

**THE AIR WE BREATHE: INVESTIGATING THE IMPACT OF AMBIENT AIR
POLLUTION EXPOSURE ON THE POTENTIAL RISK OF KIDNEY AND
BLADDER CANCERS IN CANADA**

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SUMMARY

Background

Air pollution has been classified by the International Agency for Research on Cancer as a known human carcinogen, with evidence pointing to an increased risk of lung cancer; however, epidemiological evidence on other cancer sites has been more limited to date. This project investigates the impact of ambient air pollution (AAP) exposure on the risk of developing kidney and bladder cancer. In addition to better understanding the relationship between AAP and bladder and kidney cancer we will also investigate the potential effect modification of sex, neighbourhood income and geography.

Objectives

The aim of my research is to examine ambient air pollution (*as characterized by PM_{2.5}, NO₂, and O₃*) as a potential risk factor for the development of kidney and bladder cancers in Canada. The research objective is to characterize the association between the risk of kidney and bladder cancers and AAP exposure in addition to determining whether the strength of this association is modified by sex, neighbourhood income, and geography. We hypothesize that exposure to AAP increases the risk of developing kidney and bladder cancers, and that this relationship is modified by sex, neighbourhood income, and geography.

Methods

Data are from the Canadian Urban Environmental Health Research Consortium (CANUE) and the Canadian Census Health and Environment Cohorts (CanCHEC), as well as data from the Canadian Community Health Survey. The study will use a longitudinal design in the form of a retrospective cohort study to examine the impact of air pollution - whereby incremental increases in air pollution exposure will be compared to assess the risk of kidney and bladder cancer with an exposure period from 1991-2006 and follow-up until 2017. The pollutants of interest will be explored to determine how they are correlated with one another in addition to identifying their independent effects. Data will be analyzed using Cox proportional hazard models to estimate associations - hazard ratios and their respective 95% confidence intervals - between air pollution and the risk of both cancers. We will also examine if the strength of the association between air pollution exposure and incidence of these cancers differs by sex, neighbourhood income and between urban and rural areas.

Significance

My research project will contribute to a greater understanding of the possible link between ambient air pollution and both kidney and bladder cancers. The importance of this research cannot be understated as all Canadians are exposed to some level of ambient air pollution, and

as such the quantification of potential increases in risk may help inform policies intended to reduce the risk of cancer nationally. Additionally, as the non-lung cancers investigated across both this project and the larger project have few known preventable causes, this research is important to help identify exposure-disease pairs that may contribute to the development of further cancer prevention activities. As this research uses an established large, national cohort, in conjunction with other datasets, results of this research may be generalized across the majority of Canadians and on a regional scale to help inform both provincial and national prevention efforts.

1. INTRODUCTION

Air pollution has been classified by the International Agency for Research on Cancer as a known human carcinogen, with evidence pointing to an increased risk of lung cancer; however, epidemiological evidence on other cancer sites has been more limited to date (Turner et al., 2017). As air pollution remains a growing concern globally, due in large part to production and industrial activities driving increases in exposure, it is imperative that we seek to better understand its impacts on human health – research has been done to quantify the relationship with lung cancers, however we are interested in understanding more about the distal effects of this exposure on the body. Previous research on the topic suggests that there may be a relationship between air quality and non-lung cancers, however such research has been limited to date (Turner et al., 2017). As a subset of the larger project investigating non-lung cancers and ambient air pollution, this research project specifically seeks to understand the possible links between air pollution cancer and both kidney and bladder cancers. Using a retrospective cohort study design, data from existing Canadian data sets will be used to examine whether exposure to ambient air pollution, in our case $PM_{2.5}$, O_3 and NO_2 , are associated with an increased risk of the cancers of interest (Turner et al., 2017). The analyses performed will be stratified to examine potential differences across sex, neighbourhood income, and geography.

