# The Association Between Exposure to Ambient Air Pollution and Risk of Leukemia in Canada

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# Abstract

Exposure to air pollutants, including nitrogen dioxide ($NO_2$) and particulate matter smaller than 2.5 microns ($PM_{2.5}$), have been shown to be associated with increased incidence of lung cancer, and a few recent reports found that the incidence of breast and prostate cancer may also be so related. There is, however, a paucity of studies on other sites of cancer, including adult leukemia. Occupational studies have shown that exposure to benzene increases one's risk of developing leukemia, and ambient air contains benzene and other carcinogens. As ambient air pollution contains benzene, has been shown to have causal associations with cancer of the lung, and may have associations in other organs, there is a possibility that leukemia could also be associated with exposure to air pollution. My review of the literature indicated a possible association between leukemia in children and $NO_2$. However, the available studies were limited by small numbers of cases, low and unreported response rates, and potential misclassification of exposures. In addition, only five studies were used to investigate leukemia in adults. The objective of this thesis was to determine whether ambient air pollution is associated with incidence of leukemia in adults. We used a Canadian population-based case-control study conducted in 1994-1997. Cases were 1,064 adults with incident leukemia and controls were 5,039 adults without any cancer. Using data from remote-sensing stations across Canada, we developed interpolation models to assign subjects' past exposure to $NO_2$ and $PM_{2.5}$ from 1975-1994. We used the total average exposure of a subject between the 1975-1994 period and we assigned these estimates to their place of residence. We conducted sub-analyses for individual provinces (Ontario, British Columbia, Alberta) and for individual subtypes where numbers were sufficient (chronic and acute myeloid leukemia, and chronic lymphocytic leukemia). Using logistic regression models using natural cubic splines, we found a 'n-shaped' response function between exposure to $NO_2$ and all forms of leukemia: at low concentrations, from 4.51 to 14.66 ppb, the odds ratio (OR) was 1.24 (95% confidence interval (CI) 1.00-1.54) and at higher concentrations, from 22.75 to 29.7 ppb, the OR was 0.81 (95% CI 0.69 – 0.95). For $PM_{2.5}$ we found a concentration-response function that was consistent with a slight monotonic increase: at lower

concentrations of $PM_{2.5}$, from 5.6 to 8.0 μg/$m^3$, the OR was 0.89 (95% CI 0.76 – 1.03) and at higher concentrations, from 15.6 to 19.2 μg/$m^3$, the OR was 1.20 (95% CI 0.96 – 1.51). For chronic lymphocytic leukemia we found an OR per 5 ppb of $NO_2$ of 0.92 (95% CI 0.86 – 1.00) and an OR per 10 μg/$m^3$ of $PM_{2.5}$ of 0.63 (95% CI 0.42 – 0.94). We found no association for exposure to $PM_{2.5}$. The n-shaped curve for $NO_2$ may be related to urban-rural differences and/or to possible selection bias. From this thesis it is clear that given the dearth of studies in adult leukemia further research is needed.

# Résumé

L'exposition aux polluants atmosphériques, notamment au dioxyde d'azote ($NO_2$) et aux particules fines ($PM_{2.5}$), a été associée à une augmentation de l'incidence de cancers du poumon. De récentes études épidémiologiques ont de plus montré une possible association entre la pollution atmosphérique et l'incidence de cancers de la prostate et du sein. Toutefois, il n'y a que très peu d'études s'étant intéressées à d'autres types de cancer, incluant la leucémie. Comme la pollution de l'air ambiant contient du benzène, il a été démontré que causalité associations avec le cancer du poumon, et peut-être associations dans d'autres organes, il y a une possibilité que la leucémie pourrait également être associé à l'exposition à la pollution de l'air. Ma revue de la littérature a indiqué un lien possible entre la leucémie chez les enfants et le $NO_2$. Cependant, les quelques études répertoriées présentent des limites: un petit nombre de cas, des taux de réponses faibles ou non déclarés, et des potentielles erreurs de classification d'exposition. Seulement cinq études s'intéressant à la pollution de l'air et la leucémie chez les adultes ont été répertoriées. L'objectif de cette thèse était de déterminer si la pollution de l'air ambiant est associée à l'incidence de leucémie chez les adultes. Pour se faire, nous avons réalisé une étude cas-contrôle basée sur la population adulte canadienne de 1994-1997. Nous avons utilisé 1064 cas incidents de leucémie et 5039 contrôles sans diagnostics de cancer. À partir des concentrations mesurées par le réseau canadien de station de surveillance de la qualité de l'air, nous avons développé un modèle de dispersion ajusté avec des données satellitaires afin d'interpoler l'exposition de chaque individu aux polluants de l'air ($NO_2$ et $PM_{2.5}$), basée sur le lieu de résidence. Au final, l'exposition assignée à chaque individu correspondait à l'exposition annuelle moyenne pour la période 1975-1994. Nous avons effectué des sous-analyses par provinces (Ontario, Colombie-Britannique et Alberta) et, lorsque possible, pour les différentes formes de leucémie (la leucémie myéloïde aiguë, la leucémie myéloïde chronique, et la leucémie lymphoïde chronique). En utilisant des modèles de régression logistique basés sur des 'splines' cubiques naturelles, nous avons trouvé une fonction concentration-réponse en forme de 'n' entre l'exposition au $NO_2$ et toutes les formes de leucémie : à des faibles concentration

(i.e., 4.51 à 14.66 ppb), nous avons obtenu un rapport de cote (OR) de 1.24 (IC95% : 1.00 - 1.54) alors qu'à des concentrations plus élevées (i.e., 22.75 à 29.7 ppb) le OR était de 0.81 (IC95% : 0.69 - 0.95). Pour les $PM_{2.5}$, nous avons trouvé une fonction concentration-réponse qui était compatible avec une fonction linéaire légèrement positive : à de faibles concentrations (i.e., 5.6 à 8.0 $\mu g/m^3$) le OR était de 0.89 (IC95% : 0.76 - 1.03) et à des concentrations plus élevées (i.e., 15.6 a 19.2 $\mu g/m^3$) le OR était de 1.20 (IC95% : 0.96 - 1.51). Pour la leucémie lymphoïde chronique, nos résultats montrent des OR de 0,92 (IC95% : 0,86 -1,00) par augmentation de 5 ppb de $NO_2$ et de 0,63 (IC95% : 0,42-0,94) par augmentation de 10 $g/m^3$ de $PM_{2.5}$. Nous n'avons trouvé aucune association pour l'exposition aux $PM_{2.5}$. La courbe en forme de 'n'obtenue pour le $NO_2$ pourrait être liée à des différences entre les milieux urbain-rural ou encore à une certaine forme de sélection biaisant les résultats. Compte tenu de la rareté des études portant sur la leucémie chez l'adulte, des recherches supplémentaires sont nécessaires afin de corroborer les résultats.

# Preface

## Contribution of authors

I was the primary author of this manuscript-based thesis and first author of the manuscript that will be submitted to peer-reviewed journals for publication. I conducted and wrote the review of the literature and the manuscript, and performed all statistical analyses, under the supervision and guidance of Dr. Mark Goldberg.

Dr. Mark Goldberg is full professor in the Department of Medicine, McGill University, and is both an associate member in the Department of Epidemiology and Biostatistics, and the Division of Experimental Medicine. Dr. Goldberg was my supervisor for my thesis and the primary investigator of the case-control study of incidence of leukemia in Canada. Dr. Goldberg oversaw the development of my study protocol, provided guidance on the statistical analyses and the interpretation of the results, and revised and edited all sections of my thesis.

Dr. Perry Hystad is an assistant professor in the College of Public Health and Human Sciences at Oregon State University in Corvallis, OR, and is a co-author of my manuscript. Dr. Hystad was responsible for calculating and developing all of the national level spatial surfaces for the pollutants we used in our study.

Dr. Paul Villeneuve is an associate professor in the Department of Health Sciences in the Institute of Health Science and Technology at Carleton University, in Ottawa, ON. Dr. Villeneuve was the curator of the National Enhanced Cancer Surveillance System data set for the case-control study we conducted and co-author of my manuscript. Dr. Villeneuve provided valuable information about the contents of the data set and on interpretation of results.

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First and foremost I have to thank my supervisor, Dr. Mark Goldberg, for taking me on as his student during a time when I needed both change and guidance. Mark has exceeded any expectations I have had for a supervisor, from answering emails within hours (and apologizing when he was "late" in replying) to editing numerous drafts within days of receiving them. With his guidance and comments, whether they made me think or made me laugh out loud in public, he made me a better writer and researcher. Every student should have the privilege of working with a supervisor who prioritizes his students as much as Mark does.

I would also like to thank our biostatistician, Marie-France Valois. Without her assistance with aspects of my analysis I would still be stuck searching Google for ways to debug my code. I must also thank my lab mate and friend, Stéphane Buteau for being a needed resource of information and advice, and also for translating my abstract into French.

Without Dr. Perry Hystad's work, I would not have been able to complete our study, and for this I am very grateful. Also, I would like to thank my committee members Dr. Paul Villeneuve and Dr. Marianne Hatzopoulou for their assistance, and I would especially like to thank Paul for answering countless emails about my data set.

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# Chapter 1 ~ Introduction

## 1.1 Ambient air pollution

One of the most ubiquitous environmental exposures is ambient air pollution. Everyone is exposed from birth to death, although personal exposures can vary considerably because of spatial and temporal variations and activities. Air pollution is a highly complex mixture and one of the major sources of urban air pollution is vehicular traffic (*1*), but other sources, such as industry, agriculture, power generation, and natural processes, make important contributions (*2, 3*).

Air pollution is a complex mixture comprising numerous chemicals, including ozone ($O_3$), sulphur oxide ($SO_x$), carbon monoxide (CO), carbon dioxide ($CO_2$), nitrogen oxides ($NO_x$), volatile organic carbons (VOCs), and particulate matter (PM). Particulate matter is a mixture of liquid droplets, chemicals, and solid particles that are categorized not only by their composition but also by their aerodynamic diameter (e.g., ultrafine particles (less than 0.1 μm), inhalable particulates (10 μm or less, $PM_{10}$) and fine particulates of size less than 2.5 μm ($PM_{2.5}$)) (*4, 5*). $PM_{10}$, consists of resuspended dusts, soils, crustal materials from farming and road use, pollen, and also mould spores (*6*). Fine particulates consist of particles that primarily result from combustion of hydrocarbons, including gasoline, diesel, coal, and wood burning, but also include nitrates and sulphates generated from the conversion of primary emissions of sulphur and nitrogen oxides (such as NO and $NO_2$). In rural areas, the main source of air pollution is agriculture (*7*), although long-range transport of air pollution from urban and industrial sources are important. In general, certain pollutants, such as $NO_2$, have concentrations that are considerably lower than in urban settings, and these are often considered as "background levels" (*8*). Although concentrations of pollutants in rural areas are generally lower than in urban areas, concentrations of particulate matter can be still relatively high due to agricultural processes (*9*), local burning of biomass, and long-range transport.

There are several factors that affect the concentrations of pollutants in urban areas. For instance, concentrations of pollutants are higher in areas where streets are lined with tall buildings on either side, as this tends to trap vehicular emissions (*10*). In areas with more green space, concentrations of pollutants are lower due primarily to the lower amounts of traffic but also the ability of these green spaces to absorb ambient pollutants (*8, 10, 11*). Weather has an important effect on concentrations; wind can carry pollutants from one urban or rural community to the next, and temperature inversions trap pollutants (*8, 12, 13*). As a result of these factors, concentrations of air pollutants within an urban area can be highly variable, with 50 $\mu g/m^3$ differences in $NO_2$ being observed between areas less than 50 meters apart (*8, 14*).

## 1.2 Epidemiologic studies of ambient air pollution and health outcomes

The effects of short-term exposure to air pollution (on a time scale of hours to weeks) on health have been documented for more that a half a decade. One of the sentinel events that changed our understanding of air pollution was the London smog incident in the winter of 1952. Coal was the main source of energy for industry and homes, and inefficient combustion along with a lengthy temperature inversion caused soot and sulphur dioxide to be trapped at ground level (*15*). This event caused the deaths of thousands of people (*16*). Since the smog events in London, associations have been found between short-term exposure to air pollution and daily counts of non-accidental mortality (*17-20*), cardiovascular and cardiopulmonary mortality (*6, 21-24*), and increased daily hospitalizations for respiratory diseases (*25-27*).

The effects of acute changes in air pollution appear mainly to affect the cardiovascular system. For example, findings from studies in Montreal and studies elsewhere showed that persons with heart failure (*28-33*) as well as those with diabetes and cardiovascular disease (*28, 29, 34*) are highly susceptible to the effects of daily changes in environmental conditions. Studies conducted elsewhere in the world have also shown consistently positive associations (*35-40*), especially for cardiovascular disease.

Inflammation as measured by increases in plasma fibrinogen, interleukin-6, C-reactive protein, and other complex responses (*41-43*) has also been found to be associated with increased levels of air pollution (*44*). Increasing levels of particulate air pollution (*45-54*) are associated with reduced heart rate variability and worsening heart failure and arrhythmias (*55-58*). Studies of wood smoke have shown increases in biomarkers of oxidative stress (*59*) as have other biomarker studies of particulates (*60, 61*), and possibly specifically in atrial fibrillation (*62*).

Other studies have shown positive associations between air pollution and ST-segment depression (implying that the heart is damaged or not receiving enough blood) (*63*) and in repolarization (duration, morphology, variability), suggesting that the myocardial substrate is a target of air pollution (*64-67*). A recent intervention study of cooking practises in Guatemala in which open fires were replaced by vented stoves showed an important reduction in the occurrence of ST-segment depression, thus suggesting experimentally that particulate matter and other combustion products affect ventricular repolarization (*68*).

In addition, the incidence of chronic disease is influenced by prolonged exposure to air pollution. Specifically, positive associations have been found between long-term exposure to air pollution and the incidence and mortality of diseases of the cardiovascular system (*6, 69, 70*). In addition, long-term exposure of ambient air pollution may have associations with mortality from respiratory diseases (*5, 6*).

In 1988, the International Agency for Research on Cancer considered diesel exhaust to *probably be carcinogenic to humans*, and in 2012 they updated the classification of diesel exhaust to *carcinogenic to humans* (*71*). The data supporting this conclusion were derived mostly from occupational studies, but because diesel is an important source of ambient pollution, it has important implications to environmental health. Very recently, the International Agency for Research on Cancer also classified air pollution, and particulate matter specifically, as being carcinogenic to humans (*72*). The decision to consider particulate matter as carcinogenic to humans was based primarily on studies of

lung cancer, which included individual cohort (*73-80*), and a few case control (*81-83*) studies showing consistent increases in risk of lung cancer from exposure to air pollution.

The biological mechanisms for cardiovascular disease appear to include inflammation, oxidative stress, and effects on the autonomic nervous system (*84*). The precise causes and mechanisms in which ambient pollutants can cause cancer are not known. Particulate matter is suspected to have either direct or indirect properties that can lead to the development of tumours (*85*). It has been hypothesized that components of particulate matter can generate reactive oxygen species that cause oxidative stress on cells (*6*) and carcinogens, such as some metals, can be found on their surfaces. The reactive oxidized species that are formed by particulate matter can trigger cellular events associated with inflammation and DNA damage, and when particulates are in high concentrations they can trigger tumourigenesis (*86*). In addition, certain components of particulate matter have the ability to generate free radicals, which are highly reactive species of molecule due to the presence of an unpaired electron. Free radicals damage both lipid membranes and DNA, which can eventually cause cells to become cancerous. Inhalable particulates and fine particles can be inhaled deep into the alveoli where gas exchange occurs with the blood (*6, 87*).

Air pollution also contains benzene, polycyclic aromatic hydrocarbons, and 1,3-butadiene (*88-91*), which are accepted carcinogens (*92-100*). It has been speculated that $NO_2$ may form reactive oxidized species and could therefore be part of a process that leads to cancer (*101, 102*).

Indeed, there is evidence from a few case-control studies that suggest air pollution may increase the risk of cancer in organs and tissues other than the lung (*103-105*). Considering that studies have shown that exposure to benzene and polycyclic aromatic hydrocarbons (PAHs) may increase a women's risk of developing breast cancer (*94, 106, 107*), and that air pollution contains both benzene and PAHs, it is therefore plausible that air pollution could be a cause of cancer of the breast. One investigation found positive associations between ambient air pollution exposures (using $NO_2$ as a marker) and breast

cancer (*103*) while another reported that increased incidence rates of breast cancer in the US were positively associated with exposure to $NO_2$ (*105*). In addition to cancer of the breast, a positive association was found using $NO_2$ as a marker for traffic related air pollution in a recent study of prostate cancer (*104*), and the International Agency for Research on Cancer also noted a potential increase in risk for cancers of the bladder (*108*).

The International Agency for Research on Cancer has classified benzene as *carcinogenic to humans* (*89*) and is an accepted causal risk factor for leukemia (*95, 96, 109-112*). However, in few studies has this relationship been evaluated in non-occupational settings where exposures are usually much lower (*113-116*). Furthermore, almost no studies have been conducted on the association between ambient air pollution and leukemia in adults (*115, 117-120*). As traffic-related air pollution contains benzene, has been shown to have causal associations with cancer of the lung, and may have associations in other organs, there is a possibility that leukemia could also be associated with exposure to air pollution. For these reasons, it is reasonable to investigate associations between ambient air pollution and other cancers. This is the rationale behind my thesis, which is to investigate whether the incidence of leukemia is associated with ambient air pollution.

# Chapter 2 ~ Research Objectives

## 2.1 Rationale

Almost all people are exposed to air pollution on a daily basis, and it is therefore important to identify risks to public health that are associated with this complex mixture of chemicals and particles. As indicated previously, air pollution has been shown to cause lung cancer and to be potentially associated with cancer sites other than the lung. Given the ubiquity of air pollution, it is essential to identify all of its causes, including other sites of cancer. In addition, there are few studies that have been used to investigate the effects of air pollution on the incidence of leukemia in adults. Thus, the objectives of my thesis are:

## 2.2 Objectives

1) To conduct a structured review of the epidemiologic studies in the scientific literature used to investigate the effects of exposure to air pollution and the incidence and mortality of leukemia.

2) To determine whether the incidence of leukemia in male and female adults in Canada was associated with exposure to ambient air pollution.

# Chapter 3 ~ Review of the literature

## 3.1 Leukemia

Unlike cancers that form solid tumours, leukemia is a haematological disorder and affects individuals of all ages (*121*). The malignancy affects stem cells of the blood that originate from the soft spongy marrow in the centre of the bone (*122*). Cells develop leukemia when abnormal stem cells of the blood begin to mature and grow without regulation (*122*). The main subtypes of leukemia are classified according to which stem cell of the blood they originated from: myeloid (cells that mature into red blood cells, white blood cells, and platelets) or lymphocytic (cells that mature into lymphocytes) (*123*). Leukemia is further classified into chronic, progressing over a long period, or acute, progressing quickly, leading to four main subtypes of leukemia: acute lymphocytic leukemia; acute myeloid leukemia; chronic lymphocytic leukemia; and chronic myeloid leukemia (*124, 125*).

Chronic lymphocytic leukemia occurs when lymphocytes (clonal B cells) originating in the bone marrow have their differentiation into mature B cells arrested (*126*). Chronic myeloid leukemia is a disorder of clonal myeloid cells in the bone marrow (cells that make white blood cells, red blood cells, and platelets) affecting the ability of immature stem cells to regulate their proliferation (*127*). In contrast to the chronic forms, the acute classification of myeloid or lymphocytic leukemia differs in that the leukemic cells remain immature and thus replicate more rapidly.

## 3.2 The descriptive epidemiology of leukemia

Leukemia is a rare disease, comprising less than three percent of all new cases of cancer diagnosed in both Canada and the United States (*128, 129*). In 2008, there were in the world 351,000 incident cases of all forms of leukemia and an estimated 257,000 deaths

attributed to leukemia (*130*). In Canada, the incidence rates for leukemia differ by province: the average Canadian age standardized incidence rate is 16 per 100,000 people; the highest rates occur in Saskatchewan with 18 and the lowest in Newfoundland with 10 per 100,000 (*129*). The incidence of leukemia also varies across genders in Canada; men have an overall lifetime probability of developing leukemia of 1.9% while women have an overall lifetime probability of 1.4%.

The incidence and mortality rates for all forms of leukemia differ between developed and non-developed countries. In developed countries the age standardized incidence rate was 9.1 per 100,000 people and in non-developed countries the rate was lower with an age standardized incidence rate of 4.5 per 100,000 people (*131*). Mortality rates for leukemia also differ between men and women, with men having higher rates of death: seven per 100,000 men versus four per 100,000 women (*129*). The age standardized mortality rates for men in the year 2008 in developed countries was 4.8 per 100,000 people and it was 3.7 per 100,000 people in non-developed countries (*132*). In North America, the estimated percent of both men and women of the United States of America surviving five years after their diagnosis of leukemia is about 56% (*133*).

