c] Percentages based off total number of persons
[d] The Canadian Marginalization Index, area-level indicators of marginalization

Table S2 Comparison of baseline characteristics between those ever exposed to a wildfire within a 50 km radius of their house at anytime between 1986-2015, and those never exposed to a wildfire within a 50 km radius of their house between 1986-2015

	Unexposed	**Exposed**	**p-value[b]**
Persons, N	651,440	1,389,550	
Years of follow-up, median (interquartile range)	20 (15-20)	20 (15-20)	
Personal characteristics			
Baseline age (years), median (range)	45 (37-63)	44 (35-56)	<0.0001
Female sex, n (%)	336,710 **(**52)	711,020 (51)	<0.0001
Marital status, n (%)			
Never married or common law	66,600 (10)	150,870 (11)	<0.0001
Common-law	43,925 (7)	135,445 (10)	
Married	444,520 (68)	931,660 (67)	
Separated	15,260 (2)	33,245 (2)	
Divorced	32,405 (5)	68,015 (5)	
Widowed	48,730 (7)	70,315 (5)	
Income adequacy quintile, n (%)			
1 (lowest)	120,820 (19)	252,670 (18)	<0.0001
2	135,610 (21)	269,145 (19)	
3	134,020 (21)	283,385 (20)	
4	131,850 (20)	290,115 (21)	
5 (highest)	129,145 (20)	294,240 (21)	
Highest level of education, n (%)			
Less than high school graduation	242,155 (37)	471,905 (34)	<0.0001
High school graduate with or without trade certificate	225,145 (35)	503,350 (36)	
Post-secondary non-university degree	110,570 (17)	246,105 (18)	
University degree	73,570 (11)	168,190 (12)	
Labour force status, n (%)			
Employed	376,855 (58)	875,320 (63)	<0.0001
Unemployed	29,835 (5)	86,325 (6)	
Not in labour force	244,755 (38)	427,905 (31)	
Occupational class, n (%)			
Management	38,445 (6)	92,780 (7)	<0.0001
Professional	62,610 (10)	147,545 (11)	
Skilled, technical or supervisory	132,445 (20)	319,350 (23)	
Semi-skilled	143,945 (22)	330,450 (24)	
Unskilled	47,200 (7)	110,515 (8)	

Not applicable	38,445 (6)	92,780 (7)	
Indigenous, n (%)	21,265 (3)	102,005 (7)	<0.0001
Visible minority, n (%)	13,850 (2)	31,355 (2)	<0.0001
Immigrant, n (%)	91,990 (14)	132,555 (10)	<0.0001
Neighbourhood-level covariates			
Census metropolitan area or census agglomeration (CMA/CA) population size, n (%)			
500,000-1,499,999	137,990 (21)	314,805 (23)	<0.0001
100,000-499,999	221,535 (34)	255,790 (18)	
30,000-99,999	79,730 (12)	179,010 (13)	
10,000-29,999	3,735 (6)	69,225 (5)	
Non-CMA/CA	174,810 (27)	570,720 (41)	
Urban form, n (%)			
Urban core	47,960 (7)	67,470 (5)	<0.0001
Transit-reliant suburb	27,620 (4)	44,715 (3)	
Car-reliant suburb	207,525 (32)	323,550 (23)	
Exurban	28,775 (4)	72,980 (5)	
Non-CMA/CA	3,395,585 (52)	880,835 (63)	
CAN-Marg[c]: Material deprivation, n (%)			
1 (lowest)	210,275 (32)	67,470 (5)	<0.0001
2	196,740 (30)	44,715 (3)	
3	157,475 (24)	323,550 (23)	
4	60,450 (9)	72,980 (5)	
5 (highest)	26,505 (4)	880,835 (63)	
CAN-Marg[c]: Residential instability, n (%)			
1 (lowest)	141,555 (22)	309,420 (22)	<0.0001
2	153,555 (24)	385,240 (28)	
3	145,690 (22)	345,510 (25)	
4	133,135 (20)	202,320 (15)	
5 (highest)	77,505 (12)	147,060 (11)	
CAN-Marg[c]: Dependency, n (%)			
1 (lowest)	105,015 (16)	225,415 (16)	<0.0001
2	138,640 (21)	246,365 (18)	
3	139,425 (21)	261,580 (19)	
4	150,975 (23)	316,055 (23)	
5 (highest)	117,385 (18)	340,135 (24)	

CAN-Marg[c]: Ethnic concentration, n (%)			
1 (lowest)	69905 (11)	256,200 (18)	<0.0001
2	83,685 (13)	212,055 (15)	
3	97,990 (15)	217,610 (16)	
4	174,560 (27)	294,745 (21)	
5 (highest)	225,300 (35)	408,945 (29)	
Regional airshed, n (%)			
Western Canada	12,105 (2)	177,320 (13)	<0.0001
Prairies	123,355 (19)	249,745 (18)	
West Central	17,820 (3)	169,495 (12)	
South Atlantic	58,285 (9)	231,155 (17)	
East Central	429,470 (66)	531,720 (38)	
Northern Canada	10,405 (2)	30,115 (2)	

[a] All values have been randomly rounded to the nearest five to conform to institutional confidentiality requirements
[b] P-values from chi-squared tests or Wilcoxon rank sum tests
[c] The Canadian Marginalization Index, area-level indicators of marginalization

Table S3 Descriptive statistics of the 3, 5 and 10-year moving averages of area burned within a 20 km or 50 km radius of residential location

		Categories of exposures[a]			Continuous exposure (*including* unexposed person-years)[b]	Continuous exposure (*excluding* unexposed person-years)[c]
	Total person-years[a]	Unexposed person-years, N (%)	'Low exposure' (<50th percentile) person-years, N (%)	'High exposure' (≥50th percentile) person-years, N (%)	Median (5th, 95th percentile) area burned (hectares)	Median (5th, 95th percentile) area burned (hectares)
Exposure based off 3-year moving averages with a 1-year lag						
Area burned in 20 km radius	33,765,955	29,108,150 (86%)	2,340,545 (7%)	2,317,260 (7%)	0 (0, 59)	24 (0.3, 3585)
Area burned in 50 km radius		23,443,200 (70%)	5,183,110 (15%)	5,139,650 (15%)	0 (0, 979)	56 (2, 6857)
Exposure based off 5-year moving averages with a 1-year lag						
Area burned in 20 km radius	33,530,840	27,460,925 (82%)	3,041,570 (9%)	3,028,345 (9%)	0 (0, 122)	20 (0.3, 2971)
Area burned in 50 km radius		20,821,510 (62%)	6,412,080 (19%)	6,297,250 (19%)	0 (0, 1237)	50 (2, 5470)
Exposure based off 10-year moving averages with a 1-year lag						
Area burned in 20 km radius	33,786,625	25,370,740 (75%)	4,241,805 (13%)	4,174,080 (12%)	0 (0, 244)	16 (0.2, 2566)
Area burned in 50 km radius		17,198,210 (51%)	8,365,485 (25%)	8,222,930 (24%)	0 (0, 1716)	49 (2, 4297)

[a] Counts are rounded to the nearest 5 to conform with institutional confidentiality requirements

[b] Descriptive statistics calculated for all person-years in the study, including unexposed person-years. Units are hectares.

[c] Descriptive statistics calculated only among exposed person-years (i.e., when moving averages of area burned are greater than 0). Units are hectares.

Table S4 Associations between any exposure to wildfires in the past 3, 5 or 10-years (with a 1-year lag) within a 20 km or 50 km radius of residential location in reference to the unexposed group and the incidence of lung and brain cancer, non-Hodgkin lymphoma, multiple myeloma, and leukemia, among participants in the 1996 Canadian Census Health and Environment Cohort

		Exposure based off area burned in a 20 km radius of residential location	**Exposure based off area burned in a 50 km radius of residential location**
	Events/ person-years[a]	**Hazard ratio (95% confidence interval)**	**Hazard ratio (95% confidence interval)**
Lung Cancer			
Exposure in the past 3 years (with a 1-year lag)	43,205/ 33,765,955	1.036 (1.007-1.067)	1.040 (1.017-1.064)
Exposure in the past 5 years (with a 1-year lag)	42,785/ 33,530,840	1.061 (1.034-1.089)	1.061 (1.038-1.083)
Exposure in the past 10 years (with a 1-year lag)	43,070/ 33,786,625	1.039 (1.015-1.064)	1.049 (1.028-1.071)
Brain Cancer			
Exposure in the past 3 years (with a 1-year lag)	3,770/ 33,765,955	1.064 (0.964-1.173)	1.095 (1.016-1.181)
Exposure in the past 5 years (with a 1-year lag)	3,740/ 33,530,840	1.076 (0.985-1.176)	1.096 (1.020-1.177)
Exposure in the past 10 years (with a 1-year lag)	3,755/ 33,786,625	1.091 (1.008-1.181)	1.100 (1.026-1.179)
Non-Hodgkin Lymphoma			
Exposure in the past 3 years (with a 1-year lag)	12,140/ 33,765,955	1.002 (0.949-1.059)	0.992 (0.951-1.035)
Exposure in the past 5 years (with a 1-year lag)	12,065/ 33,530,840	1.028 (0.979-1.081)	1.010 (0.970-1.051)
Exposure in the past 10 years (with a 1-year lag)	12,115/ 33,786,625	1.009 (0.965-1.055)	1.002 (0.964-1.042)
Multiple Myeloma			