This research project will contribute to a greater understanding of the possible link between ambient air pollution and both kidney and bladder cancers. As all Canadians are exposed to some level of ambient air pollution, and as such the quantification of potential increases in risk may help inform policies intended to reduce the risk of cancer nationally. Additionally, as the non-lung cancers investigated across both this project, and the larger project in which it is situated, have few known preventable causes, this research is important to help identify exposure-disease pairs that may contribute to the development of further cancer prevention activities. This research has the chance to highlight the broader implications of air pollution exposure and cancer and contribute to the current body of knowledge regarding the relationship between ambient air pollution and cancer. We will also have the ability to assess how the potential relationships between air pollution and the risk of kidney and bladder cancer varies by sex, neighbourhood income, and geography (i.e., urban, rural and suburban environments). Several health-related factors will be included in the analysis to address potential confounders. Recent research has demonstrated geographic differences in cancer rates by country and within regions – and spatial variability in cancer rates could be related to a

combination of social factors including socioeconomic status, lifestyle, and environmental exposures (Bray et al., 2018; Parkin et al., 2005).

While significant research has been conducted into understanding the relationship between ambient air pollution and lung cancer, research looking to understand the relationship between air pollution and kidney and bladder cancers remains limited. While some studies exist, the sheer size of the proposed cohort utilized in my study, in addition to the quality of the data will provide an excellent opportunity to quantify the relationship between air pollution and kidney and bladder cancers. This research provides a unique opportunity to contribute to existing literature in addition to detecting potential associations between ambient air pollution and both kidney and bladder cancer. The overall goal of this research is to identify whether environmental exposure to ambient air pollution modifies the risk of kidney and bladder cancer in addition to whether the strength of associations is modified by sex, neighbourhood income, and geography. Since these non-lung cancers do not have many known preventable causes, we aim to identify exposure-disease pairs that may benefit from cancer prevention activities.

Research Aim: To examine ambient air pollution ($PM_{2.5}$, NO_2 , and O_3) as a potential risk for kidney and bladder cancers.

Research Objectives:

- *To characterize the association between long-term exposure to ambient air pollution ($PM_{2.5}$, NO_2 , and O_3) in Canada and the risk of kidney and bladder cancers*
- *To determine whether the strength of the association between ambient air pollution exposure and incidence of kidney and bladder cancers is modified by sex, neighbourhood income, and geography*

Hypothesis: Exposure to ambient air pollution impacts the risk of developing kidney and bladder cancers in a Canadian context. Furthermore, it is hypothesized that this relationship is modified by sex, neighbourhood income, and geography.

2. LITERATURE REVIEW

Clean air is imperative to human health, and with continued urbanization and development comes the pollution of the air we breathe. Epidemiological and clinical studies have shown that ambient air pollution contributes to the risk of development of several diseases (Mabahwi et al., 2014). The World Health Organization (WHO) has noted air pollution as a critical public health problem, with more than 2 million premature deaths attributed to air pollution annually (WHO, 2006). While substantial research has been done to evaluate the impact of ambient air pollution (AAP) on the respiratory system, little work has been done to evaluate the potential effects of AAP exposure on other body systems. Prior work has demonstrated a link between AAP exposure and the development of lung cancer, however the knowledge base surrounding the relationship between AAP exposure and the development of non-lung cancers is lacking. As such, this project seeks to better understand this relationship specifically as it relates to kidney and bladder cancers.

2.1 Air Pollution

The term “air pollution” is used differently across disciplines as a catch-all term to describe both natural and man-made material in the atmosphere. As urban development and industry continually expands, concerns regarding the health impacts of deteriorating air quality continue to arise (Xing et al, 2016). The environmental burden of disease related to air pollution is growing in cities worldwide whereby exposure to pollutants have the capacity to cause severe disease in the population (Rumana et al., 2014). This project is concerned specifically with ambient air pollution (AAP). AAP is an umbrella term used to describe several different hazardous environmental exposures that include numerous carcinogenic substances that may influence systemic and chronic inflammation, stress, and DNA damage to tissues throughout the human body (Rumana et al., 2014). It is estimated that air pollution is associated with 15,300 premature deaths annually in Canada, which includes 6,600 deaths in Ontario, 4,000 in Alberta, 1,900 in British Columbia and 1,400 in Alberta (Health Canada, 2021). The total economic cost of all health impacts attributable to air pollution in Canada was estimated to be \$120 billion in 2016 – approximately 6% of Canada’s GDP (Health Canada, 2021). As scientific evidence surrounding the impact of AAP on human health, so does the need to better understand it’s impacts on those conditions beyond the traditional scope of study (i.e., lung cancer, asthma, cardiovascular disease). Global Burden of Disease (GBD) analysis completed by the Institute for Health Metrics and Evaluation (2017) ranks air pollution as the 11th largest risk factor for premature death and disability in Canada, and as the largest environment risk in the country. Changes in air-pollution attributable deaths are changing over time – however, not as a result of increased exposure, more so simply due to our understanding of the relationship between air pollution and disease and improved analysis methods (Health Canada, 2021). Moreover, Canada’s changing demographics, namely our aging population, is influencing the number of adverse health outcomes attributable to air pollution (Health Canada, 2021).