Incidence rates and survival rates differ by age among the four main subtypes of leukemia. The most common type of leukemia in adults is chronic lymphocytic leukemia, that accounts for 16 - 30% of all diagnosed subtypes in the western world (*134*). In the United States, there were an estimated 15,680 incident cases of chronic lymphocytic leukemia in 2013 (*135*). In the US, leukemia accounts for roughly 30% of all cancers diagnosed in children younger than 15 years of age (*136*). Acute lymphocytic leukemia is the most common subtype occurring in American children, and accounts for nearly three quarters of all childhood cases of leukemia (*136*) (about 58,000 new cases of all forms of leukemia; about 14,590 new cases of acute myeloid leukemia (*135*)).

Survival rates differ by age and the four main subtypes. Chronic lymphocytic leukemia has the highest five-year survival rates among all ages, which in 2010 was 80.4% (*133*). In contrast, the acute subtypes have the lowest five-year survival rates among all age

groups, with acute myeloid leukemia having the lowest, which in 2010 was 25.8%. Between 1999 and 2002 the survival rate for acute myeloid leukemia in American children between 15 and 19 years of age were 40.1% and 58.1% for those 15 years of age and younger (*137*). For adults over 65 years of age, the five-year survival relative to those younger than 45 years of age for 2002 was only 5.6% (*133*). Not only do the different subtypes of leukemia have distinctive incidence and survival rates among different ages and sexes, but each of the subtypes have also been shown to be associated with different risk factors.

## 3.3 Risk factors for leukemia

In this section, I have relied mostly on reviews and meta-analyses to summarize the observations. In the following section, the structured review on air pollution and leukemia will be found.

Case-control studies have been used mostly to identify risk factors for leukemia, as the low incidence of the disease makes it difficult to conduct cohort studies (*136*). Risk factors for leukemia are generally divided into genetic and familial or environmental factors, with each subtype apparently having a different constellation of risk factors (*136, 138*).

*Acute myeloid leukemia*. In children, genetic factors have an important role in the development of acute myeloid leukemia. Children with Down syndrome have 20-fold increase risk of developing acute myeloid leukemia (*139*), while other genetic syndromes, such as Bloom syndrome and Fanconi anaemia, have shown to be associated with a small percentage of acute myeloid leukemia cases (*140*). Preconception and prenatal exposures to certain substances may be associated with the incidence of acute myeloid leukemia: a meta-analysis on maternal alcohol intake during pregnancy and subsequent development of leukemia in infants found an estimated odds ratio (OR) of 1.56 ((95% confidence interval (CI): 1.13 – 2.15) (*141*). Parental exposure to pesticides may be associated with an increased risk of acute myeloid leukemia (*140*). In utero

exposure to ionizing radiation is an accepted risk factor for a child's risk of developing acute myeloid leukemia, with an estimated increase in absolute risk of 6% per increase of one gray of ionizing radiation (*142*).

In adults, acute myeloid leukemia has similar lifestyle and environmental risk factors as in children with the addition of benzene as it has been shown to be associated with adult acute myeloid leukemia (*89, 140, 143*). Cigarette smoke contains many carcinogenic chemicals, and epidemiological studies have found slightly increased risks between acute myeloid leukemia and smoking (*124, 144*). Ionizing radiation is an accepted risk factor for adult acute myeloid leukemia (*145*), while pesticide exposure has been shown to possibly be associated as well (*143, 146*).

*Chronic Myeloid leukemia.* A genetic factor that, if present, can cause chronic myeloid leukemia is the Philadelphia chromosome (*147*). In a majority of chronic myeloid leukemia cases the cytogenic marker of the Philadelphia chromosome is present, which then causes the formation of a new gene, the Bcr-Abl gene, that codes for a kinase enzyme. The kinase encoded by the Brc-Abl gene enables white blood cells to grow out of control, leading to the development of chronic myeloid leukemia (*148*). The only accepted environmental factor to increase the risk of chronic myeloid leukemia is exposure to ionizing radiation (*149*). Unlike acute lymphocytic and acute myeloid leukemia, benzene has not been shown to be associated with an increased risk of chronic myeloid leukemia (*96, 150, 151*).

*Chronic Lymphocytic Leukemia*. There is a possible genetic aetiology for chronic lymphocytic leukemia, as it has shown to run in families and be prevalent primarily in western societies (*152*). There are a few specific germ line genes that have been identified as possibly being susceptible to mutations that could lead to leukemia, however the specific mutations that cause chronic lymphocytic leukemia have not been identified (*153*). Meta-analyses of studies of associations between chronic lymphocytic leukemia and environmental factors have shown positive associations for both ionizing radiation (*154*) and both occupational and low-dose exposures to benzene (*96, 155, 156*).

Pesticides, diet, and viral infections such as hepatitis C and the Epstein-Barr virus have shown to be associated with the incidence of chronic lymphocytic leukemia (*152*).

*Acute Lymphocytic Leukemia*. Of the meta-analyses that summarized the effect of benzene on the incidence of all subtypes of leukemia combined, there were too few cases of acute lymphocytic leukemia to draw any meaningful conclusions (*96, 157*). Most investigations of acute lymphocytic leukemia have been conducted in children and the only risk factors that may be causal are exposure to ionizing radiation and hereditary factors (*136, 158, 159*).

In summary, little is know regarding the aetiology of leukemia, with only 10% of cases being explained by measured risk factors (*160*).

## 3.4 Review of the literature of ambient air pollution and associations with leukemia

### METHODS

I conducted a structured review (*161*) of the peer-reviewed literature in order to identify epidemiological investigations that reported on the incidence or mortality of leukemia and exposure to ambient air pollution. I first conducted an electronic search using available bibliographic databases. In particular, I made use of the online database Ovid Medline, which included both in-process and non-indexed citations. I thus searched this database for peer-reviewed articles published between January 1, 1946 and April 1, 2014. For the inclusion criteria in my structured review, I included all original papers that were available in English and that were classified as either a case-control or as a cohort study that reported associations between the incidence or mortality of leukemia and estimates of exposure to air pollution or gasoline vapours from traffic. I combined the Medical Subject Headings (MeSH) terms *leukemia* (which included all subtypes, both chronic and acute) with the MeSH term *air pollution* (which included any type of chemical in the air

that can interfere with human health or welfare including gases, particulate matter, and volatile organic compounds). Seventeen studies were found from this search, of which seven were case-control studies and one was a cohort study. The remaining studies were excluded: four were reviews; four had no air pollution component; one was an ecological study; one was a feasibility study; and one did not have leukemia as an outcome.

In addition, I performed a search combining the MeSH terms *air pollution* and *neoplasms* (which includes any type of cancer or abnormal growth of tissue). From that search, 263 articles were found, nine of which reported associations with leukemia. Three studies were excluded because they were occupational studies and three were excluded because they were reviews, and the remaining three studies (two case-control and one cohort study) were included. Seventy-four articles were excluded because they were not written in nor translated into English, 16 of which were review articles. Based on the available English abstracts and titles, the remaining articles were excluded because they did not fit the inclusion criteria because they were either an ecological study or did not investigate leukemia as an outcome.

I also perused the reference lists of all the papers and reviews found using my search and an additional seven citations were identified; six case-control studies and one cohort study. I also used Google to search for additional citations with leukemia and air pollution using the following search; “air pollution” OR “Petrochemicals” OR "traffic" OR "Vehicular" AND “Leukemia” AND ~PubMed. Using that search, I found four additional case-control studies and one additional cohort study.

In addition, it is important to note that many cohort studies on air pollution have been conducted and could be used to assess associations between leukemia and air pollution. These are the Adventist Health Study on the Health Effects of Smog study (*162, 163*) California Cancer Prevention Study (*164*), the American Cancer Society (*165*), Cohort of Norwegian Men (*166*), the French Pollution Atmosphérique et Affections Respiratoires Chroniques/Air pollution and chronic respiratory diseases (PAARC) study (*167*), the Harvard Six Cities Study (*168*), the Netherlands Cohort Study on Diet and Cancer (*169*),

the German Women's Health Study in North Rhine-Westphalia (*170*), the Ontario Cohort Study (*171*), the Oslo Cohort Study (*172*), the Pennsylvania Cohort (*173*), the USEPRI-Washington University Veterans' Cohort Mortality Study (*174*), and the Canadian Census Cohort (*175*). Only one of these studies, conducted by Mills et al., was included in this review as it was the only study in which results for leukemia were published (*119*).

Figure 1 shows the search strategy and selection process for the articles included in this review. In total 292 studies were found excluding the above cohort studies, of which 17 were case-control studies and four were cohort studies.

## RESULTS

### Case-control studies: design characteristics and conduct

Table 1 shows selected design characteristics of the 17 case-control studies included in this review. In 11 of these studies, all subtypes of leukemia were combined into one analysis. In one study, acute lymphocytic leukemia and acute myeloid leukemia (*114*) were investigated separately; in another study, acute lymphocytic and acute non-lymphocytic leukemia cases (*113*); in three studies, acute forms of leukemia combined were investigated (*116, 176, 177*); and in the remaining study acute lymphocytic leukemia was investigated (*178*). All but one study (*117*) was of children or teenagers (under 19 years of age).

Incidence was ascertained in all but three studies. In these latter studies death certificates were used (*179-181*), and deceased persons, matched by gender, age, and date of death, were used as controls.

All but one of the incident case-control studies was population-based, and this study was hospital-based (*177*). The number of participants (cases and controls combined) in the population-based studies ranged from 190 (*182*) to 82,221 (*114*), and the one hospital-based study included 565 cases and controls (*177*). Cases were selected from cancer

registries in 10 of the 17 studies (*113-115, 117, 182-187*), from death registries in three studies (*179-181*), from a hospital-based registry in one (*116*), and from hospital records in three studies (*176-178*). In one of the studies where hospital records were used, controls were selected from birth certificates (*178*).

In six of the 10 studies that made use of cancer registries, parental interviews were conducted either in person or by phone (*113, 117, 176, 183-185*), and in only one of these had authors reported a time frame for assessing information, which was indicated to be during the remission of a case (*113*). For the population-based studies that used hospital records, one used information from parental interviews (or from the subjects who were over 18 years of age) conducted when subjects were diagnosed (*117*) and one used information from parental interviews without indicating a time frame relevant to diagnosis (*176*). For the one hospital-based study, interviews of mothers of cases were conducted within the first remission period of the disease (*177*).

Interviews or questionnaires were not administered in the study where hospital-based registries were used, and information for the addresses of cases was ascertained from the hospital-based registry and from population registries for controls (*116*).

In the remaining four studies, no interviews were conducted nor questionnaires sent to subjects or proxies for subjects (*114, 182, 186, 188*), and thus these studies lack information on essential personal covariates. In one of these four studies, residential and demographic information on the mothers of subjects was taken from routine public health records (*114*). In the remaining three studies, the authors used population registries to determine residential and demographic information for subjects (*182, 186, 188*).

In 11 studies, cases were histologically-confirmed (*113, 114, 117, 179-181, 183, 184, 186-188*), however in five of these 11 studies the authors only made mention of International Classification of Disease for Oncology (ICD-O) codes (*179-181, 186, 188*) without specific mention of histological confirmation. In two studies cytological and

immunological confirmation were used (*176, 177*), and in four studies no mention of case confirmation was given (*116, 178, 182, 185*).

Response rates ranged from 64% for cases in one study (*185*) to 99% in another study (*177*), and ranged from 53% for controls in one study (*117*) to 98% for controls in another study (*177*). Three studies had large differences in response rates between case and controls. The first had a response of 91% in cases and 71% in controls (*176*), the second had a response of 91.4% in cases and 69.2 % in controls (*113*), and the third had a response of 91% in cases and 53% in controls (*117*). Response rates in six studies were not reported for either cases or controls (*116, 179, 180, 182, 186, 188*) and in one study response rates were reported only for cases (*187*).

**Exposure to ambient air pollution**

As with most studies of historical exposures to air pollution and chronic diseases (*84, 103, 104, 175, 189-191*), it is not possible to obtain estimates of personal exposure. Rather, area-wide concentrations of air pollution are used and the relationship to the individual is often according to address of residence. The implicit assumption is that individuals spend most of their time in or around their home so that obtaining a representative estimate at the residence is a proxy, albeit misclassified, of exposure to ambient air pollution. As well, if spatial variability is relatively constant in time then one spatial estimate may be sufficient to characterize current and historical ambient concentrations. However, if there is considerable spatial variability in time, then it is essential to have a history of residences across the relevant etiologic time period.

With leukemia, the latency period varies by subtype: acute leukemia develops rapidly within a few years (*192*) and chronic leukemia develops much slower over several years (*154*). In order to determine causality, exposures to pollution must be temporally relevant to the latency period of the outcome under investigation, although constancy in spatial variability can lead to valid estimates.

**Exposure assessment in the case-control studies**

Table 2 describes the exposure assessments used to assign exposures to subjects as well as the associations presented in the case-control studies. The majority of exposure assessments were assigned to the place of residence of the subject (mostly the parents) with the exception of three studies where exposures were attributed to subjects according to the municipality the child lived in (*179-181*). In the study that included adults, exposures were assigned to the subject's place of residence (*117*).

*Exposures for leukemia in studies of children.* The periods for when exposures were determined and assigned varied by study. In six of the studies, the authors assigned exposure to the case's residence at time of diagnosis (*116, 176, 182-184, 186*). In two studies, exposures were assigned to the residence during pregnancy (*114, 177*) and to the residence during both birth and entire childhood in two studies (*113, 188*). Exposures were assigned to residence at time of birth in two studies (*178, 187*) and exposures for the entire childhood of the subjects were assigned in six studies (*113, 117, 177, 178, 185, 188*). In the three studies where death certificates were used, no time frame relevant to diagnosis was given (*179-181*).

In four of the studies, no mention was made of the relevant aetiological period of time (*113, 177, 181, 187*) and in five studies, a variety of time periods were used: Amiguo et al. used traffic data from 2000 to develop concentrations of $NO_2$ for subjects diagnosed from 2003-2004 (*176*); Raaschou-Nielsen et al. used data from 1994-1995 to develop exposure for patients diagnosed from 1968-1991 (*188*); Langholz et al. used data from 1990-1994 for cases diagnoses between 1978 and 1984 (*185*); and Weng et al., in two different studies, used data from 2008 for cases diagnosed between 1995 and 2005 (*181*) and data from 1989 for cases diagnosed between 1996 and 2006 (*180*). In two studies, exposures were assigned from data obtained from the same year as when cases were diagnosed (*182, 183*). In five studies, the data used to create exposures for subjects were taken from a time period during when cases were selected (*114, 116, 178, 179, 186*).

*Exposures for leukemia in studies of adults.* In only one of the studies were adult subjects investigated and exposures were geocoded to the place of residence over their entire lifetime (*117*). No time period was given for the estimates of exposures.

*Adjustments for covariates.* As indicated above, there are very few accepted causal risk factors for leukemia, and they vary by the type of leukemia. Important factors to consider are age and gender (*160*), exposures to ionizing radiation (*136, 142, 149, 158, 159*) and benzene (*89, 96, 155, 156*), maternal or childhood exposure to pesticides (*193-195*), and possibly smoking (passive or personal) (*138, 196*).
In all of the 17 studies, the authors adjusted for age and gender of subjects. In the studies of children, smoking was controlled for in only two studies, and this was done in one study for paternal smoking during the preconception period (*176*) and for the mother's current smoking status in the other (*117*). In the one study that included adults, the authors adjusted for smoking status of the subjects themselves (*117*). In only one study was exposure to pesticides accounted for and this was done during pregnancy of the subjects' mother (*176*). Environmental exposure to benzene estimated from a dispersion model was controlled for in one study of $PM_{10}$ (*116*) and exposure to ionizing radiation was not accounted for in any of the studies.

**Cohort studies: characteristics of the design and conduct**

Table 3 describes the characteristics of the design and conduct of the four cohort studies of adults. There was no mention of the age of the subjects in the study by Michelozzi et al. (*118*). Sociodemographic characteristics of the study subjects were only described in two studies (*115, 119*).

Follow up periods ranged from five to 13 years: the study with one of the shortest follow-up periods (6 years) had the largest sample size (341,389) that led to 169 incident cases being identified (*118*). The longest follow up period, 13 years, belonged to a study with the second largest sample size, 57,053 people, for which 117 incident cases were identified (*115*). The study with the shortest follow-up period, five years, had a sample

size of 6,340, and 12 cases were identified (*119*). The study with the smallest population, 625 people, had a follow-up period of 11 years resulting in only five cases (*120*), and thus is not informative.

Response rates and completeness of follow-up of those who were enrolled were high for the studies in which they were reported, with no studies reporting less than 79% response rates nor did they report less than 94% completeness of follow-up (*115, 119, 120*). Response rates were not reported in one study (*118*), and completeness of follow-up for those who were enrolled was not reported in two studies (*118, 120*).

*Exposure assessment of the cohort studies*. Table 4 outlines the associations presented in the cohort studies, as well as detailed exposure metrics that were used and which covariates were adjusted for in their models. Raaschou-Nielson et al. used exposure data from the same time period as the follow-up period, 1993 to 2006 (*115*). In the study by Talbott et al., the place of residence at the time of when the gas spill under investigation occurred was used to assign exposure levels to subjects followed between 1990 and 2001 (*120*). Michelozzi et al. used distance of the residence of a subject from an oil refinery plant, a waste disposal site, and an incinerator based on census data from 1991 for cases that died between 1987 and 1993 (*118*). Mills et al. used exposure data from 1966 to 1977 for subjects who were followed between 1977 and 1982 (*119*).

*Adjustments for covariates.* Of the a priori risk factors described previously, age and gender were accounted for in all of the cohort studies. Current smoking status was accounted for in one of the cohort studies (*115*) and the total years of smoking was accounted for in another study (*119*). Occupational exposure to chemicals was considered as a confounder in only one of the studies (*119*). Benzene, ionising radiation, and exposures to pesticides were not assessed.

**Findings from the case-control and cohort studies**

Tables 2 and 4 present the results of the case-control and cohort studies, respectively. The majority of the findings reported below are from studies where authors only used

childhood cases of leukemia and leukemia subtypes. Table 5 shows for the case-control studies of childhood leukemia a summary of the odds ratios using binary indices of exposure.

*Gaseous Pollutants.* Of the six case-control studies that used gaseous pollutants as their main exposures, positive associations were found in three studies that made use of dispersion models to estimate exposure of $NO_2$ for the association between all forms of leukemia (*179, 182*) and acute forms of leukemia (*176*), and in one study that estimated concentrations of benzene (*186*). In the two studies in which land use regression models were used to estimate concentrations of $NO_2$ at the home of a subject, a positive association was reported in one (*114*) for childhood cases of acute lymphocytic leukemia, and a null association was reported in the other study (*113*), which also investigated acute lymphocytic leukemia in children. Associations above unity were found for nitrogen oxides ($NO_x$) and nitrogen monoxide (NO) for childhood cases of acute lymphocytic leukemia in one study (*114*) but null associations were found in the one cohort study of adult cases of leukemia where authors used $NO_x$ as one of their exposures (*115*).

*Particulate Matter.* There were two case-control studies in which the authors used $PM_{10}$ to investigate associations with air pollution and childhood cases of leukemia (*113, 116*). An odds ratio above unity was found in one of these studies for acute forms of leukemia combined (*116*). In the one cohort study where authors investigated associations between total suspended particulates and adult leukemia in women, no association was found (*119*).

*Traffic density.* In six studies of childhood leukemia, traffic densities were used as a proxy for traffic-related air pollution (*178, 183-185, 187, 188*). In all but one studies were odds ratios above unity reported, and the highest reported OR was 7.35 (95% CI 1.40 – 38.6) for only five exposed cases (*184*) and the study with the highest number of exposed cases had an OR of 0.92 (95% CI 0.73 – 1.15) (*187*).

*Other measures of exposure to air pollutants.* In the two case-control studies where authors used unconventional measurements as proxies for air pollution exposures, elevated odds ratios were found for cases of childhood leukemia in both (*117, 180*) and for cases of leukemia in subjects 20 to 29 years of age in the one case-control study that included adult cases (*117*). In two cohort studies where distance from petrochemical plants, incinerators, and an oil spill were used as exposures an elevated standardized mortality ratio was found for adult women in one (*118*) and an elevated standardized incidence ratio for both adult men and women in the other (*120*).

## DISCUSSION

Due to the varying spatial concentrations and the complex makeup of air pollution, studying the effects it has on health is complicated. Concentrations can vary by large amounts between relatively close distances. Fore example, average annual concentrations of gaseous pollutants have been shown to differ by 50 $\mu g/m^3$ at distances of only 50 m apart (*14*). In addition, all studies on the effects of exposure to air pollution and chronic health are limited by a lack of estimates of personal exposure. Therefore, it is important to not only consider sources of bias and confounding, but also to address how exposures were assessed and assigned to subjects and the etiological relevancy of the time period when these exposures were assigned.

### Sources of bias for the case-control and cohort studies

*Selection bias*. Cases selected in the case-control studies were from cancer registries, hospital records, or death registries. Controls were selected from death registries, population registries, and health service archives in all but three studies in which death certificates were used (*179-181*). In most of the case-control studies, cases and controls were properly identified through cancer registries, population registries, or hospital records with exposures being assessed without the knowledge of the subject.