Exposure in the past 3 years (with a 1-year lag)	3,925/ 33,765,955	1.027 (0.932-1.132)	0.985 (0.913-1.062)
Exposure in the past 5 years (with a 1-year lag)	3,890/ 33,530,840	1.014 (0.927-1.108)	1.004 (0.935-1.078)
Exposure in the past 10 years (with a 1-year lag)	3,895/ 33,786,625	0.998 (0.921-1.081)	1.019 (0.952-1.092)
Leukemia			
Exposure in the past 3 years (with a 1-year lag)	7,760/ 33,765,955	1.057 (0.987-1.132)	1.031 (0.979-1.087)
Exposure in the past 5 years (with a 1-year lag)	7,700/ 33,530,840	1.026 (0.964-1.093)	1.003 (0.954-1.055)
Exposure in the past 10 years (with a 1-year lag)	7,730/ 33,786,625	1.023 (0.967-1.082)	1.002 (0.955-1.052)

[a] Counts are rounded to the nearest 5 to conform with institutional confidentiality requirements

Cox proportional hazards models are stratified by baseline age (5-year categories), immigrant status (yes/no) and sex, and adjusted for the following covariates: regional airshed, community size, urban status, CAN-Marg indicators (quintiles of ethnic concentration, dependency, deprivation, instability), highest level of education, employment status, marital status, visible minority status, Indigenous status, occupation, and age (centered at the median within each 5-year category)

Table S5 Associations between area of forest burned within a 20 km and 50 km radius of residential locations, comparing categories of the 3, 5 and 10-year moving averages with a 1-year lag separated at the median area burned (i.e., 'low exposure' and 'high exposure') in reference to the unexposed group, and the incidence of lung and brain cancer, non-Hodgkin lymphoma, multiple myeloma, and leukemia, among participants in the 1996 Canadian Census Health and Environment Cohort

		Exposure based off area burned in a 20 km radius of residential location	**Exposure based off area burned in a 50 km radius of residential location**
	Events/ person-years[a]	**Hazard ratio (95% confidence interval)**	**Hazard ratio (95% confidence interval)**
Lung Cancer			
3-year moving average (with a 1-year lag)			
<50th percentile vs. unexposed	43,205/	1.049 (1.011-1.088)	1.058 (1.030-1.086)
≥50th percentile vs. unexposed	33,765,955	1.022 (0.982-1.063)	1.017 (0.986-1.048)
5-year moving average (with a 1-year lag)			
<50th percentile vs. unexposed	42,785/	1.068 (1.034-1.104)	1.074 (1.047-1.101)
≥50th percentile vs. unexposed	33,530,840	1.052 (1.016-1.090)	1.042 (1.012-1.072)
10-year moving average (with a 1-year lag)			
<50th percentile vs. unexposed	43,070/	1.035 (1.005-1.065)	1.056 (1.031-1.081)
≥50th percentile vs. unexposed	33,786,625	1.045 (1.013-1.078)	1.038 (1.011-1.067)
Brain Cancer			
3-year moving average (with a 1-year lag)			
<50th percentile vs. unexposed	3,770/	1.072 (0.945-1.216)	1.093 (0.999-1.197)
≥50th percentile vs. unexposed	33,765,955	1.054 (0.922-1.206)	1.098 (0.992-1.215)
5-year moving average (with a 1-year lag)			
<50th percentile vs. unexposed	3,740/	1.126 (1.008 -1.257)	1.120 (1.031-1.217)
≥50th percentile vs. unexposed	33,530,840	1.019 (0.902-1.150)	1.060 (0.962-1.168)
10-year moving average (with a 1-year lag)			
<50th percentile vs. unexposed	3,755/	1.144 (1.038-1.259)	1.096 (1.012-1.187)
≥50th percentile vs. unexposed	33,786,625	1.029 (0.924-1.145)	1.105 (1.009-1.210)
Non-Hodgkin Lymphoma			
3-year moving average (with a 1-year lag)			
<50th percentile vs. unexposed	12,140/	0.974 (0.907-1.046)	0.990 (0.940-1.042)
≥50th percentile vs. unexposed	33,765,955	1.036 (0.961-1.115)	0.996 (0.940-1.054)
5-year moving average (with a 1-year lag)			
<50th percentile vs. unexposed	12,065/	1.000 (0.938-1.065)	1.005 (0.958-1.054)
≥50th percentile vs. unexposed	33,530,840	1.063 (0.995-1.135)	1.017 (0.964-1.074)

10-year moving average (with a 1-year lag)			
<50th percentile vs. unexposed	12,115/	0.999 (0.945-1.056)	1.002 (0.958-1.048)
≥50th percentile vs. unexposed	33,786,625	1.022 (0.963-1.084)	1.002 (0.952-1.054)
Multiple Myeloma			
3-year moving average (with a 1-year lag)			
<50th percentile vs. unexposed	3,925/	1.083 (0.959-1.223)	1.016 (0.928-1.111)
≥50th percentile vs. unexposed	33,765,955	0.962 (0.839-1.104)	0.944 (0.851-1.047)
5-year moving average (with a 1-year lag)			
<50th percentile vs. unexposed	3,890/	1.058 (0.948-1.181)	1.017 (0.936-1.105)
≥50th percentile vs. unexposed	33,530,840	0.961 (0.850-1.087)	0.984 (0.893-1.085)
10-year moving average (with a 1-year lag)			
<50th percentile vs. unexposed	3,895/	1.054 (0.957-1.161)	1.035 (0.957-1.119)
≥50th percentile vs. unexposed	33,786,625	0.930 (0.834-1.037)	0.994 (0.907-1.090)
Leukemia			
3-year moving average (with a 1-year lag)			
<50th percentile vs. unexposed	7,760/	1.068 (0.979-1.165)	0.985 (0.923-1.051)
≥50th percentile vs. unexposed	33,765,955	1.045 (0.950-1.148)	1.091 (1.018-1.168)
5-year moving average (with a 1-year lag)			
<50th percentile vs. unexposed	7,700/	1.043 (0.964-1.129)	0.973 (0.916-1.034)
≥50th percentile vs. unexposed	33,530,840	1.007 (0.924-1.096)	1.044 (0.977-1.115)
10-year moving average (with a 1-year lag)			
<50th percentile vs. unexposed	7,730/	1.026 (0.956-1.100)	0.995 (0.940-1.053)
≥50th percentile vs. unexposed	33,786,625	1.020 (0.947-1.099)	1.012 (0.950-1.077)

[a] Counts are rounded to the nearest 5 to conform with institutional confidentiality requirements

Cox proportional hazards models are stratified by baseline age (5-year categories), immigrant status (yes/no) and sex, and adjusted for the following covariates: regional airshed, community size, urban status, CAN-Marg indicators (quintiles of ethnic concentration, dependency, deprivation, instability), highest level of education, employment status, marital status, visible minority status, Indigenous status, occupation, and age (centered at the median within each 5-year category)

Table S6 Associations between area of forest burned within a 20 km and 50 km radius of residential locations, comparing categories of the 3, 5 and 10-year moving averages with a 1-year lag separated at the median area burned (i.e., 'low exposure' and 'high exposure') in reference to the unexposed group, and the incidence of lung and brain cancer, non-Hodgkin lymphoma, multiple myeloma, and leukemia, among participants in the 1996 Canadian Census Health and Environment Cohort, among men and women separately