This project will focus on three metrics of AAP – PM_{2.5}, O₃ and NO₂ – whereby each has been shown to have impacts on human health (Demetriou and Vineis, 2014; 6). PM_{2.5} is defined as any fine particle smaller than 2.5 μm, and while small in diameter, these particles have large surface areas and the capacity to carry various toxic substances (Xing et al., 2016). Due to their small size, PM_{2.5} particles can enter the body (typically through the respiratory tract) and accumulate by diffusion – occurring through air exchange in the lungs (Xing et al., 2016). This accumulation can result in cellular damage, leading to the development of disease. O₃ or ground-level ozone is defined as a secondary pollutant – formed by the reaction of volatile organic compounds with nitrogen oxides in sunlight (Liu et al., 2018). Ground-level ozone is considered as the most damaging air pollutant in Europe with detrimental impacts on both human health and vegetation (Liu et al., 2018). Notably, as global temperatures rise ground-level ozone levels are expected to rise due to high temperatures driving increased atmospheric reaction rates for the creation of ozone (Liu et al., 2018). Prior research has shown that elevated O₃ exposure can increase the incidence and mortality of respiratory diseases among others (Liu et al., 2018). Ozone is a strong oxidant, with the capacity to induce oxidative damage and intracellular inflammatory responses within the respiratory system and beyond

(Zhang et al., 2019). Recent research has shown that the inflammatory response induced by ozone may “spill over” to the circulatory system, leading to cellular damage in other body systems (Zhang et al., 2019). Lastly, NO₂ is a common air pollutant, often used as a marker of traffic-related pollution (Richters and Richters, 1989). NO₂ exposure drives cellular injury in the lungs as a result of an inflammatory response (Petit et al., 2017). Once inhaled, NO₂ reacts with moisture along the respiratory tract to form nitric and nitrous acids –compounds which cause structural and functional damage to lung cells (Petit et al., 2017). Moreover, these compounds initiate free radical generation which results in protein oxidation and lipid peroxidation, in addition to altering macrophage and immune function (Petit et al., 2017). Overall, the presence of NO₂ in the respiratory tract leads to cellular damage and drives the inflammatory response (Petit et al., 2017). Due to air exchange happening in the lungs, the compounds produced by NO₂ in the respiratory tract have the capacity to travel into the bloodstream, and to other body systems, by diffusion (Xing et al., 2016).

2.2 Air Pollution & Cancer Mechanisms

Exposure to AAP has been shown to have major health risks across numerous body systems, including the development of stroke, heart disease, lung cancer and respiratory disease (Demetriou and Vineis, 2014). The lungs are the most common organ to experience damage from air pollution; however, recent evidence from experimental studies on animals suggests that air pollution can also damage other organs including the liver, kidneys, heart, and brain via stimulation of inflammatory mediators and the occurrence of oxidative stress (Oberdoster et al., 2004; Kreyling et al., 2009). A study using data from 1.2 million participants in the American Cancer Society’s Cancer Prevention II cohort found a link between air pollution exposure and an increased risk of kidney, bladder, and colorectal cancer deaths (Turner et al., 2017). Moreover, a meta-analysis across several countries also found a relationship between particulate matter exposure and pancreatic cancer mortality (Kim et al., 2018).

Air pollution exposure varies across Canada based on local vehicle and industrial emissions – with higher rates of air pollution being reported in areas with higher urban density and industrial activity (Hystad, et al., 2012). Regarding differences in geography, research in an American context has reported that people living in low-income neighbourhoods are disproportionately exposed to NO₂ near their homes (Clark et al., 2014). A similar relationship also appears to exist in Canada as one study reported that lower income neighbourhoods in Montreal had higher concentrations of NO₂ – pointing to increased exposure to ambient air pollution in these areas (Crouse et al., 2009). Moreover, recent research has demonstrated geographic differences in cancer rates by country and within regions (Bray et al., 2018). Differences in cancer risk by sex, as a result of both differences in exposures and biological sex, have also been noted in previous research which plays a role in incidence, mortality, and prognosis (Turner et al., 2017). Clougherty (2010) noted that a gendered approach to air pollution epidemiology is required to ensure the disaggregation of social and biological differences between men and women. As such, all these potential modifiers will be included in the analysis.