In three studies, however, controls were ascertained through the use of random digit dialling (*183-185*). The use of random digit dialling can entail undetected selection bias as it is almost impossible to know the response rates as the denominator cannot be assessed accurately; specifically, when there is no answer it may mean that the telephone number is out of order, it may be a commercial number, or it may simply mean no response. In the latter case, families with lower socio-economic status may have none or one number to be reached at, no messaging services, and may have less hours off work to be reached than families with higher socio-economic status (*197*). Thus, if the selection probabilities are related to socioeconomic status (e.g., a higher probability of selecting controls with higher socioeconomic status), bias may result as it has been shown that people of lower socioeconomic status tend to live in areas with higher levels of air pollution (*198*).

In addition, the use of death certificates may result in confounding as few covariates are available from death certificates (*199, 200*) and cumulative or long-term average exposures to air pollution cannot be computed because residential histories are also not available (*201*). Moreover, death certificates are not as accurate (*202*) as when incident cases are identified and confirmed histologically, and this can lead to misclassification bias. Use of deceased controls, as was done in these three studies, at least levels the playing field in terms of covariate information available.

Response rates were not reported in six studies (*116, 179, 180, 182, 186, 188*); not knowing response rates makes it impossible to assess validity, as one cannot determine whether the study population is comparable to the target population. In two other studies (*117, 185*) relatively low response rates were obtained (in the order of 53 to 64%), and the low response rates could, for instance, lead to biased results if the controls who participated had relatively higher or lower exposures to air pollution as compared to the target population. High response rates were reported in many studies (*113, 115, 117, 119, 176, 188*), which would likely not result in biased outcomes. Large differences between response of controls and cases can lead to biased results as well, and this was present in three studies (*113, 117, 176*). An example where differences in response rates may have

biased an association is in two similar studies where authors used land use regression models to assign estimates of $NO_2$ to subjects: one study (*113*) had relatively higher response rates in cases than in controls and found a null associations while the other study (*114*) with high response rates in both cases and controls found elevated odds ratios.

Subjects who are lost to follow up in a cohort study can cause selection bias if the percentage lost is high and those that are lost have left the study for reasons associated with their disease and exposure status (*203*). For the two studies that reported completeness of follow-up, the values were very high and any bias is unlikely. However, for the one study that did not report completeness of follow-up the degree of bias is unknown. In the one cohort study where mortality was investigated (*118*), death and residential records were properly linked through use of the Italian geographical information mortality system and thus bias is not likely have a strong effect on their reported outcome.

*Sources of exposure misclassification.* As all studies on the health effects of air pollution are limited by the fact that exposures are not assigned on an individual basis; rather, they are assigned, most commonly, to the places of residence of subjects. This is an inherent limitation of all retrospective studies, as it is impossible to measure personal exposures. In studies of acute effects (*204-206*), this limitation can be avoided.

For the exposures that were assigned using interpolation of monitoring data (such as land use regression models) or dispersion models, misclassification would probably be less than using other methods, such as traffic density or distance from roads (*207, 208*). Even the best methods have their limitations, for instance interpolation methods, such as inverse distance weighting or kriging, require high quality input data from a geographic region that contains many monitoring stations and misclassification can occur if these methods are not stringently validated (*14, 209, 210*). Exposures assigned from methods that do not take surrounding environments into account such as proximity measures, traffic densities, or exposures assigned to the municipality of a subject could result in a

greater level of misclassification between cases and controls than the methods outlined previously would have (*209*). Proximity methods are highly inaccurate because they neglect exposure to pollutants at areas other than the place of residence and the spatial variability of pollutants, they tend not to account for type of vehicle, and ignore the effects of wind and weather on dispersion of pollutants (*209, 210*) Thus, in studies where these proximity and traffic density exposure assignments were used (*177, 178, 183-185, 187, 188*) there is a greater potential for misclassification than in studies where dispersion models or interpolation methods are used.
Measurements used in the studies by Weng et al. (*179-181*) that estimate exposures using proxies such as number of petrochemical employees per municipality, and the exposure opportunity score used in the study by Yu et al. (*117*) are, for all aetiological purposes, probably meaningless because they do not represent valid surrogates of personal exposure.

As discussed previously, the latency of leukemia needs to be considered when developing indices of exposure. The majority of studies in this review were of children, and the latency period is much shorter relative to adults because it is truncated at gestation. Several studies assigned exposures to residence at time of diagnosis (*116, 176, 182-184, 186*), which does not take into account the potential migration of a subject or temporal changes in the concentration of exposure around their residence and may not represent the latent period of leukemia. Although the period when exposures can affect a child is short, studies where authors assigned exposures to subjects for their entire childhood (*113, 117, 177, 178, 185, 188*) may be more aetiologically relevant.

To assign accurate estimates that are surrogates of personal exposure, it is important to use data collected during the same time as the latent period of the case. In one study, exposures estimates from 1990 to 1994 were assigned to cases diagnosed between 1978 and 1984 (*185*). In another study, traffic data from 1990 was used to estimate exposures for cases diagnosed between 1976 and 1983 (*184*). Both of these exposure assignments can lead to misclassification if there are large temporal variations in exposure between

when the exposures were assigned and when the data for the assigned measurements were collected.

*Potential confounding factors.* Of the causal risk factors for leukemia mentioned previously, in only one study was exposure to benzene (*116*), and in only two studies was cigarette smoking (*117, 186*) accounted for. Thus, there is a possibility that bias could have resulted if these exposures were also associated with air pollution.

**Critical assessment of the results from the case-control and cohort studies**

*Nitrogen dioxide.* In five case-control studies and in one cohort study exposures to $NO_2$ were used. The case-control studies, which were all conducted using childhood cases, seemed to show an association with leukemia when contrasting the highest level of exposures to the lowest. Elevated odds ratios were found in all but one (*113*) case-control study in which $NO_2$ or $NO_x$ was used. In one study (1,346 acute lymphocytic leukemia cases) and very high response rates, the authors found, per 25 ppb increases in a pollutant, elevated odds ratios nitrogen monoxide, nitrogen oxides, and nitrogen dioxide (*114*). In the other case-control study with a relatively large number of exposed cases (620 cases of acute lymphocytic and non-lymphocytic leukemia), no associations were found (*113*). There was, however, a notable difference in response rates between controls and cases (69% and 91%, respectively). In the only cohort study that used $NO_x$ as an exposure, the authors reported null incidence rate ratios (*115*).

*Particulate matter.* In the two case-control studies of childhood leukemia and $PM_{10}$ (*113, 116*) and in the cohort study of adult women (*119*), there was no evidence of associations.

*Traffic Densities*. In six case-control studies, one reported an OR below unity (*187*) and the remaining studies all reported elevated ORs but were based on few numbers of exposed cases (from 5 to 138). Additionally, the greater degree of misclassification inherent in using traffic densities, compared to interpolation methods or dispersion models to assess exposures, may account for the fact that the majority of studies using

this exposure assessment reported elevated odds ratios when compared to the mainly null associations reported in studies where interpolation methods and dispersion models were used.

*Petrol station densities and proximities to heavy traffic roads or sources of pollution.* In one case-control study, proximity to roads with heavy traffic was the main exposure (*177*). In another case-control study by Weng et al. (*181*) petrol station density was used as the main exposure and the authors reported elevated odds ratios. In the remaining cohort study where authors used the distance of a subject from petrol chemical plants and incinerators, an elevated standardized mortality ratio was reported (*118*). Presumably, the notion was to use this exposure metric as a marker for volatile organic compounds, but its interpretation as a marker for ambient pollution is highly suspect because there is no consideration of the spatial variability of pollutants or the effects of wind and weather on dispersion of pollutants.

## CONCLUSIONS

In children, there is a suggestion that exposure to traffic-related air pollution (as measured by $NO_2$ or $NO_x$) may be associated with the incidence of leukemia, but there is a paucity of studies with a large number of incident cases to make any definite conclusions. No conclusions can be drawn for adult leukemia. The available studies are thus limited by small numbers of cases, specificity of type of leukemia, potential misclassification of exposures, low and unreported response rates, and possible confounding due to not including essential risk factors. It is not possible to conclude whether air pollution is associated with the incidence of leukemia in children or in adults.

## TABLES AND FIGURES

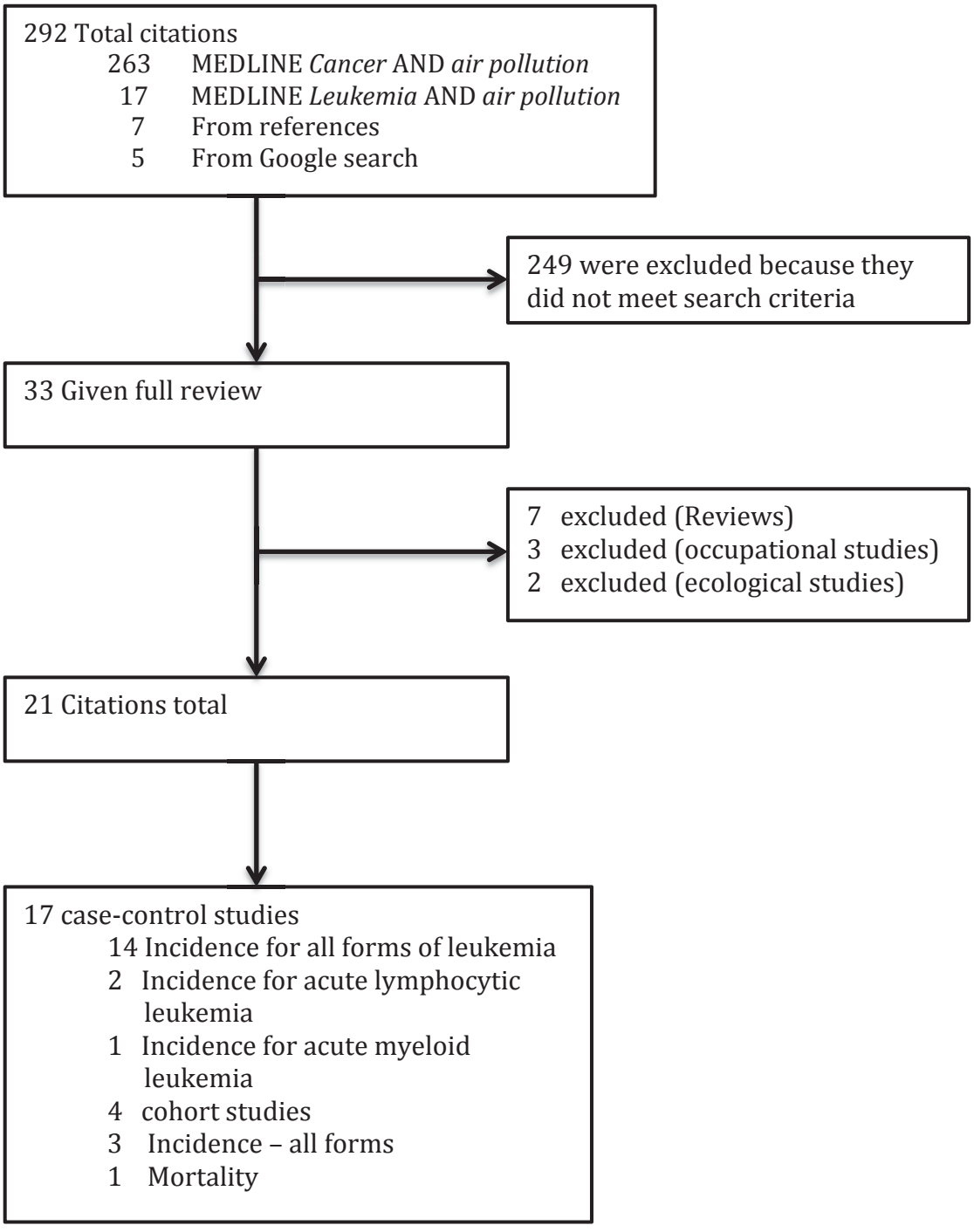



**Figure 1**. Flow diagram of search strategy and selection process in the structured literature review of the relationship between exposure to ambient air pollution and leukemia.

**Table 1.** Selected characteristics of case-control studies used to investigate the risk of leukemia in relation to exposure to ambient air pollution.

| Author, location, date, reference | Age range | No. of cases | | No. of controls | | Year diagnosed | Response rate % | | Selection of cases | Selection of controls | Outcome | Outcome assessment | Design |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total | % Male | Total | % Male | | Cases | Controls | | | | | |
| Gaseous Pollutants | | | | | | | | | | | | | |
| Feychting et al. Sweden (1998) (*182*) | 0 - 15 | 39 | NR* | 151 | NR | 1958 - 1985 | NR | NR | Cancer registry | Randomly selected from study base | Incidence - all forms | Cancer registry Death registry | Population based |
| Crosignani et al. Varese Province, Italy (2002) (*186*) | 0 - 14 | 120 | NR | 480 | NR | 1978 - 1997 | NR | NR | Cancer registry | Health Service Archives | Incidence - all forms | Histologically confirmed | Population based |
| Weng et al. Taiwan (2008) (*179*) | 0 - 14 | 308 | 60.1 | 308 | 60.1 | 1995 - 2005 | NR | NR | Death registry | Death registry | Incidence - all forms | Death certificate | Population based |
| Amigou et al. France (2011) (*176*) | 0 - 15 | 763 | 54.4 | 1681 | 55.1 | 2003 - 2004 | 91 | 71 | Hospital records | Population registry | Incidence – acute leukemia | Hospital records Bone marrow analysis | Population based |
| Particulate Matter Less Than 10 Microns ($PM_{10}$) | | | | | | | | | | | | | |
| Vinceti et al. Italy (2012) (*116*) | 0 - 14 | 83 | 60 | 332 | NR | 1998 - 2009 | NR | NR | Hospital records | Population registry | Incidence - acute leukemia | Hospital records | Population based |
| Traffic Density | | | | | | | | | | | | | |
| Savitz et al. Denver, Colorado (1989) (*183*) | 0 - 14 | 103 | 61 | 262 | 60 | 1976 - 1983 | 92 | 94 | Cancer registry | Population based - random digit dialling | Incidence - all forms | 95.2% histologically confirmed 3.1 % confirmed by visualization or radiograph | Population based |

* NR: Not Reported

| Author, location, date, reference | Age range | No. of cases | | No. of controls | | Year diagnosed | Response rate % | | Selection of cases | Selection of controls | Outcome | Outcome assessment | Design |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total | % Male | Total | % Male | | Cases | Controls | | | | | |
| Traffic Density (Cont.) | | | | | | | | | | | | | |
| Raaschou-Nielsen et al. Denmark (2001) (*188*) | <15 | 986 | NR* | 1972 | NR | 1968 - 1991 | NR | NR | Cancer registry | Population registry | Incidence - all forms | Cancer registry | Population based |
| Pearson et al. Denver (2002) (*184*) | 0 - 15 | 97 | 61 | 259 | 60 | 1976 - 1983 | 92 | 94 | Cancer registry | Population random digit dialling | Incidence - all forms | 95% histologically confirmed 3% direct visualization or radiograph | Population based |
| Langholz et al. California (2002) (*185*) | 0 - 10 | 212 | 56 | 202 | 55.6 | 1978 - 1984 | 64 | 79 | Los Angeles County Cancer Surveillance program | Random digit dialling | Incidence - all forms | Los Angeles County Cancer Surveillance program | Population based |
| Reynolds et al. California (2004) (*187*) | 0 - 5 | 1728 | 56 | 8596 | 56 | 1988 - 1997 | 84 | NR | Cancer registry | Birth certificates | Incidence - all forms | Cancer registry | Population based |
| Von Behren et al. California (2008) (*178*) | 0 - 14 | 310 | 53 | 396 | 52 | 1995 - 2002 | 86 | 84 | Hospital records | Population registry | Incidence - acute lymphocytic leukemia | Hospital records | Population based |
| Petrol Station Density and Proximity to Major roads | | | | | | | | | | | | | |
| Steffen et al. France (2004) (*177*) | 0 - 14 | 280 | 59.3 | 285 | 58.3 | 1995–99 | 99 | 98 | Four selected hospitals | Four selected hospitals | Incidence of Acute leukemia | Hospital records cytology and immunophenotype | Hospital based |
| Weng et al. Taiwan (2009) (*181*) | 0 - 14 | 359 | 55.8 | 359 | 55.8 | 1996 - 2006 | NR | NR | Death registry | Death registry | Incidence - all forms | Death certificate | Population based |

* NR: Not Reported

| Author, location, date | Age range | No. of cases | | No. of controls | | Year diagnosed | Response rate % | | Selection of cases | Selection of controls | Outcome | Outcome assessment | Design |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total | % Male | Total | % Male | | Cases | Controls | | | | | |
| Land Use Regression Models | | | | | | | | | | | | | |
| Ghosh et al. United States (2013) (*114*) | 0 - 5 | ALL* 1346 AML† 217 | 55.5 | 80658 | 50.8 | 1988-2008 | 94.9 | 94.3 | Cancer registry | Birth records | Incidence ALL AML | Cancer registry | Population based |
| Badaloni et al. Italy (2013) (*113*) | 0 - 10 | ALL* 554 ANLL‡ 76 | 54.0 | 957 | 54.5 | 1998-2001 | 91.4 | 69.2 | Cancer registry | Population registry | Incidence ALL ANLL | Histologically confirmed | Population based |
| Other Exposure Measures (number of petrochemical employees and exposure opportunity score) | | | | | | | | | | | | | |
| Yu et al. Taiwan (2006) (*117*) | 0 - 29 | 171 | 59.5 | 410 | 61.5 | 1997-2003 | 91 | 53.3 | Hospital records and the National Health Insurance System | Population registry | Incidence All forms | Histologically confirmed | Population based |
| Weng et al. Taiwan (2008) (*180*) | 0 - 19 | 405 | 55.6 | 405 | 55.6 | 1995-2005 | NR¶ | NR | Death registry | Death registry | Incidence All forms | Death certificate | Population based |

* ALL: Acute lymphocytic leukemia, † Acute myeloid leukemia, ‡ Acute non-lymphocytic leukemia, ¶ NR: Not reported

**Table 2**. Associations between the risk of leukemia and exposure to ambient air pollutants found in case-control studies.