	Women		Men		p-value[b]
	Events/ person-years[a]	Hazard ratio (95% confidence interval)	Events/ person-years[a]	Hazard ratio (95% confidence interval)	
Exposure based off area burned in a 20 km radius of residential location					
Lung cancer					
3-year moving average with a 1-year lag					
<50th percentile vs. unexposed	18,955/	1.070 (1.014-1.130)	24,255/	1.030 (0.980-1.084)	<0.001
≥50th percentile vs. unexposed	17,552,495	0.998 (0.940-1.061)	16,213,460	1.042 (0.988-1.098)	0.005
5-year moving average with a 1-year lag					
<50th percentile vs. unexposed	18,705/	1.063 (1.012-1.116)	24,080/	1.071 (1.025-1.120)	0.004
≥50th percentile vs. unexposed	17,406,010	1.009 (0.956-1.066)	16,124,830	1.089 (1.039-1.141)	0.021
10-year moving average with a 1-year lag					
<50th percentile vs. unexposed	18,775/	1.039 (0.995-1.085)	24,290/	1.032 (0.992-1.073)	0.004
≥50th percentile vs. unexposed	17,511,185	1.002 (0.955-1.051)	16,275,435	1.081 (1.038-1.126)	0.020
Brain cancer					
3-year moving average with a 1-year lag					
<50th percentile vs. unexposed	1,615/ 17,552,495	1.161 (0.962-1.401)	2,155/	1.008 (0.851-1.195)	0.195
≥50th percentile vs. unexposed		1.125 (0.919-1.378)	16,213,460	1.005 (0.840-1.202)	0.278
5-year moving average with a 1-year lag					
<50th percentile vs. unexposed	1,595/	1.204 (1.019-1.422)	2,145/	1.071 (0.924-1.241)	0.256
≥50th percentile vs. unexposed	17,406,010	1.074 (0.892-1.293)	16,124,830	0.980 (0.835-1.152)	0.353
10-year moving average with a 1-year lag					
<50th percentile vs. unexposed	1,595/	1.113 (0.957-1.293)	2,160/	1.166 (1.028-1.322)	0.631
≥50th percentile vs. unexposed	17,511,185	1.048 (0.888-1.236)	16,275,435	1.016 (0.882-1.169)	0.646
Non-Hodgkin Lymphoma					
3-year moving average with a 1-year lag					
<50th percentile vs. unexposed	5,520/	1.056 (0.953-1.169)	6,625/	0.905 (0.819-0.999)	0.003
≥50th percentile vs. unexposed	17,552,495	1.017 (0.909-1.138)	16,213,460	1.051 (0.952-1.160)	0.861
5-year moving average with a 1-year lag					
<50th percentile vs. unexposed	5,465/ 17,406,010	1.085 (0.991-1.189)	6,600/	0.928 (0.850-1.013)	0.001
≥50th percentile vs. unexposed		1.061 (0.960-1.172)	16,124,830	1.065 (0.975-1.163)	0.560
10-year moving average with a 1-year lag					
<50th percentile vs. unexposed	5,465/	1.005 (0.925-1.091)	6,650/	0.993 (0.921-1.070)	0.318
≥50th percentile vs. unexposed	17,511,185	1.040 (0.952-1.136)	16,275,435	1.008 (0.931-1.091)	0.181
Multiple Myeloma					
3-year moving average with a 1-year lag					
<50th percentile vs. unexposed	1,705/ 17,552,495	1.081 (0.897-1.302)	2,220/	1.087 (0.925-1.277)	0.883
≥50th percentile vs. unexposed		1.053 (0.859-1.291)	16,213,460	0.899 (0.747-1.082)	0.173
5-year moving average with a 1-year lag					
<50th percentile vs. unexposed	1,680/	1.013 (0.853-1.202)	2,210/	1.095 (0.948-1.264)	0.631
≥50th percentile vs. unexposed	17,406,010	1.076 (0.898-1.289)	16,124,830	0.881 (0.746-1.041)	0.048
10-year moving average with a 1-year lag					

<50th percentile vs. unexposed	1,675/	0.990 (0.851-1.151)	2,220/	1.105 (0.974-1.254)	0.349
≥50th percentile vs. unexposed	17,511,185	0.923 (0.780-1.092)	16,275,435	0.938 (0.813-1.082)	0.924
Leukemia					
3-year moving average with a 1-year lag					
<50th percentile vs. unexposed	3,030/ 17,552,495	0.960 (0.829-1.111)	4,730/	1.135 (1.019-1.265)	0.085
≥50th percentile vs. unexposed		1.030 (0.882-1.204)	16,213,460	1.054 (0.936-1.186)	0.737
5-year moving average with a 1-year lag					
<50th percentile vs. unexposed	2,980/	0.965 (0.847-1.100)	4,720/	1.091 (0.989-1.205)	0.171
≥50th percentile vs. unexposed	17,406,010	0.987 (0.857-1.137)	16,124,830	1.019 (0.915-1.134)	0.659
10-year moving average with a 1-year lag					
<50th percentile vs. unexposed	2,990/	1.024 (0.914-1.147)	4,740/	1.026 (0.938-1.122)	0.986
≥50th percentile vs. unexposed	17,511,185	1.011 (0.894-1.143)	16,275,435	1.025 (0.933-1.126)	0.804
Exposure based off area burned in a 50 km radius of residential location					
Lung cancer					
3-year moving average with a 1-year lag					
<50th percentile vs. unexposed	18,955/	1.026 (0.985-1.069)	24,255/	1.081 (1.043-1.120)	0.261
≥50th percentile vs. unexposed	17,552,495	1.008 (0.963-1.055)	16,213,460	1.024 (0.983-1.067)	<0.001
5-year moving average with a 1-year lag					
<50th percentile vs. unexposed	18,705/	1.049 (1.010-1.090)	24,080/	1.092 (1.056-1.128)	0.612
≥50th percentile vs. unexposed	17,406,010	1.028 (0.985-1.074)	16,124,830	1.052 (1.012-1.094)	<0.001
10-year moving average with a 1-year lag					
<50th percentile vs. unexposed	18,775/	1.070 (1.033-1.109)	24,290/	1.045 (1.012-1.078)	0.001
≥50th percentile vs. unexposed	17,511,185	1.027 (0.985-1.070)	16,275,435	1.046 (1.009-1.085)	<0.001
Brain cancer					
3-year moving average with a 1-year lag					
<50th percentile vs. unexposed	1,615/ 17,552,495	1.036 (0.899-1.193)	2,155/	1.135 (1.009-1.277)	0.438
≥50th percentile vs. unexposed		1.143 (0.981-1.333)	16,213,460	1.064 (0.930-1.219)	0.230
5-year moving average with a 1-year lag					
<50th percentile vs. unexposed	1,595/	1.089 (0.957-1.239)	2,145/	1.141 (1.024-1.273)	0.594
≥50th percentile vs. unexposed	17,406,010	1.111 (0.959-1.288)	16,124,830	1.023 (0.899-1.164)	0.196
10-year moving average with a 1-year lag					
<50th percentile vs. unexposed	1,595/	1.113 (0.957-1.293)	2,160/	1.137 (1.025-1.262)	0.230
≥50th percentile vs. unexposed	17,511,185	1.048 (0.888-1.236)	16,275,435	1.047 (0.928-1.181)	0.144
Non-Hodgkin Lymphoma					
3-year moving average with a 1-year lag					
<50th percentile vs. unexposed	5,520/	0.972 (0.901-1.050)	6,625/	1.003 (0.936-1.075)	0.887
≥50th percentile vs. unexposed	17,552,495	0.991 (0.910-1.078)	16,213,460	1.000 (0.926-1.081)	0.294
5-year moving average with a 1-year lag					
<50th percentile vs. unexposed	5,465/ 17,406,010	0.991 (0.923-1.064)	6,600/	1.015 (0.952-1.082)	0.999
≥50th percentile vs. unexposed		1.026 (0.948-1.112)	16,124,830	1.010 (0.939-1.086)	0.107
10-year moving average with a 1-year lag					
<50th percentile vs. unexposed	5,465/	0.966 (0.903-1.033)	6,650/	1.032 (0.971-1.095)	0.406
≥50th percentile vs. unexposed	17,511,185	0.993 (0.920-1.071)	16,275,435	1.010 (0.943-1.082)	0.229
Multiple Myeloma					
3-year moving average with a 1-year lag					
<50th percentile vs. unexposed	1,705/ 17,552,495	1.063 (0.929-1.217)	2,220/	0.982 (0.870-1.107)	0.242
≥50th percentile vs. unexposed		0.963 (0.823-1.127)	16,213,460	0.930 (0.810-1.068)	0.435
5-year moving average with a 1-year lag					
<50th percentile vs. unexposed	1,680/	1.060 (0.936-1.201)	2,210/	0.985 (0.881-1.101)	0.214
≥50th percentile vs. unexposed	17,406,010	0.961 (0.827-1.116)	16,124,830	1.003 (0.882-1.140)	0.869

10-year moving average with a 1-year lag					
<50th percentile vs. unexposed	1,675/	1.045 (0.929-1.177)	2,220/	1.027 (0.926-1.140)	0.616
≥50th percentile vs. unexposed	17,511,185	0.967 (0.840-1.113)	16,275,435	1.016 (0.901-1.146)	0.923
Leukemia					
3-year moving average with a 1-year lag					
<50th percentile vs. unexposed	3,030/ 17,552,495	1.012 (0.912-1.123)	4,730/	0.967 (0.890-1.052)	0.476
≥50th percentile vs. unexposed		1.083 (0.969-1.210)	16,213,460	1.095 (1.003-1.195)	0.711
5-year moving average with a 1-year lag					
<50th percentile vs. unexposed	2,980/	0.978 (0.887-1.078)	4,720/	0.969 (0.898-1.047)	0.974
≥50th percentile vs. unexposed	17,406,010	1.024 (0.920-1.139)	16,124,830	1.056 (0.971-1.148)	0.841
10-year moving average with a 1-year lag					
<50th percentile vs. unexposed	2,990/	1.020 (0.931-1.117)	4,740/	0.979 (0.911-1.053)	0.595
≥50th percentile vs. unexposed	17,511,185	0.997 (0.901-1.103)	16,275,435	1.021 (0.942-1.105)	0.674

[a] Counts are rounded to the nearest 5 to conform with institutional confidentiality requirements

[b] p-value is from the interaction term between wildfire exposure categories and sex ($p<0.05$ interpreted as evidence of effect modification on the multiplicative scale), while HR (95% CI) from analyses stratified by sex

Cox proportional hazards models are stratified by baseline age (5-year categories) and immigrant status, and adjusted for the following covariates: regional airshed, community size, urban status, CAN-Marg indicators (quintiles of ethnic concentration, dependency, deprivation, instability), highest level of education, employment status, marital status, visible minority status, Indigenous status, occupation and age (centered at the median within each 5-year category)