Substantial research has been done to investigate the impact of AAP on the risk of developing lung cancer, however the extent to which exposure to AAP impacts the risk of non-lung cancers, such as kidney and bladder cancer, has not been fully explored. Although the exact biological mechanisms underlying the cause of non-lung cancers as a result of AAP exposure are not fully understood, it has been suggested that antioxidant and inflammatory responses are among the key pathways (Gruzieva et al., 2017). We know that asbestos can move through the body after exposure via the lungs, as such, it can be hypothesized that other particles can translocate in a similar manner. In addition to exposure via the lungs, the skin is another pathway through which air pollution can enter the body, however the effects are not well understood (Araviiskaia et al., 2019). The primary pathway by which AAP enters the body is through the respiratory system, whereby pollutants are inhaled and transported throughout the body as a result of air exchange in the lungs. As oxygen is diffused across alveolar respiratory surfaces, these pollutants can also be exchanged into the bloodstream before travelling to other body systems (Gruzieva et al., 2017).

The presence of AAP compounds within the respiratory system can cause intracellular damage from free radical peroxidation (Xing et al., 2016). Prior research has shown that PM_{2.5} particles are rich in iron, copper, zinc, manganese, polycyclic aromatic hydrocarbons and lipopolysaccharides –compounds which can drive the production of free radicals and cause oxidative stress (Donaldson et al., 1996). Oxidative stress and damage caused by the presence of these free radicals may result in DNA damage – when such damage is not repaired carcinogenesis, mutagenesis and other irreversible damage may occur (Xing et al, 2016). Research by Mehta *et al.* has shown that the presence of these particles may also promote the replication of damaged DNA leading to carcinogenesis (2008). In addition to causing oxidative stress, it has been reported that AAP exposure, namely exposure to PM_{2.5}, is related to inflammatory injury (Xing, et al., 2016). Such exposure stimulates the overexpression of genes related to transcription and the generation of inflammatory cytokines, leading to cellular damage (Xing et al., 2016).

In addition to the aforementioned pathways, unbalanced intracellular calcium levels have also been highlighted as a potential cause of disease as a result of AAP exposure – particularly PM_{2.5} (Xing et al, 2016). The accumulation of calcium, an important messenger that regulates cellular function, across body systems, activates a series of inflammatory reactions that can lead to cellular damage (Xing et al., 2016). The introduction of PM_{2.5} into the cellular environment induces the excessive production of free radicals, decreasing the antioxidant capacity of the cell which results in the peroxidation of lipids in the cell membrane and elevated calcium concentrations (Xing et al, 2016). Prior research has shown that elevated intracellular calcium levels due to PM_{2.5} may be a mechanism for cellular damage (Brown et al., 2004). Overall, research has shown that exposure to AAP drives intracellular damage and oxidative stress which can lead to disease in the respiratory system, however, the depth of understanding on how such exposure impacts other body systems is limited. While research has shown that compounds can be transferred across the alveolar surface by diffusion into the bloodstream, the pathophysiology of these compounds in other body systems is not greatly understood.