| First author (Year) | Exposure assessment | No. Exposed cases per level of exposure (Age range) | Odds ratio/Relative Risk (95% Confidence Interval) and level of exposure | Statistical analysis | Adjusted covariates |
|---|---|---|---|---|---|
| Gaseous Pollutants | | | | | |
| Feychting et al. (1998) (*182*) | $NO_2$ concentrations averaged every hour over one year estimates from models of $NO_2$ indicators (vehicles per day, street type and width, etc.) developed by the Swedish Environmental Protection Agency, assigned to place of residence at time of diagnosis | 9/39 (0-15 yrs.) | $\geq$ 50 µg/m$^3$ vs. < 39 µg/m$^3$: 2.7 (0.3-20.6) | Matched on age, town, and living near the same power line. Conditional Logistic | Age, electromagnetic fields, SES, town |
| Crosignani et al. (2002) (*186*) | Benzene: estimated from the Caline 4 Gaussian dispersion model developed by the Environmental Protection Agency, assigned to place of residence at time of diagnosis | 7/120 (0-14 yrs.) | > 10 µg/m$^3$ vs. 0.1 µg/m$^3$ 3.91 (1.36 – 11.27) | Matched on sex and date of birth. Conditional Logistic | Age, sex, and SES |
| Weng et al. (2008) (*179*) | $NO_2$ concentrations estimated from the monitoring stations of the Environmental Protection Agency, assigned to municipality of subjects at time of diagnosis | 103/308<br>117/308 (0-14 yrs.) | 24.09 ppb vs. <17.88 ppb 1.70 (1.12–2.58)<br>29.13 ppb vs. <17.88 ppb 2.29 (1.44–3.64) | Matched on decedents' sex, year of birth, and year of death. Conditional Logistic | Socioeconomic status. Urbanization |
| Amigou et al. (2011) (*176*) | Smoothed map of annual traffic $NO_2$ concentrations from National Environmental and Energy Agency estimated from a multi-determinate model (road, transport, and emission date), to place of residence at time of diagnosis | 204/763 (0-15 yrs.) | $\leq$ 12.2 vs. $\geq$16.1 µg/m$^3$ 1.2 (1.0-1.5) | Matched on age and sex. Unconditional Logistic | parental education, type of housing, degree of urbanization, birth order, early common infections, preconception paternal smoking, maternal pesticides use during pregnancy, and proximity to gas station |
| Particulate Matter Less Than 10 Microns ($PM_{10}$) | | | | | |
| Vinceti et al. (2012) (*116*) | $PM_{10}$ and Benzene concentrations estimated from the California LINE Source Dispersion Model that estimates the dispersion and deposition of pollutants, assigned to subjects at time of diagnosis | 25/83<br>28/83 (0-14 yrs.) | $PM_{10}$ ($\geq$ 5 years old) $\geq$ 7.5 µg/m$^3$ vs. < 2.5 µg/m$^3$ 1.5 (0.5–4.9)<br>Benzene ($\geq$ 5 years old) $\geq$ 6 µg/m$^3$ vs. < 2 µg/m$^3$ 0.9 (0.5–4.9) | Matched on sex, year of birth, and province of residence. Bivariate/multivariate Conditional Logistic | Income, age, sex, province, and simultaneous PM10/Benzene |

| First author (Year) | Exposure assessment | No. Exposed cases per level of exposure (Age range) | Odds ratio/Relative Risk (95% Confidence Interval) and level of exposure | Statistical analysis | Adjusted covariates |
|---|---|---|---|---|---|
| Traffic Density | | | | | |
| Savitz et al. (1989) (*183*) | Traffic density, vehicles per day (VPD) near residence at time of diagnosis | Acute leukemia<br>17/98<br>(0-14 yrs.) | < 500 vs. ≥ 500 VPD<br>2.1 (1.1 - 4.0) | Matched on age, sex, and area code.<br>Unconditional Logistic | Age, gender, urbanization level of residence, and non-petrochemical air pollution exposure level |
| Raaschou-Nielsen et al. (2001) (*188*) | Traffic density, vehicles per day near residence at time of pregnancy and entire childhood | NA/986<br>(0-15 yrs.) | <500 vs. ≥ 10,000 VPD<br>1.1 (0.6 - 2.2) | Matched on age, sex, and calendar time.<br>Conditional Logistic | Age, sex, urban development, geographic region, type of residence, electromagnetic fields, mother's age, and birth order. |
| Pearson et al. (2002) (*184*) | Traffic density (from 1990), vehicles per day near residence at time of diagnosis | 5/98<br>(0-15 yrs.) | < 500 vs. ≥ 20,000 VPD<br>7.35 (1.40 - 38.60) | Matched on age, sex, and area code.<br>Stratified Analysis | Age, sex, and area code |
| Langholz et al. (2002) (*185*) | Traffic density, vehicles per day near residence where subject lived the longest. | 66/212<br>(0-10 yrs.) | < 500 vs. ≥ 10,000 VPD<br>1.4 (0.9 - 2.3) | Matched on age and sex.<br>Conditional Logistic | Age, sex, wire coding |
| Reynolds et al. (2004) (*187*) | Traffic density, vehicles per day near residence at time of birth | 155/1728<br>(0-5 yrs.) | < 28,000 vs. 270,000 VPD<br>0.92 (0.73 - 1.15) | Matched on birth date and sex.<br>Conditional Logistic | Age, sex, and race and ethnicity |
| Von Behren et al. (2008) (*178*) | Traffic density, vehicles per day near residence at time of diagnosis, birth, and entire lifetime. | 52/310<br>(0-14 yrs.) | ≤ 38,499 vs. ≥91,462 VPD<br>1.24 (0.74 - 2.08) | Matched on age, sex, Hispanic ethnicity, and ethnicity of the mother.<br>Conditional Logistic | Age, sex, Hispanic ethnicity, race, household income |

| First author (Year) | Exposure assessment | No. Exposed cases per level of exposure (Age range) | Odds ratio/Relative Risk (95% Confidence Interval) and level of exposure | Statistical analysis | Adjusted covariates |
|---|---|---|---|---|---|
| Petrol Station Density and Proximity to Roads With Heavy Traffic | | | | | |
| Steffen et al. (2004) (*177*) | Proximity to roads with heavy traffic and proximity to a neighbouring business (petrol station, automobile garage) near residence while in utero and during childhood. | 155/280<br><br>17/280<br>(0-14 yrs.) | Proximity to roads with heavy traffic no vs. yes<br>1.1 (0.80 – 1.6)<br>Proximity to a neighbouring business no vs. yes<br>4.0 (1.50 – 10.3) | Frequency Matched on sex, age, hospital centre, and ethnicity.<br>Unconditional Logistic | Age, sex, hospital centre, ethnicity, family history of solid tumour or haematological neoplasm, early common infection, day care attendance, and breast feeding. |
| Weng et al. (2009) (*181*) | Number of petrol stations per $km^2$ in the municipality where the subject lived (no time frame given for exposure assignment), assigned to municipality of residence. | 238/729<br><br>312/729<br>(0-14 yrs.) | > 0. 225 /$km^2$ vs. $\leq$ 0.149 / $km^2$<br>1.475(1.06 – 1.98)<br>> 0. 585 / $km^2$ vs. $\leq$ 0.149 / $km^2$<br>1.91 (1.29 – 2.82) | Matched on decedents' sex, year of birth, and year of death.<br>Conditional Logistic | Year of birth, year of death, sex, and socioeconomic status |
| Land Use Regression Models: | | | | | |
| Ghosh et al. (2013) (*114*) | NO, $NO_2$, $NO_x$, concentrations estimated from land use regression models combining data from 201 monitoring stations, major roads, industry, commercial land use, truck routes, and highway traffic. Assigned to residence at time of pregnancy | ALL¶ 1346<br>AML§ 217 | ALL per 25 ppb increase:<br>NO: 1.09 (1.02 – 1.18)<br>$NO_2$: 1.23 (0.98 – 1.53)<br>$NO_x$: 1.08 (1.01 – 1.16)<br>AML per 25 ppb increase:<br>NO: 0.84 (0.65 – 1.09)<br>$NO_2$: 0.71 (0.39 – 1.30)<br>$NO_x$: (0.88 (0.73 – 1.07) | Matched on birth year and sex.<br>Unconditional logistic regression | Age, sex, maternal age, race/ethnicity, education level, parity, prenatal care insurance type, and SES score quintile (census data on education level, income, and occupation for a given block) |
| Badaloni et al. (2013) (*113*) | $NO_2$ and $PM_{10}$ estimates from land use regression models developed from measurements taken by the European air quality database (airbase) incorporating satellite derived surface measurements. Variables included area of natural and residential land use, major and heavy traffic roads, land altitude, and traffic density, assigned to residence in utero and childhood. | Exposures are in quartiles (Q)<br>$NO_2$<br>Q2: 160<br>Q3: 161<br>Q4: 141<br>$PM_{10}$<br>Q2: 157<br>Q3: 159<br>Q4: 150 | ALL<br>$NO_2$ (Q1 is the reference)†<br>Q2: 1.09 (0.81 – 1.46)<br>Q3: 1.03 (0.76 – 1.39)<br>Q4: 0.85 (0.61 – 1.18)<br>$PM_{10}$ (Q1 is the reference)‡<br>Q2: 1.08 (0.80 – 1.47)<br>Q3: 1.08 (0.78 – 1.50)<br>Q4: 1.00 (0.70 – 1.41) | Matched on birth date, gender, and residential region.<br>Unconditional logistic regression | Birth date, sex, region, age at diagnosis, gender, region, and level of education of the parent. |

† [Q1 (7.2- 20.7), Q2 (20.7 -27), Q3 (27 – 33.3), Q4 (33.3 – 75.5)] in $\mu gm^{-3}$. ‡[Q1 (16.3-28.6), Q2 (28.6-33.3), Q3 (33.3-37.9), Q4 (37.9-55.2)] in $\mu gm^{-3}$. ¶ ALL: Acute myeloid leukemia. § AML Acute myeloid leukemia.

| First author (Year) | Exposure assessment | No. Exposed cases per level of exposure (Age range) | Odds ratio/Relative Risk (95% Confidence Interval) and level of exposure | Statistical analysis | Adjusted covariates |
|---|---|---|---|---|---|
| Other Exposure Measures (number of petrochemical employees and exposure opportunity score) | | | | | |
| Yu et al. (2006) (*117*) | 'Exposure opportunity score' (EOP) derived by taking the log transformed inverse of the distance (in km) of a subject's place of residence to a petrochemical complex located within a 90$^{o}$ wedge having a three kilometer radius of mapped out land, assigned to residence for entire lifetime | 20/171<br><br>14/171<br>(0-29 yrs.) | Per unit increase EOP (Age $\leq$ 19)<br>1.04 (0.79 – 1.38)<br>Per unit increase EOP (Age $\geq$ 20)<br>1.54 (1.14 – 2.09) | Matched on gender and age:<br>Conditional Logistic | For subjects 0 – 19 years of age:<br>Age, sex, smoking status and maternal educational status<br>For subjects $\geq$ 20 years:<br>Age, sex, smoking, education |
| Weng et al. (2008) (*180*) | Number of petrochemical employees per municipality divided by the population of that municipality and expressed as a percentage (no time given for assignment of exposure), assigned to municipality of residence. | 208/405<br><br>109/405<br>(0-19 yrs.) | $\leq$ 2.88 % vs. 8.53%<br>1.23 (0.78 – 1.93)<br>< 2.88 % vs. 21.95%<br>1.26 (0.70 – 2.26) | Matched on decedents' sex, year of birth, and year of death:<br>Conditional Logistic | Age, gender, urbanization level of residence, and non-petrochemical air pollution exposure level |

**Table 3**. Characteristics of the cohort studies that reported effects from exposure to ambient air pollutants and leukemia.

| Author, location, date | Study population | | | Number of cases | | Outcome | Outcome assessment | Follow up period | Response rate | Completeness of follow up |
|---|---|---|---|---|---|---|---|---|---|---|
| | Age Range | Total | % Male | Total | % Male | | | | | |
| Mills et al. United States (1991) (*119*) | >25 | 6340 | 36 | 12 | 50 | Incidence All leukemia | Postal questionnaire, medical records | 1977 - 1982 (5 years) | 87.0 % | 99.0 % |
| Michelozzi et al. Italy (1998) (*118*) | NR* | 341,389 | 48 | 169 | 58 | Mortality All leukemia | Geographical information mortality system | 1987 - 993 (6 years) | NR | NR |
| Talbott et al. United States (2011) (*120*) | All ages | 625 | 47 | 5 | 40 | Incidence All leukemia and Acute myeloid leukemia | Cancer Registry | 1990 - 2001 (11 years) | 79.3 % | NR |
| Raaschou-Nielsen et al. Denmark (2011) (*115*) | 50-64 | 57,053 | 48 | 117 | NR | Incidence All leukemia | Cancer Registry | 1993 - 2006 (13 years) | 95.0 % | 94.0 % |

*NR: Not reported

**Table 4**. Descriptions of the exposure assessments and the associations between leukemia and exposure to ambient air pollutants found in the cohort studies.

| First author, date, location | Exposure metrics | Exposure | Statistical analysis | Adjustments | Increment of exposure | Outcome(s) (95% confidence interval) |
|---|---|---|---|---|---|---|
| Mills et al. (1991) (*119*) | Average annual hours of exposure to concentrations of total suspended particulates in excess of 200 $\mu gm^{-3}$ (with increments of 1,000 hours per year) derived from 348 fixed-site monitoring stations from the California Air Resource Board archive to estimate total suspended particulate concentrations (data from 1966-1977 was used) and assigned to place of residence of the subject. | Total suspended particulates (TSP) | Cox Proportional hazard | Total years of smoking, education, and occupational exposure to airborne contaminants | Increasing average annual hours of exposure to TSP above 1,000 h/y | All forms of leukemia<br>Women:<br>RR 1.05 (0.33-3.37) |
| Michelozzi et al. (1998) (*118*) | Geographical information mortality system (GEOSIM) for place of residence. Subjects resided in three radii categories; 3 km, 8 km, and 10 km from a source of the pollution, during 1991. | Distance from petrochemical plants, oil refineries, and incinerators | Direct standardization | SES | $\leq$ 3 km radius from petrol station | All forms of leukemia<br>Men:<br>SMR‡ 0.82 (0.3 – 4.09)<br>Women:<br>SMR 1.37 (0.50 – 6.79) |
| Raaschou-Nielsen et al. (2011) (*115*) | Danish AirGIS modeling system: includes street traffic, urban background, and regional background for estimation of NOx. Mean concentrations of NOx from all years between 1993 and 2006, without historical estimates, geocoded to the place of residence of the subject | $NO_x$ | Cox Proportional Hazard | Age, smoking status, physical activity, education, body mass index, diet, hormone replacement therapy, contraceptives, age at first birth, sun exposure, and previous cancers | Major street within 50m (Yes vs. No)<br>Per 10,000 VPD*<br>Per 100 $\mu g/m^3$ NOx | All forms of leukemia<br>IRR§ 0.81 (0.39 – 1.66)<br>IRR 0.75 (0.51 – 1.11)<br>IRR 0.47 (0.16 – 1.39) |
| Talbott et al. (2011) (*120*) | Exposure category based on distance of subjects' residence from Tanguch gasoline spill in the Hazel Township and the City of Hazelton. Exposure levels were defined as high: within one household of the spill; medium: up to three blocks from the spill; low: more than three blocks from the spill. | Distance from gas spill | Indirect standardization | Age | "High" vs. no exposure | All forms of leukemia<br>SIR$^{Ø}$ 16.81 (2.02–60.67) |

* VPD: vehicles per day, † RR: Risk Ratio, ‡ SMR: Standardized Mortality Ratio, § IRR: Incidence Rate Ratio, Ø SIR: Standardized Incident Rate Ratio

**Table 5**. Associations found in the case-control studies of childhood leukemia using binary indices of exposure to various indices of ambient air pollution.

| First Author (Year) | Exposure Contrast | Odds Ratio (95% Confidence Interval) |
|---|---|---|
| Gaseous Pollutants (dispersion models) | | |
| Feychting et al. (1998) (*182*) | $NO_2$: < 39 μg/m$^3$ vs. ≥ 50 μg/m$^3$ | 2.70 (0.30 - 20.6) |
| Weng et al. (2008) (*179*) | $NO_2$: < 17.88 ppb vs. 29.13 ppb | 2.29 (1.44 - 3.64) |
| Amigou et al. (2011) (*176*) | $NO_2$: ≤ 12.2 μg/m$^3$ vs. ≥16.1 μg/m$^3$ | 1.20 (1.00 - 1.50) |
| Crosignani et al. (2002) (*186*) | Benzene: > 10 μg/m$^3$ vs. 0.1 μg/m$^3$ | 3.91 (1.36 - 11.3) |
| Land Use Regression Models | | |
| Ghosh et al. (2013) (*114*) | Per 25 ppb increase in $NO_2$ | 1.23 (0.98 - 1.53) |
| Badaloni et al. (2013) (*113*) | 4$^{th}$ Quartile* vs. 1$^{st}$ Quartile* $NO_2$ | 0.85 (0.61 - 1.18) |
| | 4$^{th}$ Quartile vs. 1$^{st}$ Quartile $PM_{10}$ | 1.00 (0.70 - 1.41) |
| Particulate Matter Less Than 10 Microns ($PM_{10}$) | | |
| Vinceti et al. (2012) (*116*) | < 2.5 vs. ≥7.5 μg/m$^3$ | 1.50 (0.50 - 4.90) |
| Traffic Density (vehicles per day) | | |
| Savitz et al. (1989) (*183*) | < 500 vs. ≥ 500 | 2.10 (1.10 - 4.00) |
| Raaschou-Nielsen et al. (2001) (*188*) | <500 vs. ≥ 10,000 | 1.10 (0.60 - 2.20) |
| Pearson et al. (2002) (*184*) | < 500 vs. ≥ 20,000 | 7.35 (1.40 - 38.6) |
| Langholz et al. (2002) (*185*) | < 500 vs. ≥ 10,000 | 1.40 (0.90 - 2.30) |
| Reynolds et al. (2004) (*187*) | < 28,000 vs. 270,000 | 0.92 (0.73 - 1.15) |
| Von Behren et al. (2008) (*178*) | ≤ 38,499 vs. ≥91,462 | 1.24 (0.74 - 2.08) |
| Petrol Station Density (PSD) and Proximity to Major roads | | |
| Steffen et al. (2004) (*177*) | Heavy Traffic: No vs. yes | 1.10 (0.80 - 1.60) |
| Weng et al. (2009) (*181*) | PSD: < 0.15 /km$^2$ vs. 0.59 /km$^2$ | 1.95 (1.47 - 2.59) |
| Other Exposure Measures | | |
| Yu et al. (2006) (*117*) | Per unit increase in EOP† | 1.04 (0.79 - 1.38) |
| Weng et al. (2008) (*180*) | % Employees‡ < 2.88% vs. 21.9% | 1.26 (0.70 - 2.26) |

* Quartile 4 (33.3 – 75.5 μg/m$^3$) vs. quartile 1 (7.2 – 20.7 μg/m$^3$); † EOP, exposure opportunity score; ‡ % Employees: ([Number of petrol chemical employees per municipality / population of municipality] x 100)

# Chapter 4 ~ Adult Leukemia and Exposure to Ambient Air Pollution

As is apparent from my review of the literature on leukemia and air pollution there is a lack of research in adults, with only one case-control study and four cohort studies. The case-control study was of poor quality as the exposure assessment was not an accurate representation of personal exposure (*117*). Additionally, in only two of the four cohort studies were exposure assessments accurately assigned and both studies had very few cases developing over the follow up period (*115, 119*).

Thus, new studies are needed with large sample sizes and with accurate assessment of air pollution. This is the rationale for my thesis, which is a case-control study of over a thousand cases of adult leukemia in Canadians, and the study is presented in the following chapter as a manuscript to be submitted for publication.

# Chapter 5 ~ Exposure to Ambient Air Pollution in Canada and the Risk of Adult Leukemia

**Nicholas Winters, Mark S. Goldberg, Perry Hystad, Paul Villeneuve**


## ABSTRACT

Although the effects of air pollution on cancer have been investigated mainly for lung cancer, there is a paucity of studies on other sites of cancer, including adult leukemia. To meet this gap, we used a Canadian population-based case-control study conducted in 1994-1997. Cases were 1,064 adults with incident leukemia and controls were 5,039 adults who have never had cancer. Using data from satellite estimates and remote-sensing stations across Canada, we assigned subjects' past exposure to $NO_2$ and $PM_{2.5}$ from 1975-1994. We used the total average exposure of a subject between the 1975-1994 period and we assigned these estimates to their place of residence. We conducted sub-analyses for individual provinces (Ontario, British Columbia, Alberta) and for individual subtypes where numbers were sufficient (chronic and acute myeloid leukemia, and chronic lymphocytic leukemia). Using logistic regression models using natural cubic splines, we found a 'n-shaped' response functions between exposure to $NO_2$ and all forms of leukemia: at low concentrations, from 4.51 to 14.66 ppb, the OR was 1.24; 95%CI: 1.00-1.54 and at higher concentrations, from 22.75 to 29.7 ppb, the OR was 0.81; 95% CI 0.69 – 0.95. For fine particulate matter ($PM_{2.5}$) we found a concentration-response function that was consistent with a slight monotonic increase: at lower concentrations of $PM_{2.5}$, from 5.6 to 8.0 $\mu g/m^3$, the OR was 0.89 (95% CI 0.76 – 1.03) and at higher concentrations, from 15.6 to 19.2 $\mu g/m^3$, the OR was 1.20 (95% CI 0.96 – 1.51). For chronic lymphocytic leukemia we found an OR per 5 ppb of $NO_2$ of 0.92 (95% CI 0.86 – 1.00) and an OR per 10 $\mu g/m^3$ of $PM_{2.5}$ of 0.63 (95% CI 0.42 – 0.94). We found no association for exposure to $PM_{2.5}$. The n-shaped curve for $NO_2$ may be related to urban-rural differences and/or to possible selection bias

## INTRODUCTION

Leukemia is a rare type of cancer that affects people of all ages. It comprises a number of subtypes that are characterized according to their latency (chronic; progressing slowly, and acute; progressing quickly) (*124, 125*) and by which stem cell of the blood they originated from: myeloid (cells that mature into red blood cells, white blood cells, and platelets) or lymphoid (cells that mature into lymphocytes) (*123*), leading to four main subtypes of leukemia; acute lymphocytic leukemia; acute myeloid leukemia; chronic lymphocytic leukemia; and chronic myeloid leukemia. Little is known about the aetiology of the disease (*160*). Exposure to ionizing radiation and benzene are the only accepted casual factors in the development of leukemia in all subtypes except chronic lymphocytic leukemia (*145, 146, 149, 158, 159*). Occupational studies have shown that exposure to benzene causes acute myeloid leukemia in adults (*89, 98, 140, 143, 150*) and is potentially associated with an increased risk of developing chronic and acute lymphocytic leukemia in adults (*96, 211*). Familial and genetic factors for chronic myeloid leukemia include people with Down syndrome and the Philadelphia chromosome (*124*), and similarly individuals who have a family history of acute or chronic lymphocytic leukemia carry an increased risk of developing these subtypes as well (*136, 158, 159*). There is a suggestion that smoking (*138, 196, 212*), extremely low-frequency electric and magnetic fields (*213*), body mass index (*214, 215*), and occupational exposures to pesticides (*157, 160, 216*) may be associated with the incidence of leukemia, but the data are not sufficient to make any definitive conclusions . In summary, the accepted risk factors for leukemia explain only around 10% of cases (*160*).