Table S7 Associations between area of forest burned within a 20 km and 50 km radius of residential locations, comparing categories of the 3, 5 and 10-year moving averages with a 1-year lag separated at the median area burned (i.e., 'low exposure' and 'high exposure') in reference to the unexposed group, and the incidence of lung and brain cancer, non-Hodgkin lymphoma, multiple myeloma, and leukemia, among participants in the 1996 Canadian Census Health and Environment Cohort, excluding exposures ≥95th percentile

	Exposure based off area burned in a 20 km radius of residential location		Exposure based off area burned in a 50 km radius of residential location	
	Events/ person-years[a]	**Hazard ratio (95% confidence interval)**	**Events/ person- years[a]**	**Hazard ratio (95% confidence interval)**
Lung Cancer				
3-year moving average with a 1-year lag				
<50th percentile vs. unexposed	42,740/	1.050 (1.010-1.091)	41,970/	1.052 (1.023-1.082)
≥50th percentile vs. unexposed	33,357,925	1.024 (0.984-1.067)	32,682,985	1.028 (0.997-1.060)
5-year moving average with a 1-year lag				
<50th percentile vs. unexposed	42,075/	1.062 (1.026-1.099)	40,900/	1.076 (1.049-1.105)
≥50th percentile vs. unexposed	32,900,270	1.073 (1.035-1.112)	31,939,455	1.041 (1.011-1.071)
10-year moving average with a 1-year lag				
<50th percentile vs. unexposed	43,055/	1.032 (1.002-1.063)	42,950/	1.057 (1.032-1.082)
≥50th percentile vs. unexposed	33,774,730	1.050 (1.018-1.083)	33,651,990	1.045 (1.017-1.073)
Brain Cancer				
3-year moving average with a 1-year lag				
<50th percentile vs. unexposed	3,730/	1.062 (0.931-1.212)	3,680/	1.111 (1.012-1.221)
≥50th percentile vs. unexposed	33,357,925	1.070 (0.935-1.226)	32,682,985	1.090 (0.985-1.207)
5-year moving average with a 1-year lag				
<50th percentile vs. unexposed	3,680/	1.069 (0.950-1.203)	3,600/	1.120 (1.026-1.222)
≥50th percentile vs. unexposed	32,900,270	1.097 (0.972-1.237)	31,939,455	1.078 (0.980-1.186)
10-year moving average with a 1-year lag				
<50th percentile vs. unexposed	3,750/	1.141 (1.034-1.260)	3,745/	1.116 (1.030-1.209)
≥50th percentile vs. unexposed	33,774,730	1.049 (0.944-1.166)	33,651,990	1.071 (0.978-1.171)
Non-Hodgkin Lymphoma				
3-year moving average with a 1-year lag				
<50th percentile vs. unexposed	12,015/	1.013 (0.941-1.090)	11,800/	0.991 (0.939-1.045)
≥50th percentile vs. unexposed	33,357,925	1.025 (0.949-1.106)	32,682,985	0.991 (0.935-1.050)
5-year moving average with a 1-year lag				
<50th percentile vs. unexposed	11,845/	1.013 (0.948-1.082)	11,535/	1.000 (0.951-1.051)
≥50th percentile vs. unexposed	32,900,270	1.033 (0.965-1.107)	31,939,455	1.010 (0.957-1.066)

10-year moving average with a 1-year lag				
<50th percentile vs. unexposed	12,105/	1.009 (0.954-1.068)	12,085/	1.001 (0.957-1.047)
≥50th percentile vs. unexposed	33,774,730	1.012 (0.954-1.074)	33,651,990	1.009 (0.960-1.061)
Multiple Myeloma				
3-year moving average with a 1-year lag				
<50th percentile vs. unexposed	3,875/	1.110 (0.979-1.259)	3,805/	1.030 (0.938-1.130)
≥50th percentile vs. unexposed	33,357,925	0.916 (0.794-1.057)	32,682,985	0.911 (0.819-1.013)
5-year moving average with a 1-year lag				
<50th percentile vs. unexposed	3,820/	1.071 (0.955-1.201)	3,715/	1.029 (0.943-1.123)
≥50th percentile vs. unexposed	32,900,270	0.938 (0.826-1.065)	31,939,455	0.956 (0.867-1.055)
10-year moving average with a 1-year lag				
<50th percentile vs. unexposed	3,895/	1.052 (0.953-1.161)	3,885/	1.049 (0.970-1.135)
≥50th percentile vs. unexposed	33,774,730	0.941 (0.845-1.048)	33,651,990	0.976 (0.892-1.069)
Leukemia				
3-year moving average with a 1-year lag				
<50th percentile vs. unexposed	7,675/	1.067 (0.974-1.168)	7,540/	0.981 (0.916-1.050)
≥50th percentile vs. unexposed	33,357,925	1.050 (0.954-1.157)	32,682,985	1.095 (1.021-1.173)
5-year moving average with a 1-year lag				
<50th percentile vs. unexposed	7,570/	1.048 (0.965-1.138)	7,360/	0.968 (0.908-1.032)
≥50th percentile vs. unexposed	32,900,270	1.003 (0.919-1.095)	31,939,455	1.034 (0.968-1.105)
10-year moving average with a 1-year lag				
<50th percentile vs. unexposed	7,730/	1.036 (0.965-1.113)	7,720/	0.989 (0.934-1.047)
≥50th percentile vs. unexposed	33,774,730	1.015 (0.942-1.094)	33,651,990	1.021 (0.960-1.086)

[a] Counts are rounded to the nearest 5 to conform with institutional confidentiality requirements. Events and person-years differ between exposures estimated in the 20 km and 50 km radius due to differential exclusion of extreme values (≥95th percentile) between the two radiuses

Cox proportional hazards models are stratified by sex, baseline age (5-year categories) and immigrant status, and adjusted for the following covariates: regional airshed, community size, urban status, CAN-Marg indicators (quintiles of ethnic concentration, dependency, deprivation, instability), highest level of education, employment status, marital status, visible minority status, Indigenous status, occupation and age (centered at the median within each 5-year category)

Table S8 Associations between area of forest burned within a 20 km and 50 km radius of residential locations, comparing categories of the 3, 5 and 10-year moving averages with a 1-year lag separated at the median area burned (i.e., 'low exposure' and 'high exposure') in reference to the unexposed group, and the incidence of lung and brain cancer, non-Hodgkin lymphoma, multiple myeloma, and leukemia, among participants in the 1996 Canadian Census Health and Environment Cohort, additionally adjusted for ambient $PM_{2.5}$ (using a 3-year moving average with a 1-year lag)

		Exposure based off area burned in a 20 km radius of residential location	**Exposure based off area burned in a 50 km radius of residential location**
	Events/ person-years[a]	**Hazard ratio (95% confidence interval)**	**Hazard ratio (95% confidence interval)**
Lung Cancer			
3-year moving average with a 1-year lag			
<50th percentile vs. unexposed	43,140/	1.051 (1.013-1.090)	1.060 (1.032-1.089)
≥50th percentile vs. unexposed	33,748,135	1.024 (0.984-1.065)	1.020 (0.989-1.052)
5-year moving average with a 1-year lag			
<50th percentile vs. unexposed	42,745/	1.070 (1.035-1.106)	1.075 (1.048-1.102)
≥50th percentile vs. unexposed	33,518,540	1.053 (1.017-1.092)	1.043 (1.013-1.074)
10-year moving average with a 1-year lag			
<50th percentile vs. unexposed	42,905/	1.038(1.009-1.069)	1.060 (1.035-1.085)
≥50th percentile vs. unexposed	33,745,920	1.049 (1.017-1.082)	1.043 (1.015-1.071)
Brain Cancer			
3-year moving average with a 1-year lag			
<50th percentile vs. unexposed	3,765/	1.074 (0.947-1.219)	1.097 (1.002-1.201)
≥50th percentile vs. unexposed	33,748,135	1.054 (0.922-1.206)	1.103 (0.996-1.220)
5-year moving average with a 1-year lag			
<50th percentile vs. unexposed	3,735/	1.128 (1.010-1.260)	1.123 (1.033-1.220)
≥50th percentile vs. unexposed	33,518,540	1.019 (0.902-1.151)	1.064 (0.965-1.173)
10-year moving average with a 1-year lag			
<50th percentile vs. unexposed	3,745/	1.147 (1.042-1.264)	1.101 (1.016-1.192)
≥50th percentile vs. unexposed	33,745,920	1.027 (0.922-1.143)	1.108 (1.011-1.214)
Non-Hodgkin Lymphoma			
3-year moving average with a 1-year lag			
<50th percentile vs. unexposed	12,135/	0.974 (0.907-1.045)	0.989 (0.940-1.041)
≥50th percentile vs. unexposed	33,748,135	1.036 (0.962-1.116)	0.996 (0.940-1.054)
5-year moving average with a 1-year lag			
<50th percentile vs. unexposed	12,060/	0.999 (0.938-1.065)	1.004 (0.958-1.053)