2.3 Kidney & Bladder Cancer

2.3.1 General overview of Kidney Cancer

Kidney cancer encompasses a number of different cancers that occur in the kidneys – each caused by mutations to different genes (Linehan et al., 2010). Renal cell carcinoma (RCC) constitutes the largest proportion of kidney cancers, with 90% of renal tumours being RCC (Motzer et al., 2011). The incidence of kidney cancer, mainly RCC, has risen in Canada since 1986 driven primarily by the detection of incidental tumours and growing rates of obesity and hypertension in the country (De et al., 2014). Approximately 90% of all kidney cancers diagnosed occur in those over the age of 45, with approximately 6,000 new cases and 1,750 deaths attributable to the disease each year in Canada (De et al., 2014). The age-standardized incidence rate of kidney cancers in Canada rose from 13.4 to 17.9 per 100,000 in men, and 7.7 to 10.3 per 100,000 in women between 1986 and 2007 in Canada (De et al., 2014). The projected estimate of new kidney cancer cases in Canada for 2020 was 7500, with an age-standardized incidence rate of 23.6 in men, and 11.5 in women (Brenner et al., 2020). Smoking and obesity are among the most notable risk factors for the development of kidney cancer, while several hereditary types of kidney cancer also exist whereby an autosomal mutation to the VHL gene predisposes an individual to kidney cancer (Motzer et al., 2011). Known risk factors for the development of kidney cancer include tobacco smoking, radiation, and trichloroethylene exposure (IARC, 2020). Other possible risk factors, with limited evidence, include exposure to arsenic in drinking water, cadmium, perfluorooctanoic acid and some occupational exposures (ie. printing processes & welding fumes) (De et al., 2014; IARC, 2020). Additionally, the consumption of certain medications may also play a role in increasing the risk of kidney cancers including acetaminophen and non-aspirin NSAIDs – however, there is little agreement regarding this association at present (De et al., 2014). It should also be noted that moderate alcohol consumption has been highlighted as a protective factor against kidney cancer, whereby it is associated with a reduced risk of RCC (De et al., 2014). Prior research has highlighted the important role that metabolic pathways play in the development of cancer, specifically those involved in energy, nutrient, iron, and oxygen sensing (Linehan et al., 2010). To date, researchers have pinpointed seven genes specifically related to the development of kidney cancer, each of which is related to at least one metabolic pathway, suggesting that kidney cancer is a “disease of dysregulated cellular metabolism” (Linehan et al., 2010).

2.3.2 General overview of bladder cancer

Bladder cancer is a heterogenous disease varying from low-grade tumours with low progression rates to high-grade highly malignant tumours (Kirkali et al., 2005). In high-income countries, bladder cancers are the fourth most common malignancy among men, with men being 3 to 4 times more likely to develop the disease than women (Kirkali et al., 2005). While bladder cancers are more common in men, research has shown that the survival rate in women is worse than in men (Prout et al., 2004). The predicted incidence of bladder cancer in Canada for 2020 is 12200, with an age-standardized incidence rate of 42.0 in men, and 10.7 in women (Brenner

et al., 2020). Bladder cancer remains the 4th most commonly diagnosed cancer among men in Canada accounting for about 8% of new cancer cases (Brenner et al., 2020). Prior research using animal models has shown that rats treated with androgenic hormones develop more bladder tumours than those treated with estrogenic hormones (Reid, et al., 1984). The most common subset of bladder cancers are urothelial carcinomas, which can develop anywhere transitional epithelium is present (ie. renal pelvis, ureter, bladder) (Clark et al., 2013). Approximately 90% of urothelial tumours originate in the bladder, with 8% occurring in the pelvis and the remaining 2% in the ureter and urethra (Clark et al., 2013). Overall, 70% of bladder tumours present as superficial disease with the remainder comprised of muscle-invasive disease (Kirkali et al., 2005). The most notable risk factors for bladder cancer are smoking and occupational exposure (Kirkali et al., 2005). Many of the known risk factors listed by IARC include dyes, in addition to radiation, tobacco smoking, and the consumption of opium (2020). Some of the suspected carcinogenic agents associated with bladder cancer – those with limited evidence in humans – include coal tar pitch, dry cleaning, diesel engine exhaust, soot, and those compounds used in printing, textile manufacturing and hairdressing (IARC, 2020). Smoking is the most important risk factor for bladder cancers, however specific external agents, such as the consumption of vitamin supplements, may modify the susceptibility of an individual to smoking-induced bladder cancers (Kirkali et al., 2005). Occupational exposures also contribute to one's risk of bladder cancer, namely for those working in the textile, tire, leather, and painting fields (Markowitz & Levin, 2004). Moreover, research suggests that women who have given birth have a lower risk of bladder cancer than those who have never had children – most likely due to the hormonal changes related to pregnancy – and this number increases with parity (Cantor, et al., 1992). With regards to racial differences, prior research has also shown that individuals of African descent have only half the risk of developing bladder cancers than those of European descent, although survival rates are much lower in this group – these differences have not yet been fully explored (Ries, 2002). In addition to racial differences, Canadian researchers have demonstrated a higher incidence of bladder cancer among those of lower socio-economic status (Densmore et al., 2019).