Ambient air pollution is a complex mixture of chemicals that varies in time and space. It comprises inter alia particulates (from ultrafine to coarse sizes), nitrogen dioxide ($NO_2$), benzene and many other volatile organic compounds, sulphur dioxide, carbon monoxide, carbon dioxide, and polycyclic aromatic hydrocarbons. Numerous cohort (*73-80*) and case-control studies (*81-83*) have shown positive associations between lung cancer and ambient air pollution (particulate matter specifically) as well as with occupational

exposure to diesel exhaust (*217-220*). Indeed, the International Agency for Research on Cancer has classified both air pollution and diesel exhaust as being human carcinogens (*71, 72*). The relationship between air pollution and other sites of cancer have not been as well investigated, but recently associations between air pollution and the risk of cancer in other organs and tissues have been found in several case-control and cohort studies. Specifically, ambient exposure to benzene and polycyclic aromatic hydrocarbons (*94, 106, 107*) and to markers of ambient air pollution (*103, 105*) were found to be associated with the incidence of breast cancer, and traffic-related air pollution was found to be associated with the incidence of prostate cancer (*104*).

As results of occupational studies have indicated positive associations between benzene and leukemia, and because air pollution contains benzene and other carcinogens it is plausible that it increases the risk of leukemia in non-occupational settings. There have been few studies of air pollution and leukemia, and the majority of these have focussed on children (*113-120, 176, 185, 186*); the data suggest that there are no associations with childhood leukemia (*221*). There are only a few cohort studies (*115, 118-120*) and one case-control study (*117*) that investigated leukemia in adults. In addition, previous studies of leukemia and ambient air pollution have been hindered by inaccurate exposure estimates, lack of individual assignments of exposure, and relatively small sample sizes. Our study includes over a thousand incident cases of leukemia in adults, makes use of national level spatial surfaces, and uses exposure assignments derived from 20-year residential histories.

In the present population-based case-control study, we investigated whether the incidence of leukemia among Canadian adults was associated with important components of ambient air pollution, specifically ambient nitrogen dioxide ($NO_2$), a marker for traffic-related air pollution (*222*), and fine particulate matter having an aerodynamic diameter of 2.5 microns and less (fine particles; $PM_{2.5}$).

## MATERIALS AND METHODS

*Study design*

The analyses reported herein are derived from a multi-site, cancer case-control study that was conducted between 1994 and 1997 in all Canadian provinces except Quebec and New Brunswick. The original objectives of the study were to determine whether there were associations between the incidence of 18 different sites of adult cancer (leukemia being just one of them) and occupational, lifestyle, and environmental risk factors, but here we have exploited this dataset to investigate selected indicators of air pollution.

The methods have been described in detail elsewhere (*223-227*). Briefly, the present analysis is derived from all 1,066 incident cases of leukemia and 5,039 controls of men and women between the ages of 19 and 77 years. Subjects with a histologically confirmed cancer were identified using each province's cancer registry. Data collection was performed under the authority of the individual Provincial Cancer Registries with their existing ethical approval and all participants provided informed consent.

Cases of leukemia included in the study were confirmed histologically and defined by the International Classification of Diseases for Oncology (ICD-O-2) system and French-American-British classification system. The French-American-British classification system was introduced in 1976 to classify acute leukemia based on which cells the leukemia developed from and the maturity of the resulting cells. The classification comprises subtypes M0 through M7, with M0 to M5 representing acute myeloid leukemia that originated from white blood cells, M6 being acute myeloid leukemia that originated in young red blood cells, and M7 indicates acute myeloid leukemia that originated in precursors to the cells that make platelets (*228*). Acute lymphocytic leukemia is subdivided by the classification of L1 to L3, each having distinctive morphological characteristics: L1 has no visible nucleoli; L2 has one or more nucleoli present; and L3 has a one or many prominent nucleoli (*229*).

All control subjects included in the original case-control study were included in this analysis and they were selected from a random sample of individuals from each of the eight participating provinces and frequency-matched to all case subjects on sex and five-year age categories. British Columbia, Saskatchewan, Manitoba, Prince Edward Island, and Nova Scotia utilized provincial health insurance registration databases; Ontario used the Ontario Ministry of Finance Property Assessment Database for control selection; Newfoundland and Alberta both used random digit dialling to recruit controls.

*Data collection*

After obtaining the consent of the treating physician, questionnaires were sent to potential participants within one to four months of diagnosis. Controls were mailed the same questionnaires and all participants completed the questionnaires and were returned by post. A telephone interview was administered if the information provided was ambiguous. Next of kin were contacted if cases were too ill to answer the questionnaire or if they had died after selection.

The questionnaire asked participants to provide demographic information on their gender, age, and which cultural or ethnic group their ancestors belonged to (e.g., French, English, Jewish), highest level of education acquired (in years), and approximate household income (categories ranged from less than $10,000 to more than $100,000 with the option to not say). The questionnaire also inquired information on residence including residential histories (for all residences that subjects lived in for more than one year, they were asked to report the period of residency, the address of street and number or lot, their town, city, municipality, and/or county, and province). In addition, inquiries were made regarding the source of drinking water, type of heating, and the number of smokers in the home. Occupational histories (including self-reported occupational exposures to potential carcinogens, such as benzene and ionizing radiation) were also ascertained through the questionnaire. In addition, lifestyle factors were ascertained and included height and weight, alcohol intake (how many drinks a subject had per week), exposure to environmental tobacco smoke, and smoking history (smoking status – former, current,

never – and the total number of years they have smoked). The data were entered using a standardized data entry program.

*Assessment of exposure to ambient air pollution*

All of the calculations were performed by one of us (PH) and these have been described in detail previously (*230*); the following summarizes the construction of the exposure models that we used.

The basis of the exposure assessment, as is customary in most studies of air pollution and chronic disease (*231*), was according to the residences of subjects through time. Thus, for each subject, the 6-character postal codes of all residences were geocoded to latitude and longitude 1994 DMTI Inc. postal codes (*230*). A six-character postal code typically represents in urban areas a specific block (one side of a street between two intersecting streets), a single building or sometimes a large volume mail receiver (*11*), but in rural regions represents larger areas (*232*).

Four air pollution surfaces were developed and used to estimate concentrations of $NO_2$ and $PM_{2.5}$ at subjects' home addresses. We used two $NO_2$ and two $PM_{2.5}$ surfaces that were first derived from satellite data and then were rescaled using Environment Canada's National Air Pollution Surveillance fixed-site monitoring network to account for historical changes in the exposure period (1975-1994), as described below.

*Satellite based national spatial pollutant surfaces.*

Spatial models of concentrations of $NO_2$ and $PM_{2.5}$ were estimated from satellite measurements using a two-stage approach (*230*). In the first stage, we estimated concentrations of $PM_{2.5}$ using aerosol optical depth data from the Moderate Resolution Imaging Spectroradiometer and the Multiangle Imaging Spectroradiometer instruments on the National Aeronautics and Space Administration's Terra satellite. This stage entailed combining the satellite data with coincident simulated vertical aerosol structure and scattering properties from a chemical transport model provided by Goddard Earth Observing System (GEOS-Chem) to estimate the relationship between the aerosol optical

depth and ground level $PM_{2.5}$ (*233*). To ensure representative estimates, the composite concentrations of $PM_{2.5}$ developed from 2001 to 2006 were taken only from locations with more than 100 valid instrument measurements. Surfaces were estimated at an approximate resolution of 10 × 10km.

Data from 2005 to 2007 were used to estimate concentrations of $NO_2$ because that was the period when the Dutch Ozone Monitoring Instrument onboard the Earth Observing System Aura satellite began taking measurements. Tropospheric $NO_2$ columns determined by the Ozone Monitoring Instrument were used to infer ground level $NO_2$ surfaces at a 10 × 10 km resolution. The relationship between the $NO_2$ column and $NO_2$ at ground level was calculated in a similar manner as $PM_{2.5}$. Fixed-site ground level monitoring data were used then to compare the concentrations obtained by the chemical transport model. The correlation coefficient between estimated tropospheric concentrations of $NO_2$ and the ground level readings was 0.86 (*234*). We refer to these surfaces as "$NO_2$ Satellite" and "$PM_{2.5}$ Satellite".

A second set of surfaces for $NO_2$ and $PM_{2.5}$ were derived to account for long-term spatial and temporal trends in air pollution. The goal was to estimate concentrations of fine particles and $NO_2$ for the period of time 1975 - 1994. We used data from the network of fixed-site monitoring stations in the country for that purpose. Measurements for $NO_2$ were taken from 120 fixed-site monitoring stations, which began collecting data in 1975. Because fine particles were only measured starting in 1984, we inferred changes in $PM_{2.5}$ using changes in total suspended particulates, which were measured for the period 1970-2000.

Thus, measurements from 1975 for total suspended particulates were taken from 177 fixed-site monitoring stations. Measurements of total suspended particulates began in 1970, but $PM_{2.5}$ measurements did not being until 1984. Thus, we used measurements from fixed-site stations that had co-located total suspended particulate and $PM_{2.5}$ between 1984 and 2000. We then developed a random effects linear regression model using census metropolitan indicators as explanatory variables to estimate $PM_{2.5}$ from before

1984. The overall coefficient of determination for the $PM_{2.5}$ estimated by the random effects model was 0.67.

We then extrapolated current $PM_{2.5}$ and $NO_2$ concentrations to estimate annual concentrations by calibrating the satellite surfaces with the annual monitoring station data. We then performed smoothed inverse distance weighting interpolation using the ratios of the monitoring station measurements to the satellite surfaces estimates and applied these surfaces to adjust the spatial pollutant surfaces for each year between 1975 and 1994. We then assigned these annual averages of $NO_2$ and $PM_{2.5}$ to the geocode of the residences of subjects. We refer to these two surfaces as $NO_2$ Fused (adjusted with annual average $NO_2$ measurements from the fixed-site monitoring network between 1975-1994) and $PM_{2.5}$ Fused (adjusted with annual average $PM_{2.5}$ (collocated with total suspended particulate measurements from the network between 1975-1994).

*Statistical Analysis*

We conducted analyses for all types of leukemia combined as well as for specific subtypes of leukemia where numbers were sufficient (acute myeloid leukemia, chronic myeloid leukemia, and chronic lymphocytic leukemia). We used ordinary logistic regression to estimate odds ratios (OR) and associated 95% confidence intervals (CI). Control subjects were frequency-matched to all cancer sites in the original study, by five-year age group, gender, and province. We included these variables in all models (referred to as the "base model").

All continuous covariates were included in the regression models on their native scales but we did not assume that effects were linear. Rather, we assessed response functions using natural cubic spline smoothers having two, three, or four degrees of freedom. For each continuous variable, we assessed the functional forms adjusting for the three matching variables (age, sex, province) and we plotted the fitted smoothers (*235*) and computed the Akaike information criterion (AIC) (*236*). Functional forms that were clearly linear and those that could be easily converted to a parametric form were then included in the adjusted models using these transformations. Otherwise, we used the

natural cubic spline that fitted the data best in the sense that the smooth curve did not include excessive variability.

To account for temporal changes in exposure and for migration we computed, as our main exposure metric, the total average exposure of all annual averages at all residences where a subject lived over the years of 1975 to 1994 (henceforth referred to as 'total average exposure'). We also made use of concentrations at time of interview (1994).

Exposure to benzene and ionizing radiation are accepted causal risk factors for leukemia (*96, 157, 211, 216*). Both of these exposures were assessed in the questionnaires as self-reported exposures; subjects were asked "have you worked with any of the following for more than one year?" with the choices of never, do not know, at work, and at home. They were also asked to report the number of years exposed. Thus, we included variables for benzene and ionizing radiation representing exposure status (never, ever, missing) as well as variables for the number of years of self-reported exposure. There was no evidence of non-linearity.

Active and former cigarette smoking may also be causally associated with the development of adult leukemia and specific subtypes of leukemia (*196, 212*). Smoking was assessed in the questionnaire by first asking if the subject had smoked at least 100 cigarettes in their entire life; those who answered no were considered never smokers and those who answered yes were asked questions regarding the age at which they started smoking, whether they still smoked and at what age they stopped, the number of years they smoked, and the average number of cigarettes they smoked per day. We included smoking as a categorical variable (never, former, current, and missing). We also modeled the number of years smoked as a continuous linear variable as there was no evidence of non-linearity. Pack years were calculated as the number of cigarettes per day divided by the number of cigarettes in a pack (in this instance 25 cigarettes were used) and then multiplied by the total number of years a person had smoked. We included pack years in our models as a continuous linear variable. However, adding the variable lead to an increase loss of subjects due to missing data and since our pack-year variable showed no

association with leukemia in the base model (data not shown), we thus excluded it from our final models.

Body mass index (weight/height$^2$) may also be associated with an increased risk for specific subtypes of leukemia (*214, 215*) and this was included as a natural cubic spline having two degrees of freedom.

We were concerned that other variables that are not considered as a priori risk factors may also confound the association between the incidence of leukemia and air pollution. The assessment of exposure to air pollution is spatially derived and not on an individual basis, so that one can conceive that spatially-related effects could mediate associations. For example, household income and level of education in Canada is spatially heterogeneous and in general is inversely associated with air pollution (*237*). Even though Canada has an universal health care system, it is known that increased access to health care services is associated with higher social status (*238*), and that leukemia has been shown to have lower case ascertainment in the Provincial Cancer Registries than other cancers (*239*), so it is conceivable that educational status and income may be associated with seeking care and thus these variables too could be associated with the incidence of leukemia and with air pollution. Thus, additional analyses were conducted that included these two variables. Income was assessed in the questionnaire by asking the following question "What was the approximate total income for all household members from all sources, before income taxes, in an average year during the last 5 years"? The available options were; less than $10,000, $10,000 - $19,999, $20,000 - $29,999, $30,000 - $49,999, $50,000 - $99,999, greater than $100,000, and prefer not to say. We included income as a categorical variable using these levels. Education was assessed in the questionnaire by asking subjects for the highest grade (high school or elementary) completed and also the number of post secondary years completed. We used was the sum of years of post secondary, high school, and elementary school and was included as a continuous, linear variable.

We constructed three models with the same covariates for each of the four pollutant surfaces. The baseline model included only the matching variables (five year age group, gender, province) and pollutant surfaces for total average exposure of all residence between 1975 and 1994 of $NO_2$ (Satellite or Fused) or $PM_{2.5}$ (Satellite or Fused). All pollutants were fitted with natural cubic splines of two, three, or four degrees of freedom to assess linearity. After visual inspection, it was determined that many of the functional forms were non-linear, and that splines of two degrees of freedom provided the best fit with the least amount of fine-scale variability. We created two additional models by adding variables to account for known risk factors and potential confounding factors. In the second model, we added only known and suspected risk factors for leukemia: total years of self-reported exposure to benzene; total years of self-reported exposure to ionizing radiation; smoking status (never, former, current); and total years a subject has smoked. The last model, the fully adjusted model, included total years of education as a continuous variable, total household income as a categorical variable, and body mass index as a continuous variable.

For categorical variables, missing values were assigned to a 'missing' category, and for continuous variables subjects with missing values were excluded from the analysis

*Sensitivity analyses*

In addition to the total average exposure at all residences of a subject between 1975 and 1994, we also investigated subjects who had at least 20 full years of residential information over that time period, as well as using the exposure at their address at time of interview (1994). The latter analysis was conducted to ensure that in the analysis of average exposure losing subjects because of missing address information did not lead to different conclusions.

We also performed additional analyses to determine if there was an association between air pollution and individual subtypes of leukemia (acute myeloid leukemia, chronic myeloid leukemia, and chronic lymphoid leukemia). Additionally, we conducted analyses of specific provinces (Ontario, Alberta, and British Columbia) individually to determine

whether associations differed between the provinces. Finally, we conducted analyses to compare the associations found in subjects who lived in rural areas to subjects who lived in urban areas.

All coding of variables and the merging of data sets were completed using Stata ® Statistical/Data Analysis version 12.0 (http://www.stata.com/stata12/) and all analyses were conducted using R version 3.1.0 (http://cran.r-project.org/).

## RESULTS

The cancer registries from the eight provinces identified a total of 1,997 incident cases of leukemia, 14% were excluded due to having recently been deceased and 8% were not granted physician consent. In total 1,478 questionnaires were sent to cases and 1,066 were returned giving a response rate of 72%. Table 1 shows the number of cases for each of the subtypes of leukemia. For the subtypes we included in our sensitivity analyses there were 401 cases of chronic lymphocytic leukemia, 307 cases of acute myeloid leukemia, and 168 cases of chronic myeloid leukemia. Two cases were excluded from the analysis: one was coded for B-cell lymphoma and the other had an ICD-O-2 code that did not identify any form of leukemia. In our final analysis we included 1,064 cases of all forms of leukemia.

For controls, 8,117 questionnaires were sent and 573 were sent to old or wrong addresses, 565 potential controls refused participation, and 1,940 questionnaires were not returned. Of the 8,117 questionnaires sent 5,039 were returned, resulting in a response rate of 62%. Ten controls were excluded from our analysis due to either having a missing or an improperly coded age. In our final analysis we included a total of 5,029 controls.

Table 2 shows for all types of leukemia the distributions, ORs, and 95% CIs of selected characteristics, adjusted for five-year age group, sex, and province. Although men comprised 52% of the total study population, they represented 60.3% of the cases. The average ages of the cases and controls were about 57 years. The distributions for self

reported exposure to benzene and self reported exposure to ionizing radiation were similar between unexposed cases and controls, but among subjects who reported that they had been exposed to benzene, cases had a greater number of years of exposure compared to controls. Current smoking status was slightly higher in controls (19.5%) than in cases (12.6%). The remaining variables all had similar distributions between cases and controls.

*Exposure surfaces*

We analyzed the satellite derived and fused surfaces for $NO_2$ and for $PM_{2.5}$ for the entire data set for all forms of leukemia combined, all forms of leukemia combined in each individual province, and for three sub-types of leukemia (acute myeloid leukemia, chronic lymphocytic leukemia, and chronic myeloid leukemia) across all provinces for both cases and controls combined. We performed these analyses for the baseline model, the model adjusted for known and suspected risk factors, and for the fully adjusted model and found no substantive variation between odds ratios or confidence intervals. Table 3 shows the Spearman correlation coefficients between all four surfaces, and we found that between the Satellite surfaces and the Fused surfaces correlations were 0.89 for $NO_2$ and 0.48 for $PM_{2.5}$.

In what follows, we present in the text the results for all forms of leukemia and for chronic lymphocytic leukemia and the results for the other subtypes are shown in the Appendix. The rationale was that the response functions for chronic lymphocytic leukemia were different from the response functions for all forms of leukemia, whereas the response functions for chronic myeloid and acute myeloid leukemia were similar to all forms of leukemia.

Table 4 shows the distributions of concentrations of $NO_2$ and $PM_{2.5}$ for cases and controls for all forms of leukemia and for chronic lymphocytic leukemia. The total mean concentrations for both $NO_2$ Fused and $PM_{2.5}$ Fused were similar between cases and controls for all forms of leukemia; $NO_2$: for cases it was 15.8 ppb and for controls was 15.1 ppb; $PM_{2.5}$: for cases it was 11.7 $\mu g/m^3$ and for controls it was 11.6 $\mu g/m^3$.

Distributions between cases and controls were similar for chronic lymphocytic leukemia as well.

*Associations between leukemia and ambient air pollution*

We found the most consistent surfaces to be the 'Fused' surfaces, because the response functions for these surfaces showed less variation between analyses for all forms of leukemia combined, the analyses for Ontario, BC, and Alberta, and the analyses of the subtypes than the response functions for the 'satellite' surfaces showed. Furthermore, the fused surfaces provide a more representative exposure of subjects due to the adjustments made based on the monitoring station data to account for temporal changes in ambient air pollution. Thus, we only include below the results for the 'Fused' surfaces but the Appendix contains the results for the Satellite-derived measures.

Figures 1 and 2 show for all forms of leukemia combined the concentration-response functions for $NO_2$ and $PM_{2.5}$, respectively. These response functions were derived from the fully adjusted model (including five year age groups, gender, reporting province, self reported total years of exposure to benzene, self reported total years of exposure to ionizing radiation, total years of smoking, smoking category (never, current, former), total years of education, body mass index, and income category). The odds ratios were derived using a natural cubic spline function on 2 degrees of freedom and were computed with respect to the median concentration of both cases and controls (14.6 ppb for $NO_2$ and 11.4 $\mu g/m^3$ for $PM_{2.5}$). The concentration-response function for $NO_2$ (Figure 1) is highly non-linear, exhibiting a "n-shaped" curve. The concentration-response function for $PM_{2.5}$ (Figure 2) is consistent with a linear function and shows a slight monotonic increase.

Figures 3 and 4 show for chronic lymphocytic leukemia the fully-adjusted concentration-response functions for $NO_2$ and $PM_{2.5}$, respectively. (The appendices show the results for the base model, which were similar to the fully adjusted results.) The odds ratios were computed with respect to the median concentration for all controls and only cases of chronic lymphocytic leukemia combined (14.5 ppb and 11.4 $\mu g/m^3$ $NO_2$ and $PM_{2.5}$ respectively). The concentration-response function for exposure to $NO_2$ (Figure 3) was

consistent with a linear function and shows a monotonic decrease. For $PM_{2.5}$, the concentration-response function (Figure 4) is compatible with a linear function and shows a slight decrease.