≥50th percentile vs. unexposed	33,518,540	1.063 (0.995-1.136)	1.017 (0.963-1.073)
10-year moving average with a 1-year lag			
<50th percentile vs. unexposed	12,100/	0.999 (0.945-1.056)	1.002 (0.958-1.047)
≥50th percentile vs. unexposed	33,745,920	1.022 (0.963-1.084)	1.002 (0.952-1.055)
Multiple Myeloma			
3-year moving average with a 1-year lag			
<50th percentile vs. unexposed	3,920/	1.086 (0.961-1.227)	1.021 (0.933-1.118)
≥50th percentile vs. unexposed	33,748,135	0.959 (0.836-1.101)	0.948 (0.855-1.052)
5-year moving average with a 1-year lag			
<50th percentile vs. unexposed	3,890/	1.060 (0.950-1.184)	1.023 (0.941-1.112)
≥50th percentile vs. unexposed	33,518,540	0.958 (0.847-1.083)	0.988 (0.896-1.089)
10-year moving average with a 1-year lag			
<50th percentile vs. unexposed	3,890/	1.063 (0.965-1.171)	1.048 (0.969-1.134)
≥50th percentile vs. unexposed	33,745,920	0.937 (0.840-1.045)	1.008 (0.919-1.105)
Leukemia			
3-year moving average with a 1-year lag			
<50th percentile vs. unexposed	7,755/	1.068 (0.979-1.166)	0.986 (0.924-1.052)
≥50th percentile vs. unexposed	33,748,135	1.044 (0.950-1.147)	1.091 (1.018-1.169)
5-year moving average with a 1-year lag			
<50th percentile vs. unexposed	7,695/	1.044 (0.965-1.130)	0.974 (0.917-1.035)
≥50th percentile vs. unexposed	33,518,540	1.007 (0.924-1.096)	1.044 (0.978-1.115)
10-year moving average with a 1-year lag			
<50th percentile vs. unexposed	7,720/	1.027 (0.957-1.102)	0.997 (0.942-1.055)
≥50th percentile vs. unexposed	33,745,920	1.022 (0.949-1.101)	1.014 (0.952-1.080)

[a] Counts are rounded to the nearest 5 to conform with institutional confidentiality requirements

Cox proportional hazards models are stratified by sex, baseline age (5-year categories) and immigrant status (yes/no), and adjusted for the following covariates: regional airshed, community size, urban status, CAN-Marg indicators (quintiles of ethnic concentration, dependency, deprivation, instability), highest level of education, employment status, marital status, visible minority status, Indigenous status, occupation, age (centered at the median within each 5-year category), and ambient $PM_{2.5}$ (3-year moving average with a 1-year lag)

Table S9 Associations between area of forest burned within a 20 km and 50 km radius of residential locations, comparing categories of the 3, 5 and 10-year moving averages with a **3-year lag** separated at the median area burned (i.e., 'low exposure' and 'high exposure') in reference to the unexposed group, and the incidence of lung and brain cancer, non-Hodgkin lymphoma, multiple myeloma, and leukemia, among participants in the 1996 Canadian Census Health and Environment Cohort

		Exposure based off area burned in a 20 km radius of residential location	**Exposure based off area burned in a 50 km radius of residential location**
	Events/ person-years[a]	**Hazard ratio (95% confidence interval)**	**Hazard ratio (95% confidence interval)**
Lung Cancer			
3-year moving average with a 3-year lag			
<50th percentile vs. unexposed	42,975/	1.079 (1.038-1.121)	1.082 (1.052-1.111)
≥50th percentile vs. unexposed	33,688,250	1.062 (1.020-1.107)	1.037 (1.005-1.070)
5-year moving average with a 3-year lag			
<50th percentile vs. unexposed	42,425/	1.070 (1.034-1.107)	1.071 (1.044-1.098)
≥50th percentile vs. unexposed	33,396,245	1.068 (1.029-1.107)	1.060 (1.030-1.091)
10-year moving average with a 3-year lag			
<50th percentile vs. unexposed	42,595/	1.042 (1.011-1.073)	1.067 (1.042-1.093)
≥50th percentile vs. unexposed	33,518,220	1.052 (1.018-1.087)	1.045 (1.017-1.074)
Brain Cancer			
3-year moving average with a 3-year lag			
<50th percentile vs. unexposed	3,750/	1.144 (1.005-1.301)	1.097 (1.001-1.202)
≥50th percentile vs. unexposed	33,688,250	0.976 (0.845-1.128)	0.968 (0.869-1.077)
5-year moving average with a 3-year lag			
<50th percentile vs. unexposed	3,705/	1.126 (1.005-1.262)	1.080 (0.992-1.175)
≥50th percentile vs. unexposed	33,396,245	1.016 (0.895-1.153)	0.993 (0.898-1.097)
10-year moving average with a 3-year lag			
<50th percentile vs. unexposed	3,715/	1.139 (1.032-1.256)	1.102 (1.016-1.195)
≥50th percentile vs. unexposed	33,518,220	1.047 (0.936-1.171)	1.075 (0.980-1.178)
Non-Hodgkin Lymphoma			
3-year moving average with a 3-year lag			
<50th percentile vs. unexposed	12,110/	1.077 (1.002 -1.158)	1.001 (0.950-1.055)
≥50th percentile vs. unexposed	33,688,250	1.032 (0.955-1.116)	1.024 (0.966-1.085)
5-year moving average with a 3-year lag			
<50th percentile vs. unexposed	11,990/	1.037 (0.973-1.107)	1.023 (0.975-1.074)
≥50th percentile vs. unexposed	33,396,245	1.037 (0.968-1.112)	1.022 (0.967-1.079)

10-year moving average with a 3-year lag			
<50th percentile vs. unexposed	12,000/	0.992 (0.937-1.050)	0.992 (0.948-1.039)
≥50th percentile vs. unexposed	33,518,220	1.021 (0.959-1.086)	1.014 (0.963-1.067)
Multiple Myeloma			
3-year moving average with a 3-year lag			
<50th percentile vs. unexposed	3,895/	1.077 (0.948-1.224)	1.018 (0.929-1.116)
≥50th percentile vs. unexposed	33,688,250	0.886 (0.765-1.027)	0.969 (0.872-1.077)
5-year moving average with a 3-year lag			
<50th percentile vs. unexposed	3,860/	1.049 (0.936-1.175)	1.036 (0.953-1.127)
≥50th percentile vs. unexposed	33,396,245	0.890 (0.781-1.014)	0.983 (0.890-1.085)
10-year moving average with a 3-year lag			
<50th percentile vs. unexposed	3,860/	1.006 (0.911-1.112)	1.010 (0.932-1.094)
≥50th percentile vs. unexposed	33,518,220	0.923 (0.823-1.035)	0.991 (0.904-1.086)
Leukemia			
3-year moving average with a 3-year lag			
<50th percentile vs. unexposed	7,720/	1.047 (0.955-1.149)	0.957 (0.895-1.023)
≥50th percentile vs. unexposed	33,688,250	1.038 (0.940-1.145)	1.074 (1.001-1.152)
5-year moving average with a 3-year lag			
<50th percentile vs. unexposed	7,660/	1.026 (0.945-1.114)	0.988 (0.930-1.051)
≥50th percentile vs. unexposed	33,396,245	1.006 (0.920-1.099)	1.006 (0.940-1.076)
10-year moving average with a 3-year lag			
<50th percentile vs. unexposed	7,655/	1.024 (0.953-1.110)	1.005 (0.949-1.065)
≥50th percentile vs. unexposed	33,518,220	1.025 (0.948-1.109)	1.016 (0.953-1.082)

[a] Counts are rounded to the nearest 5 to conform with institutional confidentiality requirements

Cox proportional hazards models are stratified by sex, baseline age (5-year categories) and immigrant status (yes/no), and adjusted for the following covariates: regional airshed, community size, urban status, CAN-Marg indicators (quintiles of ethnic concentration, dependency, deprivation, instability), highest level of education, employment status, marital status, visible minority status, Indigenous status, occupation, and age (centered at the median within each 5-year category)

Table S10 Associations between area of forest burned within a 20 km and 50 km radius of residential locations and the incidence of lung cancer among participants in the 1996 Canadian Census Health and Environment Cohort, indirectly adjusted for smoking status (never, former, current) and body mass index (25-29.9, 30-34.9, 35-39.9, or ≥40 kg/m^2)

	Exposure based off area burned in a 20 km radius of residential location	**Exposure based off area burned in a 50 km radius of residential location**
	Indirectly adjusted hazard ratio and 95% confidence interval	**Indirectly adjusted hazard ratio and 95% confidence interval**
Dichotomous exposures		
Any exposure within the past 3 years (with a 1-year lag)	1.033 (0.999, 1.068)	1.037 (1.010, 1.063)
Any exposure within the past 5 years (with a 1-year lag)	1.057 (1.026, 1.089)	1.051 (1.026, 1.077)
Any exposure within the past 10 years (with a 1-year lag)	1.027 (0.999, 1.055)	1.039 (1.014, 1.064)
Categorical Exposures		
3-year moving average with a 1-year lag		
$<50^{th}$ percentile vs. unexposed	1.047 (1.003-1.093)	1.049 (1.017-1.082)
$\geq 50^{th}$ percentile vs. unexposed	1.015 (0.971-1.062)	1.016 (0.982-1.052)
5-year moving average with a 1-year lag		
$<50^{th}$ percentile vs. unexposed	1.071 (1.031-1.113)	1.056 (1.026-1.087)
$\geq 50^{th}$ percentile vs. unexposed	1.040 (0.998-1.083)	1.039 (1.006-1.074)
10-year moving average with a 1-year lag		
$<50^{th}$ percentile vs. unexposed	1.028 (0.993-1.063)	1.043 (1.015-1.073)
$\geq 50^{th}$ percentile vs. unexposed	1.027 (0.991-1.065)	1.030 (0.999-1.063)

Indirect adjustment method: Shin HH, Cakmak S, Brion O, Villeneuve P, Turner MC, Goldberg MS, Jerrett M, Chen H, Crouse D, Peters P, Pope CA 3rd, Burnett RT. Indirect adjustment for multiple missing variables applicable to environmental epidemiology. Environ Res. 2014 Oct;134:482-7. doi: 10.1016/j.envres.2014.05.016.