2.3.3 Current research

Previous research has pointed to a link between air pollution and kidney cancer, although this relationship has not been fully explored (Raaschou-Nielsen et al., 2017). Moreover, a relationship between air pollution and bladder cancer has also been noted by researchers, although the degree of understanding regarding this relationship is still limited to date (Scelo et al., 2018). A 2020 systematic review by Sakhvidi et al., noted a positive association between air pollution and bladder and kidney cancer (2020). It should be noted that this positive association was considered weak by the researchers as very few studies reached statistical significance (Sakhvidi et al., 2020). Although an association was noted, few articles were included – only 20 met the inclusion criteria for the study – and as such the researchers noted that little research has been done to fully quantify the relationship between ambient air pollution and kidney and bladder cancer (Sakhvidi et al., 2020). Of those bladder cancer studies included only three reached statistical significance when considering the incidence of bladder cancer related to AAP exposure – with weak evidence of a relationship (Sakhvidi et al., 2020). One additional study

noted an increased risk of developing bladder cancer as a result of AAP exposure, however, these results did not reach statistical significance (Sakhvidi et al., 2020). Of those kidney cancer studies included, five found a positive association between AAP exposure and the incidence of kidney cancer – however none reached statistical significance (Sakhvidi et al., 2020). Sakhvidi et al., noted that future studies should be rigorous in their adjustment, exposure assessment methods and follow- ups (2020). Other research on the relationship between ambient air pollution and non-lung cancers has shown that the resulting inflammation and cell damage impacts several organs, including the kidneys (Brook et al., 2010; Afsar et al., 2019). Research from Europe suggests that exposure to particulate air pollution near the home is associated with a higher risk for kidney parenchyma cancer (Turner et al., 2017). Additional studies have also found that air pollution near the place of residence may also play a role in bladder cancer etiology (Castano-Vinyals et al., 2008). Overall, while research has shown a relationship between ambient air pollution and kidney and bladder cancers, there still exists gaps in current literature with regards to this relationship. Moreover, gaps exist with regards to how the relationship between AAP exposure and kidney/bladder cancers is potentially modified by income, sex and geography – several previous studies have not found a relationship; however, this could mean that a) there was no relationship, b) that the study was too small to detect a relationship, or c) that a relationship exists however the study design was flawed. To date, the largest study to investigate this relationship to date – Turner, et al. (2017) – did find a link even with limited data. The sheer size of my study, which will allow for substantial power to detect small changes in risk, in conjunction with excellent exposure and cancer data will help to overcome the challenges associated with previous studies in this area. Given the size of the dataset used, we have the best chance of finding even small changes to the overall risk of kidney and bladder cancers as a result of AAP exposure. Overall, my study seeks to contribute to the current body of knowledge regarding AAP and non-lung cancers and will help to fill the gaps by characterizing the relationship between the exposure and both kidney and bladder cancers.

3. METHODS

This research project will use a retrospective cohort study to examine the impact of ambient air pollution exposure metrics on the risk of kidney and bladder cancers. With an exposure period from 1991 to 2006, and follow-up until 2015, we will compare incremental increases in exposure to see if AAP is associated with an increased risk of cancer to examine the potential impacts of ambient air pollution on the risk of kidney and bladder cancer. Follow-up data were collected each year – a July 1st date will be used each year to examine disease outcomes across time-period. Air pollution surfaces will be used as a proxy to determine the amount of individual exposure to AAP. Differences across sex, neighbourhood income and geography will also be examined to assess potential disparities in cancer risk factors. Examining differences by sex, neighbourhood income and geography will allow an assessment into potential disparities in cancer risk factors. Ethics approval from the Health Research Ethics Board of Alberta – Cancer Committee has already been approved for the project.

3.1 Project Datasets

Analysis will be conducted using data from the Canadian Urban Environmental Health Consortium (CANUE), Canadian Census Health and Environment Cohorts (CanCHEC) and the Canadian Community Health Survey (CCHS). As prior research has shown success in using these three databases for this type of analysis, there are no concerns regarding data quality (Crouse et al., 2015). With regards to missing data, appropriate measures, as outlined in research by Crouse, et al., will be used (2015).