The graphs showing the concentration-response functions between total average exposure of both fused and satellite surfaces of $NO_2$ and $PM_{2.5}$ for all sub-analyses can be found in the appendix (for all forms of leukemia in each individual province of Ontario, BC, and Alberta: see Appendix Figures 1 and 2, for $NO_2$ and $PM_{2.5}$ respectively; for the individual subtypes of leukemia in all provinces combined: see Appendix Figures 3 and 4, for $NO_2$ and $PM_{2.5}$ respectively).

Table 5 shows the estimated odds ratios, derived using a natural cubic spline function on 2 degrees of freedom, for associations between exposures to $NO_2$ and $PM_{2.5}$ and all forms of leukemia combined and for chronic lymphocytic leukemia. The cut-points were derived based on the range of concentrations for both cases and controls combined (1st, 10th, median, 75th, 90th, and 99th percentiles), and the output represents the OR for each level as concentration changes from the lower percentile (reference level) to the higher percentile, as these were the reference levels used in our program for calculating odds ratios from cubic splines (*235*). For the fused $NO_2$ surface, there is a clear increase in risk at low concentrations (e.g., from 4.51 to 14.66 ppb, the OR was 1.24; 95%CI: 1.00-1.54), but at higher concentrations risk decreases with increasing exposure (e.g., from 22.75 to 29.7 ppb, the OR was 0.81; 95% CI 0.69 – 0.95). For the fused $PM_{2.5}$ surface, there is an increase in risk as concentrations increase. For example at lower concentrations, from 5.6 to 8.0 $\mu g/m^3$, the OR was 0.89 (95% CI 0.76 – 1.03) and at higher concentrations, from 15.6 to 19.2 $\mu g/m^3$, the OR was 1.20 (95% CI 0.96 – 1.51).

For chronic lymphocytic leukemia, the ORs were consistent with linear functions: thus, for a 5 ppb increase in concentrations of $NO_2$ the OR was 0.92 (95% CI 0.86 – 1.00) and for a 10 $\mu g/m^3$ increase in concentrations of $PM_{2.5}$ the OR was 0.63 (95% CI 0.42 – 0.94).

*Sensitivity analyses*

We investigated the effect that temporal changes in exposure and migration of subjects could have on our findings. In order to account for these temporal changes, and to determine whether loss of subjects affected the outcomes, we developed regression models using the average exposure for subjects who had 20 full years of residential history between 1975-1994 (referred to as '20 years of exposure') and for the exposure of a subject at time of their interview in 1994 (referred to as 'exposure at interview'). We found no differences in the graphs of the response functions or in the odds ratios when comparing those with 20 years of exposure and exposure at interview to the total average exposure. For instance, Appendix Figure 5 shows that the concentration-response functions for the $NO_2$ fused surface for all three periods of time for all subtypes of leukemia combined in the entire case-control study were are similar. The odds ratios were similar as well, for example: for subjects who had 20 years of exposure (see Appendix Table 1 for estimated odds ratios for exposure to $NO_2$ for subjects with 20 years of exposure and all forms of leukemia combined), the OR was 1.30 (95% CI 1.00 – 1.68) for a change from 4.51 to 14.66 ppb in concentration of $NO_2$, as compared to an OR of 1.24 (95% CI 1.00 – 1.54) for total average exposure for the same change in concentration of $NO_2$ in the fully adjusted models. All tables of the estimated odds ratios and graphs of the concentrations-response functions for the association between both the $NO_2$ and $PM_{2.5}$ fused surfaces, for three different time periods, and all forms of leukemia can be found in the appendix (see Appendix Tables 1 and 2, and Appendix Figures 5 and 6).

We also conducted separate analyses for the provinces that had sufficient numbers of cases: Ontario (412 cases, 1,933 controls); Alberta (207 cases, 618 controls); and British Columbia (178 cases, 869 controls) for total average exposure, 20 years of exposure, and exposure at interview. Appendix Tables 3 and 4 show the distributions of concentrations of $NO_2$ and $PM_{2.5}$, respectively, as well as distributions for cases with chronic myeloid leukemia and acute myeloid leukemia. Again, we found no substantive differences between the response functions when compared to the analysis of all provinces combined (see Appendix Figures 7 and 8 for the graphs of the concentration-response functions and

Appendix Tables 5-10 for the estimated odds ratios of the associations in individual provinces between $NO_2$ and $PM_{2.5}$ exposure from three different time periods).

We also estimated the response functions for chronic myeloid leukemia, chronic lymphocytic leukemia, and acute myeloid leukemia, using the same set of covariates as above (Appendix Figures 9 and 10; Appendix Tables 11-16) and found that the concentration-response functions and the estimated odds ratios for the individual subtypes were all similar to the analysis of all forms of leukemia combined, with the exception of chronic lymphocytic leukemia mentioned previously.

In addition, we analysed the effect that living in a rural area could have on the association between air pollution and incidence of all forms of leukemia. For subjects who were living in rural areas (cases: 279, controls: 1,430) at time of interview there was a noticeable difference from those who were living in urban areas (cases: 785, controls 3517) (Figure 5). These response functions were derived from the fully adjusted model as described previously, however exposure at time of interview was used. The concentration-response functions for $NO_2$ and $PM_{2.5}$ for rural subjects were compatible with linear functions and showed slight monotonic increases. The concentration-response function for exposure to $NO_2$ and all forms of leukemia in urban subjects showed a non-linear decrease and for exposure to $PM_{2.5}$ a somewhat linear, decreasing response was observed. Table 6 shows, separately for rural and urban subjects, the estimated ORs derived using a natural cubic spline function on 2 degrees of freedom between exposures to $NO_2$ and $PM_{2.5}$ at time of interview and all forms of leukemia combined. For the fused $NO_2$ surface in urban subjects, there is a higher risk at low concentrations (e.g., from 4.2 to 15.5 ppb, the OR was 0.84; 95%CI: 0.65 – 1.08) but at higher concentrations risk decreases with increasing exposure (e.g., from 24.4 to 29.5 ppb, the OR was 0.78; 95% CI 0.64 – 0.95). For the fused $PM_{2.5}$ surface in urban subjects, there is an increase in risk as concentrations increase that is similar to the analysis of the entire data set. For example at lower concentrations, from 4.5 to 6.5 $\mu g/m^3$, the OR was 0.88 (95% CI 0.75 – 1.03) and at higher concentrations, from 13.3 to 17.4 $\mu g/m^3$, the OR was 1.03 (95% CI 0.72 – 1.48). For rural subjects, the OR per 5 ppb increase in exposure to $NO_2$ was 1.18 (95% CI

0.98 - 1.43) and the OR per 10 $\mu g/m^3$ increase in exposure to $PM_{2.5}$ was 1.50 (95% CI 0.79 - 2.86).

## DISCUSSION

We conducted a case-control study to estimate the association between exposure to ambient air pollution and incidence of all forms of leukemia in all provinces in Canada except Quebec in New Brunswick. We analysed two different exposure surfaces for both $NO_2$ and $PM_{2.5}$ and found that the 'fused' surfaces were more consistent than the 'Satellite' surfaces in that their response functions for all analyses and sub-analyses showed the least amount of variation between each other. We also found no differences in the ORs or the CIs between the for the baseline model, the model adjusted for known and suspected risk factors, and for the fully adjusted model.

For $PM_{2.5}$ fused surfaces we found a concentration-response function that was consistent with a linear function with a slight increase in risk of all forms of leukemia as concentrations increased. This was consistent across all provinces and for each of the subtypes of leukemia. We found that the concentration-response function for chronic lymphocytic leukemia was also linear for the $PM_{2.5}$ fused surface.

For exposure to $NO_2$ and incidence of all forms of leukemia combined, a non-linear, 'n-shaped' concentration-response function was found. We found that as concentrations of $NO_2$ increased to about the median, the odds ratio increased, but at concentrations greater than the median the odds ratio decreased for risk of all forms of leukemia. This effect for exposure to $NO_2$ and all forms of leukemia combined was consistent across all provinces. We found consistent response function for each sub-type of leukemia, with the exception of chronic lymphocytic leukemia, which showed a decreasing linear trend.

The n-shaped curve for $NO_2$ appears to be related to urban-rural differences in which we observed an increasing trend in rural areas but a decreasing trend in urban ones.

Comparing our results to that of other studies is difficult as the majority of studies conducted on air pollution and leukemia have been on children (*221*). In one case-control study that had only 40 adult cases of leukemia (between the age of 20-29 years), an elevated OR was found: per one unit increase in the log transformed inverse of the distance (in km) a subject lived from a petrochemical plant of 1.54 (95% CI: 1.14 - 2.09) (*117*). In only two cohort studies have results for incidence of leukemia been reported. In two of these cohort studies, exposure assessments were assigned through use of the interpolation of monitoring station data for $NO_x$ (*119*) and through dispersion models for total suspended particulates (*115*). Both of these cohort studies had very few cases developing during the follow up period and both reported null associations.

Our study had several strengths. It was population-based, including subjects from both rural and urban areas nationwide, and had 20-year residential histories of subjects that were geocoded. Our exposure assessments were calculated from high-resolution estimates of pollutants derived from satellite measurements and we also incorporated fixed-site monitoring station data into our estimates to account for temporal variability. Additionally, the 20-year residential histories of subjects allowed us to characterize residential histories over a long time period. We were thus able to investigate the effect that both temporal changes in concentrations and the migration of subjects could have on the associations, and we were able to show that the effects for $NO_2$ and $PM_{2.5}$ were consistent across all time frames we investigated. We were also able, by creating national models of pollutant surfaces, to include subjects from rural areas in addition to subjects from urban areas where the majority of studies on air pollution have been conducted. We also adjusted for a number of risk factors for leukemia but did not find that these adjustments altered the results from the base model.

Our study also had several limitations. First, although our study had a relatively large sample size that included 1,064 cases of leukemia, one of the major limitations was the low response rate of 72% for cases and 62% for controls. If the identified cases that were excluded in the study had higher levels of exposure than those who were in the study, or

if the controls that were included had higher levels of exposure than those who were excluded, then we would expect bias.

The negative associations at higher concentrations of $NO_2$, which are counter-intuitive, especially in the urban areas, could of course be a chance finding but could be related to some form of selection bias, such as referred to above. It is of interest that analyses of other sites of cancer in this study have shown positive, linear associations between air pollution and lung cancer (Hystad, (*191*)), breast cancer (Hystad, submitted), and prostate cancer (Hystad, in preparation). One may thus hypothesize that there could be issues of response related to having leukemia and this may be associated with lower socioeconomic status. Leukemia is one of the more difficult cancers to ascertain, due to the rapid onset of acute forms and the failure to capture these cases while they are alive, and has shown to have lower coverage than other cancers in the Provincial Cancer Registries (*239*). In addition, many environmental studies conducted using incident cases of leukemia have noted possible bias through difficulties in case ascertainment (*240*). Indeed, It is often the case that higher concentrations of $NO_2$ are related to a greater density in the road network and higher volumes of traffic (*222*) and these areas more often than not comprise people in lower socioeconomic groups (*198*). Thus, under-ascertainment of leukemia in lower socioeconomic populations who experience higher exposures to air pollution may be responsible for this effect.

As $PM_{2.5}$ has lower spatial variability than $NO_2$ (*230*), it is likely that the response function for $PM_{2.5}$ would be less affected by previously mentioned selection bias. We found a null association for $PM_{2.5}$, however if there was a true effect then the potential bias may have lead to attenuation of the results.

## CONCLUSION

Although our results likely suggest a positive association at low concentrations and a protective effect at high concentrations, and there is no obvious biological explanation for a protective effect, it would appear that there may be selection bias. In addition, we found no association for exposure to $PM_{2.5}$. It is clear that given the paucity of studies in adult leukemia further research is needed.

## TABLES AND FIGURES

**Table 1**. Distribution of leukemia cases by subtype based on international classification of disease codes (ICD-O-2) and French-American-British (FAB) classification system

| Leukemia Subtypes | ICD-O-2 Histology Codes | FAB Classification | Number of Cases (1,064) |
|---|---|---|---|
| Acute Myeloid Leukemia | | | |
| Acute stem cell leukemia | 9801/3, 9801/39 | FAB M0 | 39 |
| Acute myeloid leukemia | 9861/3, 9861/39, 9861/0 | FAB M1, 2 | 234 |
| Acute promyelocytic leukemia | 9866/3, 9866/39 | FAB M3 | 7 |
| Acute myelocytic leukemia | 9867/3 | FAB M4 | 5 |
| Acute monocytic leukemia | 9891/3 | FAB M5 | 16 |
| Acute erthroleukemia | 9840/3 | FAB M6 | 1 |
| Acute megakaryocytic leukemia | 9910/3 | FAB M7 | 5 |
| TOTAL | | | 307 |
| Acute Lymphocytic Leukemia | | | |
| Acute lymphocytic leukemia | 9821/3 | FAB L1 and L2 | 50 |
| Acute lymphocytic leukemia (Burkett's) | 9826/3 | FAB L3 | 1 |
| TOTAL | | | 51 |
| Chronic Myeloid Leukemia | | | |
| Chronic myeloid leukemia | 9863/3, 9863/39 | N/A | 159 |
| Chronic myelomonocytic leukemia | 9868/3 | N/A | 9 |
| TOTAL | | | 168 |
| Chronic Lymphocytic Leukemia | | | |
| Chronic lymphocytic leukemia | 9823/3, 9823/39 | N/A | 410 |
| TOTAL | | | 410 |
| Hairy Cell Leukemia | | | |
| Hairy cell leukemia | 9940/3 | N/A | 63 |
| TOTAL | | | 63 |
| Leukemia not otherwise specified (NOS) | | | |
| Lymphoid Leukemia, NOS | 9820/3 | N/A | 10 |
| Leukemia, NOS | 9800/3 | N/A | 27 |
| Chronic Leukemia, NOS | 9803/3 | N/A | 2 |
| Lymphoid Leukemia, NOS | 9820/39 | N/A | 1 |
| Prolymphocytic leukemia | 9825/3 | N/A | 4 |
| Myeloid leukemia, NOS | 9860/3 | N/A | 15 |
| Monocytic leukemia, NOS (FAB-M5) | 9890/3 | N/A | 2 |
| Chronic lymphocytic leukemia | 9923/3 | N/A | 1 |
| Prolymphocytic leukemia, NOS | 9932/3 | N/A | 2 |
| Post-transplant lymphoproliferative | 9970/3 | N/A | 1 |
| TOTAL | | | 65 |

**Table 2.** Distributions and odds ratios (95% Confidence Interval) of the associations for categorical and continuous variables adjusted for age (five-year categories), gender, and reporting province with all forms of leukemia in adults from all provinces in Canada (excluding Quebec and New Brunswick).

| Categorical Variables | Cases (1,064) [number (%)] | Controls (5,029) [number (%)] | Odds Ratio (95% CI) |
|---|---|---|---|
| Gender* | | | |
| Female | 422 (39.7) | 2490 (50.5) | 1 |
| Male | 642 (60.3) | 2539 (49.5) | 1.53 (1.33 – 1.76) |
| Age* [average (standard deviation)] | 57 (13.3) | 57 (13.6) | |
| 19 to 29 | 247 (23.2) | 923 (18.3) | 1.45 (1.16 – 1.75) |
| 30 to 39 | 51 (4.8) | 226 (4.5) | 1.06 (0.73 – 1.51) |
| 40 to 49 | 78 (7.3) | 457 (9.1) | 0.83 (0.61 – 1.12) |
| 50 to 59 | 144 (13.5) | 788 (15.6) | 1 |
| 60 to 69 | 340 (31.9) | 1,645 (32.7) | 1.05 (0.84 – 1.30) |
| 70 to 77 | 204 (19.2) | 990 (19.7) | 1.02 (0.80 – 1.30) |
| Province* | | | |
| Ontario | 412 (38.72) | 1933 (38.39) | 1 |
| Newfoundland | 24 (2.26) | 241 (4.79) | 0.45 (0.28 – 0.68) |
| PEI | 12 (1.13) | 220 (4.37) | 0.25 (0.13 – 0.44) |
| Nova Scotia | 61 (5.73) | 571 (11.36) | 0.46 (0.34 – 0.61) |
| Manitoba | 97 (9.12) | 307 (6.14) | 1.43 (1.10 – 1.84) |
| Saskatchewan | 73 (6.86) | 270 (5.4) | 1.19 (0.90 – 1.58) |
| Alberta | 207 (19.45) | 618 (12.27) | 1.54 (1.27 – 1.87) |
| British Columbia | 178 (16.73) | 869 (17.28) | 0.93 (0.77 – 1.13) |
| Total years smoking (linear model) | | | |
| Per 1 year increase | 16.7 (17.0)§ | 16.0 (17.4)§ | 1.00 (0.99 – 1.00) |
| Missing | 5 (0.5) | 33 (0.7) | |
| Smoking category | | | |
| Never | 374 (35.2) | 1926 (38.3) | 1 |
| Former | 461 (43.3) | 1969 (39.1) | 1.09 (0.93 – 1.26) |
| Current | 135 (12.6) | 981 (19.5) | 0.65 (0.52 – 0.81) |
| Missing | 94 (8.8) | 159 (3.2) | 2.95 (2.21 – 3.92) |
| Ethnicity | | | |
| Western European† | 900 (94.9) | 4,161 (93.1) | 1 |
| Black | 7 (0.7) | 36 (0.8) | 0.86 (0.34 – 1.86) |
| Jewish | 16 (1.7) | 54 (1.2) | 1.25 (0.68 – 2.16) |
| Chinese | 14 (1.5) | 125 (2.8) | 0.46 (0.25 – 0.78) |
| Native Canadian | 11 (1.2) | 95 (2.1) | 0.49 (0.24 – 0.89) |
| Missing | 116 (10.9) | 565 (11.2) | 0.81 (0.65 – 1.01) |

* Matching variables, § Average (standard deviation), ‡ NE: Not estimated, † Subjects who were English, French, German, Italian, Irish, Ukrainian, Dutch, Polish, and Scottish

**Table 2.** Continued.

| Categorical Variables | Cases (1,064) [number (%)] | Controls (5,029) [number (%)] | Odds Ratio (95% CI) |
|---|---|---|---|
| Marital status | | | |
| Married/Common Law | 828 (77.8) | 3806 (75.5) | 1 |
| Divorced or widowed | 150 (14.1) | 813 (16.2) | 0.98 (0.80 – 1.19) |
| Single | 86 (8.1) | 404 (8.0) | 1.04 (0.78 – 1.36) |
| Missing | 0 (0) | 12 (0.2) | NE‡ |
| Self-reported occupational exposure to benzene | | | |
| Never exposed | 1024 (96.2) | 4,899 (97.3) | 1 |
| Ever exposed | 38 (3.6) | 123 (2.4) | 1.24 (0.84 – 1.79) |
| Missing | 2 (0.2) | 13 (0.3) | 0.88 (0.13 – 3.30) |
| Number of years (per 1 year increase) | 0.54 (3.6)§ | 0.32 (2.8)§ | 1.01 (0.99 – 1.03) |
| Self-reported occupational exposure to ionizing radiation | | | |
| Never exposed | 1,010 (94.9) | 4,799 (95.3) | 1 |
| Ever exposed | 49 (4.6) | 221 (4.4) | 0.90 (0.64 – 1.23) |
| Missing | 5 (0.5) | 15 (0.3) | 1.84 (0.58 – 4.95) |
| Number of years (per 1 year increase) | 0.59 (3.6)§ | 0.59 (3.7)§ | 0.99 (0.97 – 1.01) |
| Total household income (1995 $) | | | |
| > $100,000 | 46 (4.32) | 210 (4.17) | 1 |
| $50,000 - $99,999 | 217 (20.38) | 947 (18.79) | 1.04 (0.73 – 1.54) |
| $30,000 - $49,999 | 255 (23.94) | 1184 (23.5) | 1.06 (0.75 – 1.54) |
| $20,000 - $29,999 | 148 (13.9) | 737 (14.62) | 1.05 (0.79 – 1.73) |
| $10,000 - $19,999 | 115 (10.8) | 552 (10.95) | 1.16 (0.79 – 1.73) |
| < $10,000 | 17 (1.6) | 166 (3.29) | 0.56 (0.30 – 1.02) |
| Prefer not to say | 223 (20.94) | 1079 (21.4) | 1.06 (0.75 – 1.54) |
| Missing | 44 (4.13) | 165 (3.27) | 1.49 (0.92 – 2.39) |
| Body Mass Index† [Avg. (SD)]* | 26.5 (4.5) | 25.7 (4.8) | |
| Missing | 5 (0.5) | 24 (0.5) | NE |
| 25th to the median | 373 (35.1) | 2072 (41.2) | 1.14 (1.08– 1.21) |
| Median to the 75th | 281 (26.4) | 1260 (25.1) | 1.15 (1.09 – 1.21) |
| 75th to the 90th | 200 (18.8) | 687 (13.7) | 1.10 (1.05 – 1.15) |
| Education total years [Avg. (SD)] | 12.1 (3.6) | 12.2 (3.7) | 0.98 (0.96 – 1.00) |
| Missing | 12 (1.1) | 74 (1.5) | NE |

‡ NE: Not estimated, § Average (standard deviation), † Natural spline with 2 degrees of freedom, cut-points derived from percentiles (25th, median, 75th, and 90th), OR represent the change in response as body mass index changes from a lower percentile to a higher percentile, * Avg. (SD); average (standard deviation).