Table S11 Associations between area of forest burned within a 20 km and 50 km radius of residential locations, comparing categories of the 3, 5 and 10-year moving averages with a 1-year lag separated at quintiles in reference to the unexposed group, and the incidence of lung cancer among participants in the 1996 Canadian Census Health and Environment Cohort

		Exposure based off area burned in a 20 km radius of residential location	**Exposure based off area burned in a 50 km radius of residential location**
	Events/ person-years[a]	**Hazard ratio (95% confidence interval)**	**Hazard ratio (95% confidence interval)**
3-year moving average with a 1-year lag[b]			
Q1 vs unexposed	43,205/ 33,765,955	1.065 (1.007-1.125)	1.044 (1.003-1.086)
Q2 vs unexposed		1.076 (1.018-1.138)	1.056 (1.016-1.098)
Q3 vs unexposed		1.001 (0.945-1.059)	1.085 (1.043-1.129)
Q4 vs unexposed		1.032 (0.973-1.095)	1.001 (0.959-1.045)
Q5 vs unexposed		1.000 (0.940-1.065)	0.988 (0.943-1.036)
5-year moving average 1-year lag[b]			
Q1 vs unexposed	42,785/ 33,530,840	1.054 (1.003-1.107)	1.075 (1.036-1.114)
Q2 vs unexposed		1.073 (1.022-1.127)	1.061 (1.025-1.099)
Q3 vs unexposed		1.080 (1.027-1.136)	1.091 (1.052-1.131)
Q4 vs unexposed		1.051 (0.999-1.106)	1.021 (0.981-1.063)
Q5 vs unexposed		1.042 (0.986-1.101)	1.037 (0.994-1.083)
10-year moving average 1-year lag[b]			
Q1 vs unexposed	43,070/ 33,786,625	1.019 (0.976-1.064)	1.052 (1.018-1.086)
Q2 vs unexposed		1.022 (0.979-1.066)	1.066 (1.032-1.101)
Q3 vs unexposed		1.087 (1.041-1.135)	1.053 (1.018-1.090)
Q4 vs unexposed		1.041 (0.995-1.089)	1.033 (0.997-1.071)
Q5 vs unexposed		1.026 (0.978-1.076)	1.023 (0.983-1.065)

[a] Counts are rounded to the nearest 5 to conform with institutional confidentiality requirements

[b] Q1=lowest area burned, Q5=highest area burned

Cox proportional hazards models are stratified by baseline age (5-year categories), sex and immigrant status, and adjusted for the following covariates: regional airshed, community size, urban status, CAN-Marg indicators (quintiles of ethnic concentration, dependency, deprivation, instability), highest level of education, employment status, marital status, visible minority status, Indigenous status, occupation, and age (centered at the median within each 5-year category)

Table S12 Associations between cumulative number of fires in a 10-year moving window (with a 1-year lag) and lung cancer incidence

		Exposure based off area burned in a 20 km radius of residential location	Exposure based off area burned in a 50 km radius of residential location
	Events/ person-years[a]	**Hazard ratio (95% confidence interval)**	**Hazard ratio (95% confidence interval)**
Number of fires modelled as a categorical variable			
1-3 fires vs. 0 fires	41,295/ 32,625,225	1.043 (1.017-1.069)	1.055 (1.031-1.079)
4-6 fires vs. 0 fires		1.071 (1.012-1.132)	1.067 (1.029-1.106)
7-10 fires vs. 0 fires		1.055 (0.963-1.156)	1.080 (1.031-1.131)
Number of fires modelled as a continuous variable	41,295/ 32,625,225	1.013 (1.005-1.021)	1.011 (1.006,1.016)

[a] Counts are rounded to the nearest 5 to conform with institutional confidentiality requirements.

Cox proportional hazards models are stratified by baseline age (5-year categories), sex and immigrant status, and adjusted for the following covariates: regional airshed, community size, urban status, CAN-Marg indicators (quintiles of ethnic concentration, dependency, deprivation, instability), highest level of education, employment status, marital status, visible minority status, Indigenous status, occupation, and age (centered at the median within each 5-year category)

Table S13 Association between area of forest burned within a 20 km and 50 km of residential locations and the incidence of lung and brain cancer, non-Hodgkin lymphoma, multiple myeloma, and leukemia, among participants in the 1996 Canadian Census Health and Environment Cohort (models include a dichotomous exposure variable reflecting ever/never exposure, and a continuous exposure variable reflecting hectares burned)

		Exposure based off area burned in a 20 km radius of residential location	**Exposure based off area burned in a 50 km radius of residential location**
	Events/ person-years[a]	**Hazard ratio (95% confidence interval)**	**Hazard ratio (95% confidence interval)**
Lung Cancer			
3-year moving average with 1-year lag			
Continuous[b]	43,205/	1.001 (0.997-1.005)	1.001 (0.997-1.004)
Dichotomous[c]	33,765,955	1.036 (1.006-1.066)	1.040 (1.017-1.064)
5-year moving average with 1-year lag			
Continuous[b]	42,785/	0.998 (0.992-1.005)	0.999 (0.994-1.003)
Dichotomous[c]	33,530,840	1.062 (1.034-1.090)	1.061 (1.039-1.084)
10-year moving average with 1-year lag			
Continuous[b]	43,070/	0.996 (0.988-1.004)	0.997 (0.992-1.003)
Dichotomous[c]	33,786,625	1.040 (1.016-1.065)	1.050 (1.028-1.072)
Brain Cancer			
3-year moving average with 1-year lag			
Continuous[b]	3,770/	0.962 (0.903-1.024)	0.977 (0.950-1.005)
Dichotomous[c]	33,765,955	1.075 (0.974-1.187)	1.104 (1.024-1.191)
5-year moving average with 1-year lag			
Continuous[b]	3,740/	0.944 (0.873-1.020)	0.976 (0.946-1.006)
Dichotomous[c]	33,530,840	1.089 (0.996-1.191)	1.103 (1.027-1.185)
10-year moving average with 1-year lag			
Continuous[b]	3,755/	0.971 (0.925-1.019)	0.979 (0.952-1.007)
Dichotomous[c]	33,786,625	1.097 (1.013-1.188)	1.105 (1.031-1.185)
Non-Hodgkin Lymphoma			
3-year moving average with 1-year lag			
Continuous[b]	12,140/	1.001 (0.993-1.009)	1.002 (0.995-1.008)
Dichotomous[c]	33,765,955	1.002 (0.948-1.058)	0.991(0.950-1.035)

5-year moving average with 1-year lag			
Continuous[b]	12,065/	1.001 (0.989-1.013)	1.002 (0.994-1.011)
Dichotomous[c]	33,530,840	1.028 (0.978-1.080)	1.009 (0.969-1.050)
10-year moving average with 1-year lag			
Continuous[b]	12,115/	1.006 (0.991-1.020)	1.007 (0.997-1.017)
Dichotomous[c]	33,786,625	1.008 (0.963-1.054)	1.000 (0.962-1.040)
Multiple Myeloma			
3-year moving average with 1-year lag			
Continuous[b]	3,925/	1.001 (0.986-1.015)	1.001 (0.989-1.012)
Dichotomous[c]	33,765,955	1.027 (0.932-1.132)	0.985 (0.913-1.062)
5-year moving average with 1-year lag			
Continuous[b]	3,890/	0.993 (0.966-1.021)	0.994 (0.976-1.013)
Dichotomous[c]	33,530,840	1.016 (0.929-1.110)	1.005 (0.936-1.080)
10-year moving average with 1-year lag			
Continuous[b]	3,895/	0.981 (0.944-1.019)	0.981 (0.957-1.006)
Dichotomous[c]	33,786,625	1.002 (0.925-1.086)	1.024 (0.956-1.097)
Leukemia			
3-year moving average with 1-year lag			
Continuous[b]	7,760/	0.977 (0.945-1.010)	0.991 (0.977-1.005)
Dichotomous[c]	33,765,955	1.065 (0.994-1.141)	1.036 (0.982-1.092)
5-year moving average with 1-year lag			
Continuous[b]	7,700/	0.975 (0.941-1.010)	0.984 (0.966-1.002)
Dichotomous[c]	33,530,840	1.033 (0.970-1.100)	1.008 (0.959-1.060)
10-year moving average with 1-year lag			
Continuous[b]	7,730/	0.976 (0.946-1.007)	0.988 (0.971-1.005)
Dichotomous[c]	33,786,625	1.028 (0.972-1.088)	1.005 (0.957-1.056)

[a] Counts are rounded to the nearest 5 to conform with institutional confidentiality requirements

[b] HRs and 95% CIs are scaled per 2000-hectare increase in area burned. For exposed person-years (i.e., when area burned was greater than 0), area burned was centered at the median.