CANUE offers a large data platform of environmental exposures available to Canadian researchers that includes numerous datasets including air pollution data at a neighbourhood level (Crouse et al., 2015). While the CANUE platform contains numerous environmental and health datasets, our project will be utilizing geospatial pollution layers to quantify exposure (Crouse et al., 2015). CanCHEC was created from a data linkage that brought together demographic, socioeconomic, residence, mortality, and cancer outcomes for millions of Canadians with follow-up to 2015 (Crouse et al., 2015). Each CanCHEC dataset (previous iterations exist including the 1991, 1996, 2001, and 2006 CanCHEC's) combines data from the long-form census with administrative health data and postal code – thus creating a robust cohort that can be utilized to examine differences in outcomes across a variety of variables (Tjepkema, et al., 2019). CanCHEC data is created by linking census and national household survey data to the derived record depository which contains birth, death, immigration, and tax data, with subsequent linkage to the Canadian Vital Statistics Death Database (CVSD), Discharge Abstract Database (DAD), and National Ambulatory Care Reporting System (NACRS) (Tjepkema et al., 2019). Trends over time can be examined within and between CanCHECs as a result of consistent methodology used to create each cohort – my study will use a stacked cohort of CanCHECs which is useful in identifying rarer health outcomes (Tjepkema et al., 2019). It is important to highlight that the CanCHEC dataset includes individual level data on cancer incidence rather than ecological or neighbourhood-level outcomes (Tjepkema et al., 2019). Data from the Canadian Community Health Survey will also be incorporated to use an indirect adjustment procedure to help account for health behavior-related risk factors that are not available in the CanCHEC cohorts, such as smoking and physical activity (Pinault et al., 2017). Exposure data will be obtained from the CANUE platform, which contains spatial pollution surfaces in metropolitan areas of Canada for ground level ozone, annual average PM_{2.5} and annual land use regression estimates of NO₂, and all available at the 6-digit postal code level. The spatial pollution surfaces included in CANUE are raster models that provide values for PM_{2.5}, O₃ and NO₂ – these values can be utilized to estimate exposure values for any given geographic point within the bounds of the surface layer – these values will be categorized into incremental exposure groups which will be analyzed to evaluate changes in the risk of kidney and bladder cancer. This data will be linked with data from both the stacked CanCHEC cohort and the CCHS. The CANUE air pollution exposure metrics can be used to assess individual-level exposure to ambient residential PM_{2.5}, O₃ and NO₂, which can be matched to most records in the CanCHEC cohort on an annual basis. Using these linked exposure values, in addition to cancer diagnosis data we will be able to evaluate whether those with increased exposure to air pollutants are at higher risk of kidney and bladder cancer (Crouse et al., 2015). Most of the

research using CanCHEC to date has examined mortality outcomes, and we have an opportunity to investigate cancer incidence in this large, population-based dataset with approximately 150 million person-years of follow-up for those aged 25+ at the time of the census, giving extraordinary statistical power to detect smaller relationships (Crouse et al., 2015). Given the presence of socioeconomic data, sex, and geographic identity data within the cohort we have the capacity to examine changes in risk across these groups.

3.2 Data Organization & Stratification

The focus of this project will be on Canadians living in a Census Metropolitan Area (CMA), which includes urban, suburban and rural areas near larger city centers (Crouse et al., 2015). As of 2016, over 70% of the Canadian population lives in a CMA – pointing to the applicability of our findings to the majority of Canadians (Statistics Canada, 2016). We will restrict our analyses to those CanCHEC study participants whose residential postal code fell within the CMA boundaries in 1991 - coinciding with the first CanCHEC cohort - or those who moved into the CMA provided they lived there for at least seven years before the end of the study, or they were diagnosed with kidney or bladder cancer. Based on the approach used by Crouse et al., a seven-year moving window will be applied, where exposure data must be available for at least four of the seven years – this allows adequate exposure data over time for participants within a CMA but also does not include those who have moved or fall below the threshold for missing data (2009). Air pollution exposures have been assigned to a set of coordinates for each CanCHEC participant's six-digit postal code, during each year - postal codes are an accurate proxy for residential location (Bow et al., 2004). Differences across neighbourhood income, and geography will be examined using the same postal code method by which participants are stratified across these values. Neighbourhood income will be derived from census level income from the Canadian Marginalization Index (Matheson et al., 2012). Geography – urban, rural or suburban – will be defined using Gordon & Janzen's Urbanization Index approach to define participants as living in one of the three geographical zones (Jerrett et al., 2013). Analysis will also be stratified by sex using data available within the CanCHEC cohort.