**Table 3.** Spearman correlation coefficients between $NO_2$ and $PM_{2.5}$ for both fused and satellite exposure surfaces, 1975 to 1994.

| Pollutant Surface | $NO_2$ Fused | $NO_2$ Satellite | $PM_{2.5}$ Fused | $PM_{2.5}$ Satellite |
|---|---|---|---|---|
| $NO_2$ Fused | 1 | | | |
| $NO_2$ Satellite | 0.89 | 1 | | |
| $PM_{2.5}$ Fused | 0.56 | 0.39 | 1 | |
| $PM_{2.5}$ Satellite | 0.65 | 0.75 | 0.48 | 1 |

**Table 4.** Distributions of total average concentrations of $NO_2$ and $PM_{2.5}$ from fused surfaces for all forms of leukemia and for chronic lymphocytic leukemia, 1975 to 1994.

| Exposure surface (Exposed / total subjects) | Mean | Standard Deviation | Minimum | 25th percentile | Median | 75th percentile | Maximum |
|---|---|---|---|---|---|---|---|
| **$NO_2$ Fused (ppb)** | | | | | | | |
| All forms of leukemia | | | | | | | |
| Cases (1047/1064) | 15.8 | 8.1 | 0.5 | 8.4 | 15.7 | 22.7 | 34.1 |
| Controls (4922/5035) | 15.1 | 8.8 | 0.4 | 6.7 | 14.5 | 22.9 | 33.9 |
| Chronic lymphocytic leukemia | | | | | | | |
| Cases (402/1064) | 15.5 | 8.4 | 0.5 | 7.7 | 15.2 | 22.3 | 33.3 |
| Controls (4922/5035) | 15.1 | 8.8 | 0.4 | 6.7 | 14.5 | 22.9 | 33.9 |
| **$PM_{2.5}$ Fused ($\mu g/m^3$)** | | | | | | | |
| All forms of leukemia | | | | | | | |
| Cases (1047/1064) | 11.7 | 2.9 | 4.2 | 9.7 | 11.5 | 13.4 | 20.3 |
| Controls (4921/5035) | 11.6 | 2.9 | 3.8 | 9.5 | 11.5 | 13.3 | 24.2 |
| Chronic lymphocytic leukemia | | | | | | | |
| Cases (402/1064) | 11.4 | 2.9 | 4.2 | 9.6 | 11.1 | 13.0 | 19.7 |
| Controls (4922/5035) | 11.6 | 2.9 | 3.8 | 9.5 | 11.5 | 13.3 | 24.2 |

**Table 5** Associations between ambient concentrations, for total average exposure from 1975 to 994, of $NO_2$ and $PM_{2.5}$ and incidence of all forms of leukemia and chronic lymphocytic leukemia in Canada.

| | All forms of leukemia | | | Chronic lymphocytic leukemia | | |
|---|---|---|---|---|---|---|
| | Fully adjusted model‡ | | | Fully adjusted model‡ | | |
| Exposure surface | Cases (1,064) | Controls (5,039) | Odds ratio (95% Confidence interval) | Cases (410) | Controls (5,039) | Odds ratio (95% Confidence interval) |
| $NO_2$ Fused | | | | | | |
| Linear (per 5 ppb increase) | | | NL¶ | 402 | 4,922 | 0.92 (0.86 – 1.00) |
| Percentiles of exposure (splines)† | | | | | | |
| 1.69 to 4.51 ppb | 59 | 454 | 1.10 (1.01 - 1.19) | | | NE§ |
| 4.51 to 14.66 ppb | 401 | 1,885 | 1.24 (1.00 - 1.54) | | | NE |
| 14.66 to 22.75 ppb | 298 | 1,152 | 0.92 (0.84 - 1.01) | | | NE |
| 22.75 to 29.7 ppb | 197 | 974 | 0.81 (0.69 - 0.95) | | | NE |
| 29.7 to 32.52 ppb | 37 | 171 | 0.90 (0.83 - 0.97) | | | NE |
| $PM_{2.5}$ Fused | | | | | | |
| Linear (per 10 μg/m$^3$ increase) | | | NL | 402 | 4,921 | 0.63 (0.42 - 0.94) |
| Percentiles of exposure (splines)† | | | | | | |
| 5.6 to 8.0 μg/m$^3$ | 91 | 479 | 0.89 (0.76 - 1.03) | | | NE |
| 8.0 to 11.5 μg/m$^3$ | 414 | 1,869 | 0.91 (0.79 - 1.05) | | | NE |
| 11.5 to 13.3 μg/m$^3$ | 234 | 1,198 | 1.00 (0.96 - 1.05) | | | NE |
| 13.3 to 15.6 μg/m$^3$ | 151 | 715 | 1.06 (0.97 - 1.16) | | | NE |
| 15.6 to 19.2 μg/m$^3$ | 106 | 424 | 1.20 (0.96 - 1.51) | | | NE |

† Based on natural spline models with 2 degrees of freedom; effect reported is the OR as exposure changes from the lower percentile the higher percentile. ‡ Unconditional logistic regression models adjusted for five year age category, gender, province where subject resided in when diagnosed, smoking status (current, former, never), total number of years a subject has smoked, self reported exposures to ionizing radiation and benzene, total years of education, body mass index, and income category. ¶ Non-linear, was not estimable by use of linear functions. § Not estimated

**Table 6.** Associations between ambient concentrations, at time of interview, of $NO_2$ and $PM_{2.5}$ and incidence of all forms of leukemia in subjects living in rural and urban areas of Canada at the time of interview (1994).

| | Rural Canada | | | Urban Canada | | |
|---|---|---|---|---|---|---|
| | | | Fully adjusted model‡ | | | Fully adjusted model‡ |
| Exposure surface | Cases (279) | Controls (1,430) | Odds ratio (95% Confidence interval) | Cases (767) | Controls (3,517) | Odds ratio (95% Confidence interval) |
| $NO_2$ Fused | | | | | | |
| Linear (per 5 ppb increase) | 270 | | 1.18 (0.98 - 1.43) | | | NL¶ |
| Percentiles of exposure (splines)† | | | | | | |
| 2.2 to 4.2 ppb | | | NE§ | 62 | 289 | 0.98 (0.91 – 1.05) |
| 4.2 to 15.5 ppb | | | NE | 315 | 1,308 | 0.84 (0.65 – 1.08) |
| 15.5 to 20.2 ppb | | | NE | 169 | 773 | 0.85 (0.78 – 0.93) |
| 20.2 to 24.4 ppb | | | NE | 128 | 528 | 0.83 (0.73 – 0.94) |
| 24.4 to 29.5 ppb | | | NE | 51 | 327 | 0.78 (0.64 – 0.95) |
| $PM_{2.5}$ Fused | | | | | | |
| Linear (per 10 μg/m$^3$ increase) | 270 | | 1.50 (0.79 - 2.86) | | | NL |
| Percentiles of exposure (splines)† | | | | | | |
| 4.5 to 6.5 μg/m$^3$ | | | NE | 72 | 312 | 0.88 (0.75 – 1.03) |
| 6.5 to 10.7 μg/m$^3$ | | | NE | 323 | 1,236 | 0.82 (0.66 – 1.01) |
| 10.7 to 12.1 μg/m$^3$ | | | NE | 156 | 834 | 0.97 (0.91 – 1.02) |
| 12.1 to 13.3 μg/m$^3$ | | | NE | 101 | 537 | 0.98 (0.92 – 1.05) |
| 13.3 to 17.4 μg/m$^3$ | | | NE | 65 | 318 | 1.03 (0.72 – 1.48) |

† Based on natural spline models with 2 degrees of freedom; effect reported is the OR as exposure changes from the lower percentile the higher percentile. ‡ Unconditional logistic regression models without random effects adjusted for five year age category, gender, province where subject resided in when diagnosed, smoking status (current, former, never), total number of years a subject has smoked, self reported exposures to ionizing radiation and benzene, total years of education, body mass index, and income category. ¶ Non-linear, was not estimable by use of linear functions. § Not estimated

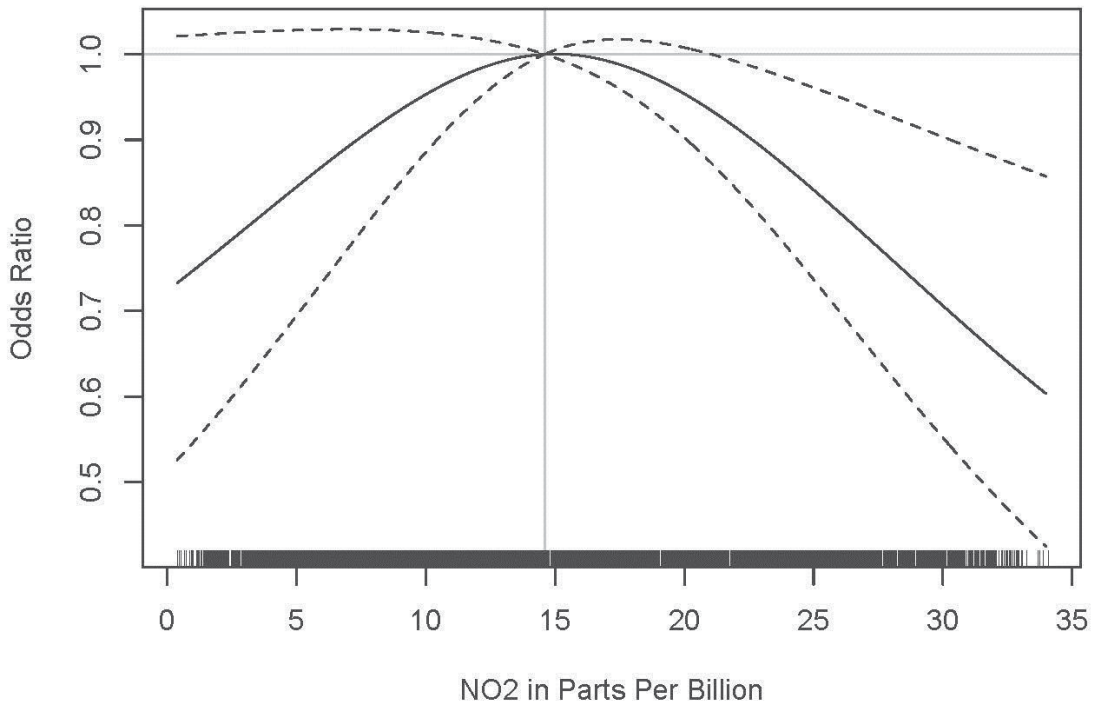



**Fig. 1** Concentration-response function for the $NO_2$ fused model (solid line) and 95% confidence interval (dashed lines) using a natural cubic spline model of 2 degrees of freedom for the analysis of all forms of leukemia combined. The odds ratios are computed with respect to the reference value of 14.6 parts per billion (the horizontal line represents the null value). This function was derived from an unconditional logistic regression model, adjusted for five year age groups, gender, reporting province, self reported total years of exposure to benzene, self reported total years of exposure to ionizing radiation, total years of smoking, smoking category (never, current, former), total years of education, body mass index, and income category.

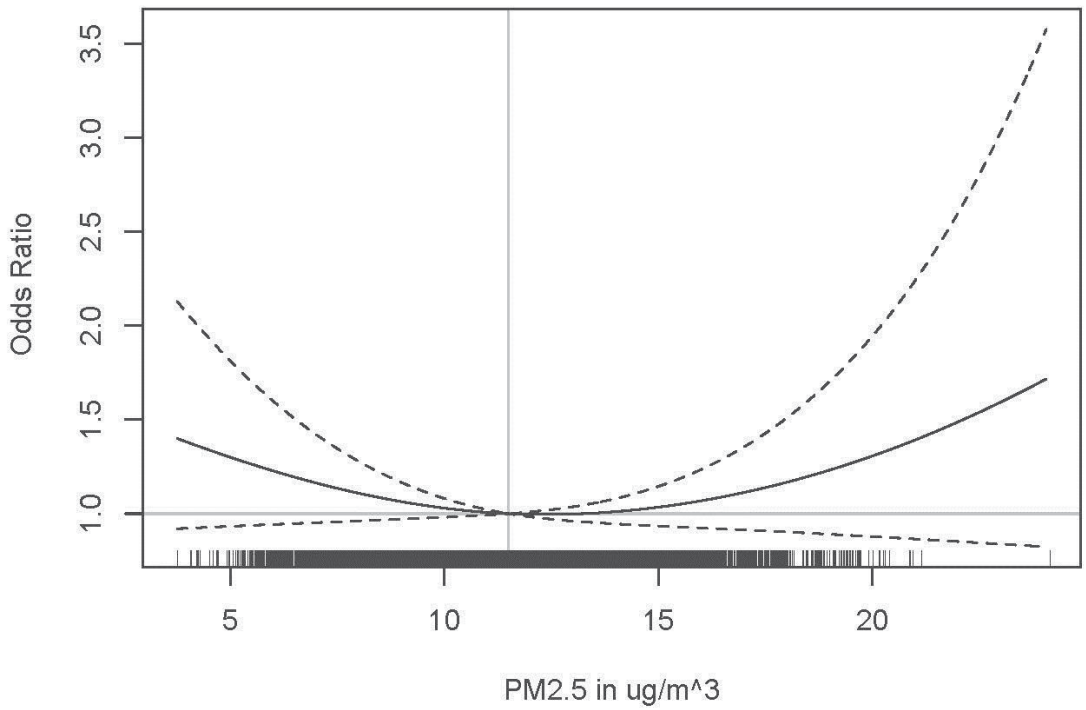



**Fig. 2** Concentration-response function for the $PM_{2.5}$ fused model (solid line) and 95% confidence interval (dashed lines) using a natural cubic spline model of 2 degrees of freedom for the analysis of all forms of leukemia combined. The odds ratios are computed with respect to the reference value of 11.5 $\mu g/m^3$ (the horizontal line represents the null value). This function was derived from an unconditional logistic regression model, adjusted for five year age groups, gender, reporting province, self reported total years of exposure to benzene, self reported total years of exposure to ionizing radiation, total years of smoking, smoking category (never, current, former), total years of education, body mass index, and income category.

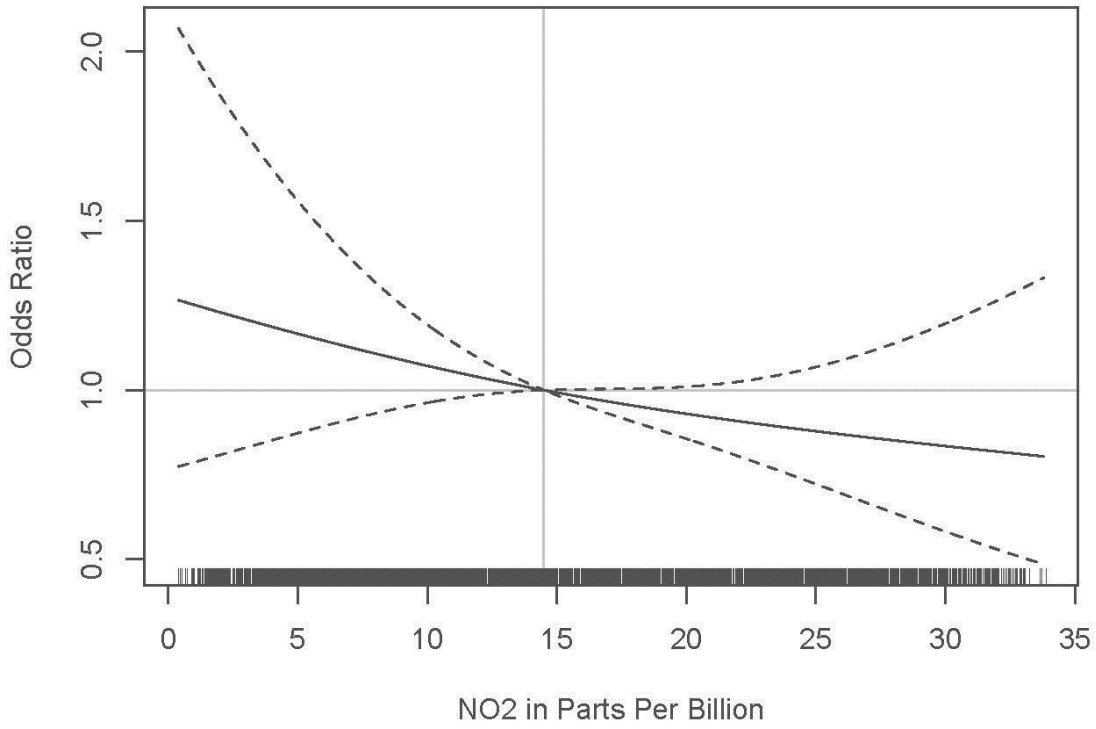



**Fig. 3** Concentration-response function for the $NO_2$ fused model (solid line) and 95% confidence interval (dashed lines) using a natural cubic spline model of 2 degrees of freedom for the analysis of chronic lymphocytic leukemia. The odds ratios are computed with respect to the reference value of 14.5 parts per billion (the horizontal line represents the null value). This function was derived from an unconditional logistic regression model, adjusted for five year age groups, gender, reporting province, self reported total years of exposure to benzene, self reported total years of exposure to ionizing radiation, total years of smoking, smoking category (never, current, former), total years of education, body mass index, and income category.

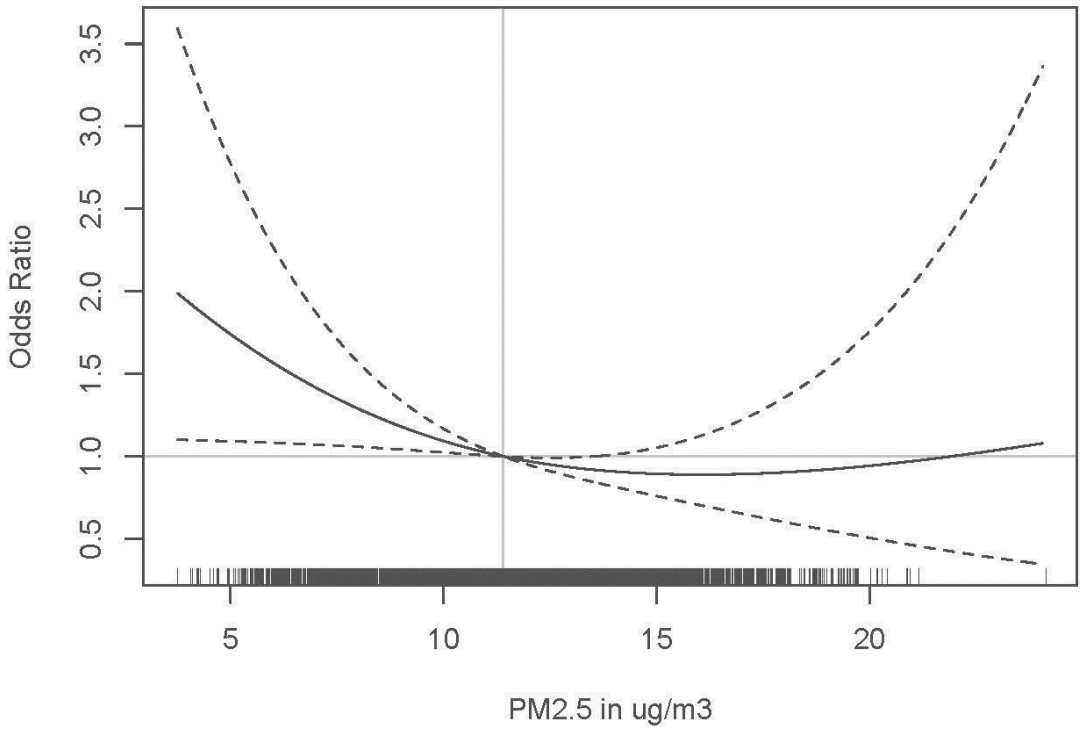



**Fig. 4** Concentration-response function for the $PM_{2.5}$ fused model (solid line) and 95% confidence interval (dashed lines) using a natural cubic spline model of 2 degrees of freedom for the analysis of chronic lymphocytic leukemia. The odds ratios are computed with respect to the reference value of 11.5 $\mu g/m^3$ (the horizontal line represents the null value). This function was derived from an unconditional logistic regression model, adjusted for five year age groups, gender, reporting province, self reported total years of exposure to benzene, self reported total years of exposure to ionizing radiation, total years of smoking, smoking category (never, current, former), total years of education, body mass index, and income category.