[c] The dichotomous exposure variable was coded as 1 if area burned was greater than zero, and 0 if unexposed. The HR therefore compares risk between those with a median level of exposure relative to the unexposed group

Cox proportional hazards models are stratified by baseline age (5-year categories), sex and immigrant status, and adjusted for the following covariates: regional airshed, community size, urban status, CAN-Marg indicators (quintiles of ethnic concentration,

dependency, deprivation, instability), highest level of education, employment status, marital status, visible minority status, Indigenous status, occupation, and age (centered at the median within each 5-year category)

CHAPTER 6: Discussion

6.1 Summary of findings

The goal of this thesis was to move beyond evaluating the health impacts of $PM_{2.5}$ mass concentration and instead focus on different sources, constituents, and oxidative properties of air pollution in Canada.

In Chapter 3 (Manuscript 1), I investigated associations between short-term and sub-chronic ambient $PM_{2.5}$, oxidant gases and markers of cardiovascular health in school-aged children living in a setting where residential biomass burning is prevalent during the cold months. This repeated-measures panel study included original data collection from 71 students recruited from two elementary schools in Courtenay and Cumberland, British Columbia, from 2018-2020. Outcomes were measured a median of 6 times per student throughout the school year. Multivariable linear mixed-effect models were used to evaluate associations between exposure to outdoor $PM_{2.5}$ or oxidant gases and retinal blood vessel diameter and blood pressure, and interactions between $PM_{2.5}$ and oxidant gases were also considered. The results of this study show that oxidant gases are inversely associated with retinal arteriolar diameter, which is consistent with other studies that observed negative associations between outdoor air pollution and retinal arteriolar diameter. Moreover, oxidant gases modified associations between $PM_{2.5}$ and retinal arteriolar diameter, with weak positive associations observed when concentrations of oxidant gases were low and weak negative associations when concentrations of oxidant gases were elevated.

In Chapter 4 (Manuscript 2), I explored whether associations between short-term ambient $PM_{2.5}$ mass concentration or oxidant gases and respiratory hospitalizations in children were modified by monthly estimates of $PM_{2.5}$ constituents (metals and sulfur) or particle oxidative

potential. This was a case-crossover study that included approximately 10,500 children hospitalized for respiratory diseases from 2016-2017 across 34 Canadian cities. Stronger associations between $PM_{2.5}$ mass, oxidant gases and respiratory hospitalizations were observed when particle oxidative potential and metals/sulfur in $PM_{2.5}$ were elevated, which is consistent with other studies that observed effect modification by particle oxidative potential[15,22,63,181] and $PM_{2.5}$ constituents[15].

In Chapter 5 (Manuscript 3), I investigated associations between wildfires and the incidence of lung and brain cancer, non-Hodgkin lymphoma, multiple myeloma, and leukemia among approximately 2 million participants in the 1996 Canadian Census Health and Environment Cohort. Exposures were estimated based on area burned within a 20 and 50 km radius of residential locations, and 3-year, 5-year, and 10-year moving averages of area burned (with a 1-year lag) were calculated to capture longer-term exposures. We modelled exposures as a dichotomous term (ever vs. never exposed), categorical terms (never exposed, area burned $<50^{th}$ percentile, area burned$\geq 50^{th}$ percentile), and a continuous term. Multivariable Cox proportional hazards models were used to estimate associations between wildfire exposures and cancer incidence. We observed positive associations between wildfires and lung and brain cancer when exposures were modelled as dichotomous and categorical variables. No associations were observed with hematologic cancers, or when area burned was modelled as a continuous term (for all cancer outcomes).

6.2 Strengths and limitations

Overall, this dissertation makes important contributions to the field of air pollution epidemiology by moving beyond studying the health effects of $PM_{2.5}$ mass concentration and

instead focusing on specific sources, oxidative properties, and constituents of particulate air pollution. Substantively, Objective 1 fills important gaps in knowledge related to the cardiovascular health impacts of air pollution in children and more broadly the health impacts of exposures to ambient residential biomass burning. Regarding Objective 2, although many studies have investigated the acute respiratory health effects of air pollution in children, to our knowledge no studies have explored whether associations are modified by constituents or oxidative properties of $PM_{2.5}$, which is relevant information to help inform more efficient regulatory measures. Objective 3 is the first study in the world to examine associations between wildfire exposure and cancer incidence, the results of which are important on a global scale given that wildfires are increasing in frequency and severity throughout the world.

In addition to the substantive strengths of this thesis, a methodological strength is that there is generally good confounding control in all studies, either through the study design or measurement and adjustment of confounding variables. More specifically, personal-level covariates are adjusted for by design in Objectives 1 and 2 because both study designs (repeated-measures panel study and case-crossover study) rely on within-individual comparisons. Intrinsic to the time-stratified case-crossover study, some time-varying covariates (including day of week, season, and year) are also adjusted for by design, while in both studies, additional time-varying covariates (meteorological variables) are adjusted for through modelling.

Regarding Objective 3, confounding control was performed through modelling and the CanCHEC database collects rich information on individual and neighbourhood-level covariates compared to many other large administrative datasets. However, it should be recognized that some important personal-level predictors of chronic disease were not measured, including body mass index and smoking status. In our sensitivity analysis that indirectly adjusted the hazard

ratios for smoking and body mass index, we observed some attenuation of effect estimates, although results were generally consistent. Although these individual-level covariates are undoubtedly strong predictors of cancer and other long-term health outcomes, it is plausible they are not strongly related to wildfires or air pollution exposures and therefore do not end up being important confounding variables. Alternatively, it is also possible that through adjusting for many other individual and neighbourhood-level covariates that are strong determinants of smoking status and body mass index (socioeconomic variables, age, sex, etc.), we've mitigated much of the confounding by these variables. Results from analyses investigating associations between air pollution exposures and mortality in the Canadian Community Health Survey-Mortality cohort, in which many individual-level predictors of chronic disease (smoking, diet, exercise, body mass index, etc.) are measured, found that additional adjustment for these risk factors did not meaningfully impact the air pollution exposure effect estimates[14], providing some empirical evidence that these covariates do no end up being essential variables to control for. That being said, theoretically it has been demonstrated that not adjusting for important risk factors of the outcome (irrespective of whether the variables are related to the exposure, i.e., whether they are true confounding variables) can still lead to biased effect estimates in time-to-event analyses[240], so ideally these variables would have been measured and directly adjusted for in our CanCHEC analysis.

Another important strength of this dissertation is the availability of detailed exposure information. For Objective 1 and 2, multiple air pollutants are measured on a continuous scale over several years, and Objective 2 also includes prospectively measured $PM_{2.5}$ components and oxidative potential. Objective 3 uses approximately 30 years of wildfire data maintained by Natural Resources Canada, who record the location of wildfires and total area burned throughout

the country each year. The availability of this unique database from as far back as the mid-1980's enabled us to evaluate the long-term health impacts of living near wildfires.

This thesis also has some limitations. In all objectives, exposure measurement error is a concern. In Objectives 1 and 2, Berkson-type exposure measurement error likely occurred because true personal $PM_{2.5}$ or O_x differ from outdoor concentrations measured at a central location. This type of measurement error was likely non-differential in respect to the outcomes studied, and results in a reduction in precision without any systematic bias[174]. For Objective 3, exposure measurement error likely impacted the estimates of area burned within various buffers around residential locations several ways. For example, there are likely spatial errors in the methods used to identify wildfire perimeters and area burned, which is a type of classical measurement error that would result in bias towards the null[174]. In addition, 6-digit residential postal codes are imperfect estimates of residential home addresses and assigning the same wildfire exposure to all individuals who share the same postal code results in Berkson-type exposure measurement error (leading to a loss in precision)[174]. This may be particularly true in rural locations compared to more urban areas; for example, for community sizes between 10,000-1.49 million, the median distance between a 6-digit postal code centroid and a full home address is less than 330 m, while in communities with a population size smaller than 10, 000, the median distance is approximately 560 m[241]. In addition, another limitation in our approach to assign exposure in Objective 3 is that the chemical composition of wildfire emissions is affected by numerous factors (including fuel type, burning conditions, climate, etc.) and this probably contributes to heterogeneity in the toxicity of emitted pollutants and subsequent health effects. As well, one obvious final limitation of assigning exposures to wildfires based on residential proximity is that we are not capturing pollutants from wildfires that travel long distances in wind.

Regardless, we would anticipate that individuals living near wildfires that occur regularly in the same area would be more consistently exposed to local wildfire pollutants than individuals exposed to pollutants transported over long distances from remote fires.