3.3 Statistical Methodology

We will first conduct a descriptive analysis of the pollutants, followed by an examination into how our pollutants of interest ($PM_{2.5}$, O_3 and NO_2) are correlated with one another, and then to identify their independent effects. We will consider linear associations as well as non-linear relationships between the pollutants of interest. Following a similar approach to recent work examining air pollution and health we will then analyze data using Cox proportional hazards models to estimate associations (hazard ratios and the 95% confidence intervals) between air pollution exposure metrics and the risk of kidney and bladder cancer (Jerrett et al., 2013). Moreover, the strength of association between air pollution exposure and incidence of kidney and bladder cancers will be evaluated to determine how they differs by sex, neighbourhood income and between urban and rural areas. The potential confounding effect of smoking and overweight/obesity will be indirectly adjusted for with data from the CCHS (Pinault et al., 2017).

Age will be examined through a time scale, as this approach does not assume there is a direct relationship between age and disease (Cologne et al., 2012). This modelling approach has been used in previous work and will help gain consistency in the body of knowledge related to air pollution and kidney/bladder cancer (Turner et al., 2017).

4. SIGNIFICANCE, IMPACT & KNOWLEDGE TRANSLATION

4.1 Significance & Impact

Based on the results found by Turner et al., who found a link between air pollution exposures and kidney and bladder cancer deaths, we have a unique opportunity in Canada to address these outstanding research questions (Turner et al., 2017). As CanCHEC is even larger than the cohort that Turner et al. used, with access to cancer incidence data rather than just mortality, we have a high degree of power to detect associations should they exist. While research has been conducted examining exposure to air pollution and the risk of lung cancer, recent evidence suggests that we must now move to study other potential pathways to carcinogenicity at a variety of cancer sites. The results of this project have the potential to shine a light on the broader impacts of air pollution exposure on kidney and bladder cancer.

This study will add to the current literature by examining how kidney and bladder cancer relate to ambient air quality in Canada. Moreover, we also have the ability to assess how the potential relationships between air pollution and the risk of these cancers vary by sex, neighbourhood income, and geography. To date, there is little information on how varying exposure to air pollution, socioeconomic status and place of residence relates to cancer risk in Canada. Overall, this project will allow us to contribute to the body of knowledge surrounding the potential relationship between ambient air pollution and kidney and bladder cancer. By creating a better understanding of the risk factors associated with kidney and bladder cancer we can help prevent these conditions – through cancer prevention policies and regulations – without the need for modification at an individual level. While this research does not impact individual patients specifically, it has the potential to help mitigate possible risk factors for individuals. This research will contribute to the body of knowledge surrounding ambient air pollution and non-lung cancers while supporting and guiding future research into the topic.

4.2 Knowledge Translation

The results of our project will primarily be shared in two ways – through presentations, and publication. Presentations, albeit virtual, will include those at academic conferences, as well as presentations for stakeholders such as government policy makers, and advocacy/lobbying group. Government policy makers include those at a provincial and federal level, with the exclusion of municipal governments as they have little power to institute regulatory requirements regarding emission standards. Provincial and Federal departments of health, and environment will be specifically targeted – ex: Public Health

Agency of Canada, Alberta Ministry of Health, Health PEI and all other provincial health administrations. The presentations will be delivered in addition to an easily digestible report outlining the key findings of our study and the potential public health impacts of our results. While the results will not be shared specifically with the general public, our findings have the potential to impact policy development regarding emission standards and air pollution which in turn impacts individual health. Publication will be sought in an academic journal to further disseminate our findings with an academic audience as well as contribute to the current body of evidence on the topic. The larger knowledge translation plan, as part of the larger research project on the potential impacts of ambient air pollution on non- lung cancers has been included in the Appendix of this document. While the specific knowledge translation plans for this smaller project have been outlined above, the results of this study will also be included in the KT plans associated with the larger project.

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