Another consideration for all studies is the potential for selection bias. For Objective 1, the study relied on volunteers, and it is possible that volunteers may come from more educated families and be healthier than those who did not volunteer to participate in the study. It is also possible that the general health of children may affect their individual response to changes in air pollution; for example, it's conceivable that healthy children may be physiologically more resilient towards environmental stressors and thus their retinal arterioles may not restrict as much with increases in air pollution compared to less healthy children, which would lead to a different association observed in the sample compared to the target population. Regarding Objective 2, selection bias is largely eliminated through the case-crossover design. Unlike in case control studies, where selection bias can occur when controls do not represent the exposure distribution of the source population from which the cases arose, case-crossover studies do not encounter this issue because the control periods reflect the cases' exposures themselves[183,242]. Regardless, selection bias can still occur in case-crossover studies if the exposure (in our study, ambient $PM_{2.5}$ or O_x) influences an individual's willingness to participate in the study or their survival[242]. Given the study uses administrative data and does not rely on volunteers, ambient air pollution exposure would not influence an individuals' participation, and similarly, survival is not influenced by ambient air pollution among children in Canada (i.e., children are not dying from ambient air pollution in Canada). Selection bias in a case-crossover study can also result if the control time windows are selected dependent on the exposure, such that the exposure distribution in the control periods are not representative of the exposure distribution in the person-time giving

rise to the cases[242]. In our study, the selection of control windows were matched on the day, month and year of the case day and were not influenced by the exposures, so again the possibility of selection bias seems unlikely. Regarding Objective 3, opportunities for selection bias relate to who is included in the study and who is lost to follow-up. To first address who is included in the study, the CanCHEC is a subset of the Canadian longform census and is meant to represent the Canadian population; however, people who live in institutions (nursing homes, penitentiaries, and group homes) at the time of census collection are excluded. It is plausible that those included in the study (the non-institutionalized) differ in their cancer risk compared to those who are institutionalized, and if there are also differences in wildfire exposures (perhaps attributed to spatial differences in where institutions are located), then selection bias is a possibility. Loss to follow-up in this study only occurs if individuals stop filing their tax returns and residential locations are therefore unknown. Certain groups (e.g., unhoused, unemployed) may be less likely to file tax returns, and these people may have different cancer risks than those who file their tax returns and are not lost to follow-up. Similarly, if there are spatial differences in where these people live that relate to wildfire exposures, selection bias could result.

6.3 Public health significance

Ambient (outdoor) air pollution is a leading contributor to disability-adjusted life years and mortality worldwide[1], and even though Canada has some of the cleanest air in the world[10,11], adverse health impacts of air pollution are still observed[12–14]. Objectives 1 and 2 of this thesis investigate the short-term/sub-chronic cardiovascular and respiratory health impacts of ambient $PM_{2.5}$ and O_x exposure in Canadian children, and suggest negative impacts of ambient air pollution on retinal arteriolar diameter and respiratory hospitalizations. Importantly, both studies

observe effect modification by co-exposures or constituents and oxidative properties of particulate matter: Objective 1 found the direction of association between $PM_{2.5}$ and arteriolar diameter depended on concentrations of O_x (and visa versa) and Objective 2 observed stronger associations between $PM_{2.5}$ mass and O_x when the metal and sulfur content of $PM_{2.5}$ and oxidative potential were elevated. These findings contribute to the growing body of evidence that suggest the strength of associations between $PM_{2.5}$ mass concentrations and health outcomes depend on the source/composition of $PM_{2.5}$[15–19] or co-exposure to other pollutants[14,22,23,181], which may help explain the observed heterogeneity in the health impacts of $PM_{2.5}$. Together, these results highlight the need to consider effect modification by co-exposures in epidemiological air pollution studies, which can be easily incorporated into studies taking place in Canada because data on oxidant gases are readily available through continuous monitoring by the National Air Pollution Surveillance Program. Furthermore, the results also highlight the potential benefits of incorporating information related to sources of $PM_{2.5}$ and $PM_{2.5}$ constituents, which is becoming increasingly feasible as national estimates of source-specific $PM_{2.5}$ mass concentrations and $PM_{2.5}$ constituents are available through source apportionment methods and hybrid satellite-land use regression modelling[243]. $PM_{2.5}$ composition data will enable researchers to better understand what specifically about $PM_{2.5}$ causes adverse health outcomes, which can help inform more efficient regulatory measures (for example, we can target specific sources of $PM_{2.5}$ that are elevated in harmful constituents). Moreover, although to our knowledge no other studies have investigated how $PM_{2.5}$ constituents/oxidative properties modify the health effects of oxidative gases, the results suggest that regulatory measures targeted at specific $PM_{2.5}$ constituents may have considerable co-benefits in reducing the health effects of oxidant gases, which is important because ozone (an oxidant gas) is notoriously challenging to regulate.

Additionally, the findings from Objective 3 which suggest that wildfire exposures are positively associated with lung and brain cancer is of global importance. A comprehensive report published by the United Nations Environment Programme in 2022 outlines the widespread threat wildfires pose to human health, the environment, and the economy, and the role of human activity in exacerbating these events[81]. Although our study by no means establishes a causal effect of wildfires on lung and brain cancer (this study is the first of its kind with various limitations; much more work is needed), the results are concerning to populations that are repeatedly exposed to wildfire events, such as those living in Western Canada or the United States. This study, in addition to the existing body of evidence on the harmful short-term health effects of wildfires, can inform policy related to reducing the health risks posed by wildfires. For example, forest management practices including prescribed burns (which act to manage the available fuel before a fire breaks out) is one such hazard mitigation action that can reduce the intensity, severity and size of a wildfire. Similarly, given that climate change strongly influences the behaviour of wildfires, countries should meet their commitments to the Paris Agreement to reduce global warming. Policies related to maintaining indoor air quality (e.g., building codes, HVAC systems, etc.) may also help alleviate the health risks associated with wildfires because individuals generally spend most their time inside.

6.4 Future research

There are several opportunities for future research related to the subject matters covered in this thesis. Regarding Objective 1, an important gap in knowledge is whether the impacts of air pollution on short-term changes in the microvasculature in children, as measured by retinal arteriolar diameter, lead to more chronic changes over time. If the microvasculature of children is

resilient and can easily bounce back from acute injury caused by air pollution exposure, then the impacts of air pollution in childhood on the microvasculature might not be a major concern. Conversely, if these short-term changes eventually lead to more chronic injury, then regulatory measures aimed at improving air quality should be a priority to protect children's cardiovascular health. Existing evidence with other cardiovascular health markers indicate that early life exposures to air pollution can alter an individual's health trajectory and increase their risk of poor cardiovascular health in later life[244], so we suspect a similar effect on the microvasculature may exist. A study design that evaluates the associations between childhood air pollution exposure and the structure of the microvasculature in adulthood could provide important information related to whether air pollution in childhood has long-term impacts on microvascular health. In addition, despite residential biomass burning being an important source of air pollution in Canada, limited research has investigated associations between this source of air pollution specifically and adverse health outcomes, which is relevant to directly inform policy changes.

Regarding Objective 2, it would be of interest to evaluate whether $PM_{2.5}$ constituents or oxidative potential modify associations with longer-term health outcomes in children, such as the incidence of asthma or childhood cancers. In fact, long-term estimates of particulate matter constituents and oxidative potential are available in Canada and we may link this data to the appropriate health outcomes datasets to pursue this avenue of research in the future.

As for Objective 3, much more work is needed to better understand the potential long-term health effects of wildfires. Specifically, exploring different health outcomes, including all-cause/cause-specific mortality as well as alternative cancer types, is of interest, in addition to the impacts on vulnerable populations such as those with pre-existing health conditions, pregnant women, children, and the elderly. Moreover, area burned is a crude estimate of wildfire exposure

and other exposure assessment methods may offer complementary insights into the long-term health effects of wildfires. For example, the recently developed Canadian Optimized Statistical Smoke Exposure Model (Canossem)[245] estimates daily biomass burning-specific $PM_{2.5}$ across the country from 2010-2019 and can be linked to existing cohort studies or other administrative datasets. An important strength of this approach to exposure assessment compared to area burned is that wildfire-derived smoke that travels long distances in the wind is accounted for, although this dataset is currently limited in its utility for evaluating long-term wildfire exposures because only 10 years of smoke exposure are available. Lastly, from a toxicological standpoint, there is also a need to further study what pollutants are emitted during wildfire events and what pollutants persist in the environment after a wildfire. This would require sampling active smoke plumes, nearby bodies of water, soil and indoor environments affected by wildfires.

6.5 Conclusion

In conclusion, this dissertation observed harmful effects of short-term and sub-chronic exposures to residential biomass burning on the cardiovascular health of children (Objective 1), the important modifying role of metals, sulfur and particle oxidative potential in associations between short-term $PM_{2.5,}$ oxidant gases and respiratory hospitalizations (Objective 2), and positive associations between long-term wildfire exposures and lung and brain cancer (Objective 3). Through focusing on specific sources, constituents, or oxidative properties of air pollution, as well as through considering interactions between co-pollutants, this dissertation aimed to provide a more refined understanding of the health effects of ambient air pollution in Canada and such information may be useful to help inform future policymaking.

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