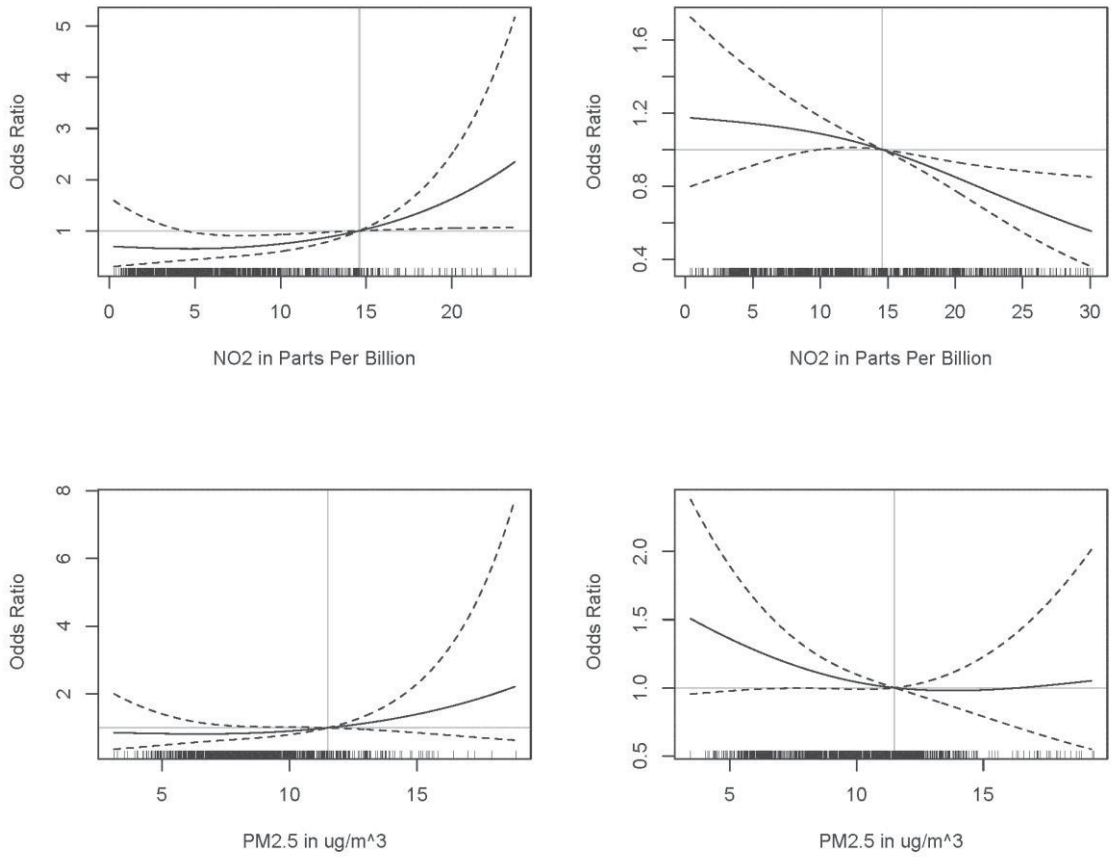
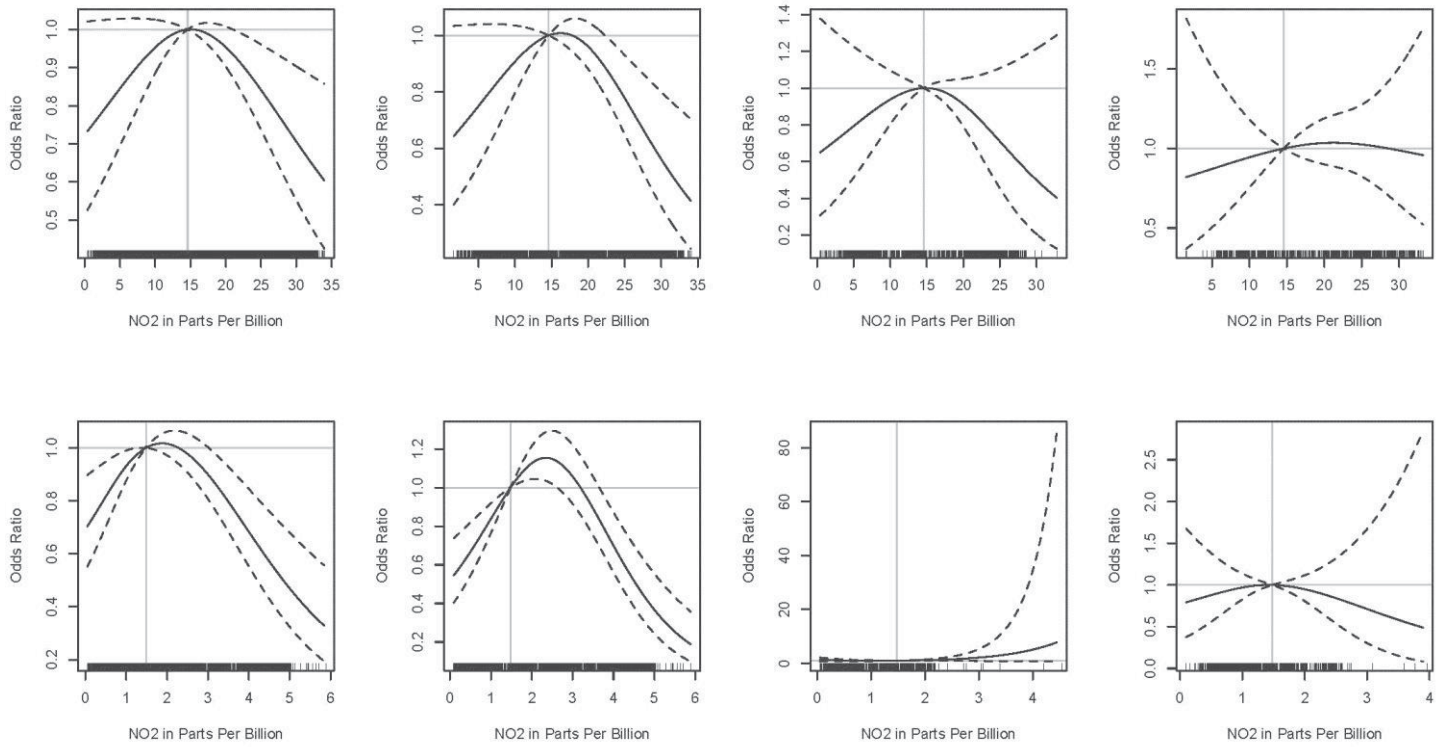
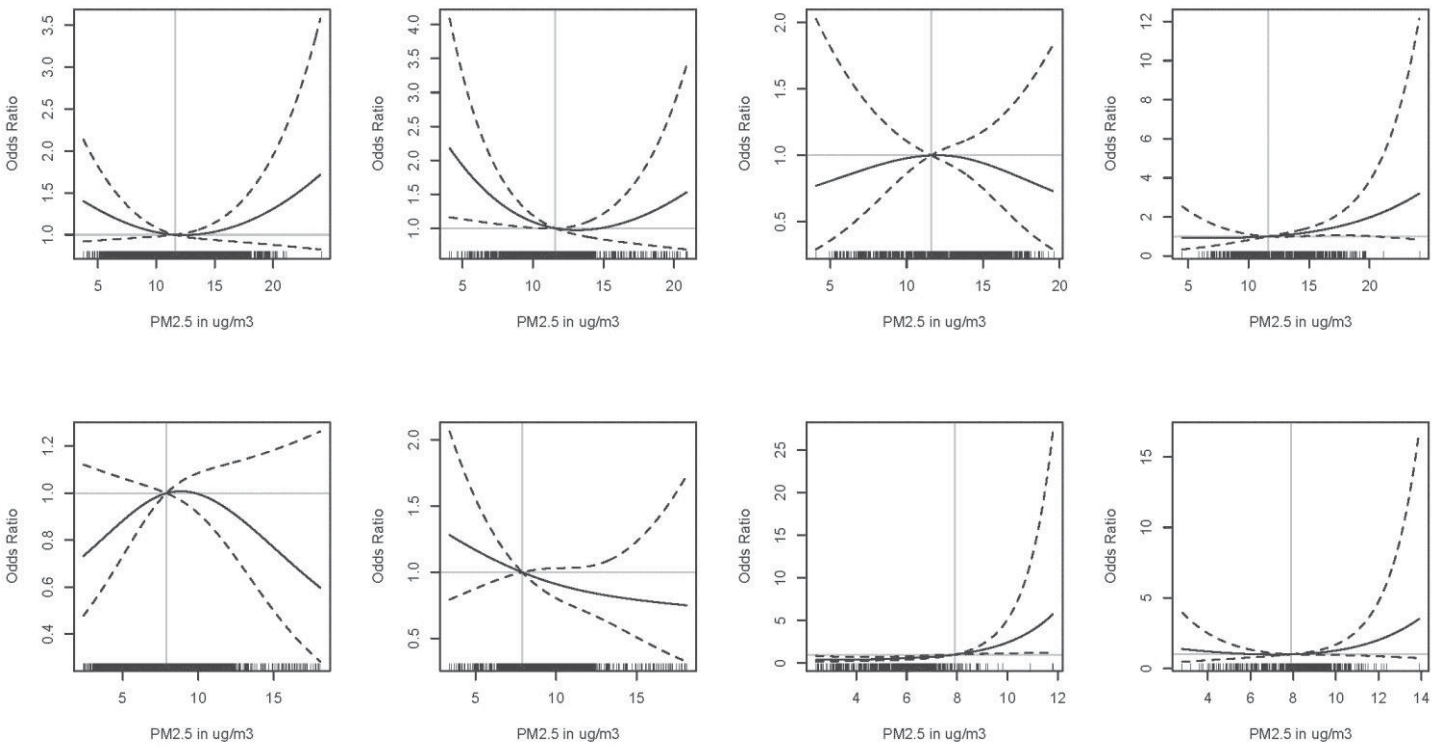



**Fig. 5** Concentration-response functions (solid line) and 95% confidence interval (dashed lines) using a natural cubic spline model of 2 degrees of freedom for exposures predicted using the $NO_2$ fused (top row of graphs) and $PM_{2.5}$ fused (bottom row of graphs) pollutant surfaces for exposure at year of interview (1994) for the analysis of all forms of leukemia combined. The left column of graphs: subjects residing in rural areas at time of interview; the right column of graphs: subjects residing in urban areas at time of interview. The vertical line represents the reference value of 14.6 parts per billion for $NO_2$ and 11.5 $\mu g/m^3$ for $PM_{2.5}$, and the horizontal line represents the null value. This function was derived from an unconditional logistic regression model, adjusted for five year age groups, gender, reporting province, self reported total years of exposure to benzene, self reported total years of exposure to ionizing radiation, total years of smoking, smoking category (never, current, former), total years of education, body mass index, and income category

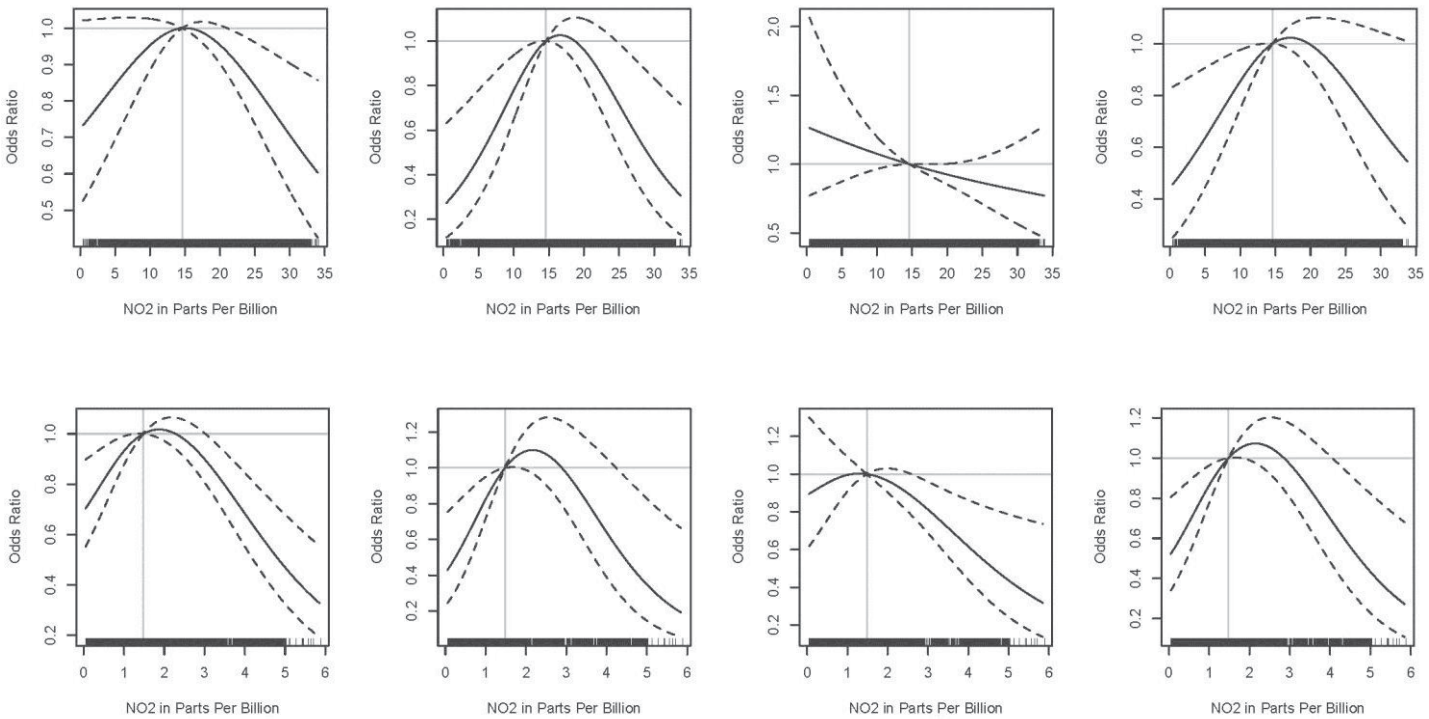
## APPENDIX



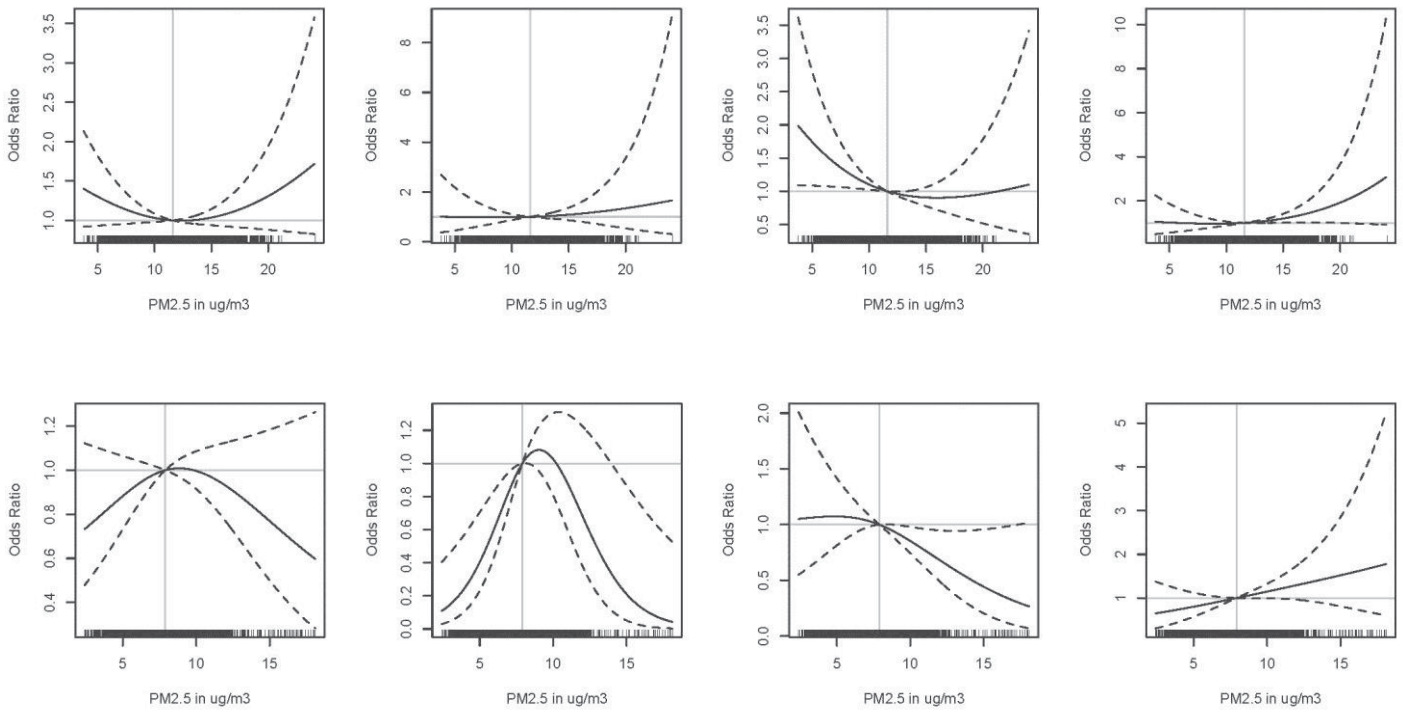

**Appendix Fig. 1** Concentration-response function (solid line) and 95% confidence interval (dashed lines) for the $NO_2$ fused model (top row) and $NO_2$ Satellite model (bottom row) using a natural cubic spline model of 2 degrees of freedom for the analysis of all forms of leukemia. Columns represent from left to right: Full data set, Ontario, BC, and Alberta. The odds ratios are computed with respect to the reference value of 14.6 parts per billion (the horizontal line represents the null value). This function was derived from an unconditional logistic regression model, adjusted for five year age groups, gender, reporting province, self reported total years of exposure to benzene, self reported total years of exposure to ionizing radiation, total years of smoking, smoking category (never, current, former), total years of education, body mass index, and income category.



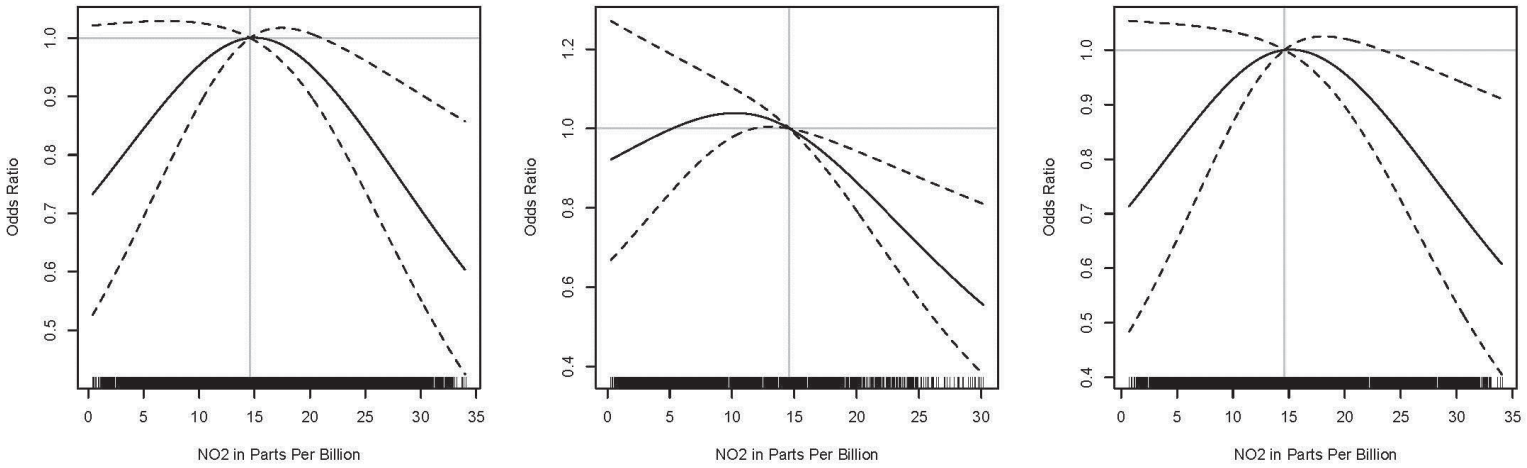

**Appendix Fig. 2** Concentration-response function (solid line) and 95% confidence interval (dashed lines) for the $PM_{2.5}$ fused model (top row) and $PM_{2.5}$ Satellite model (bottom row) using a natural cubic spline model of 2 degrees of freedom for analysis of all forms of leukemia. Columns represent from left to right: the full data set, Ontario, BC, and Alberta. The odds ratios are computed with respect to the reference value of 11.5 μg/m$^3$ (the horizontal line represents the null value). This function was derived from an unconditional logistic regression model, adjusted for five year age groups, gender, reporting province, self reported total years of exposure to benzene, self reported total years of exposure to ionizing radiation, total years of smoking, smoking category (never, current, former), total years of education, body mass index, and income category.



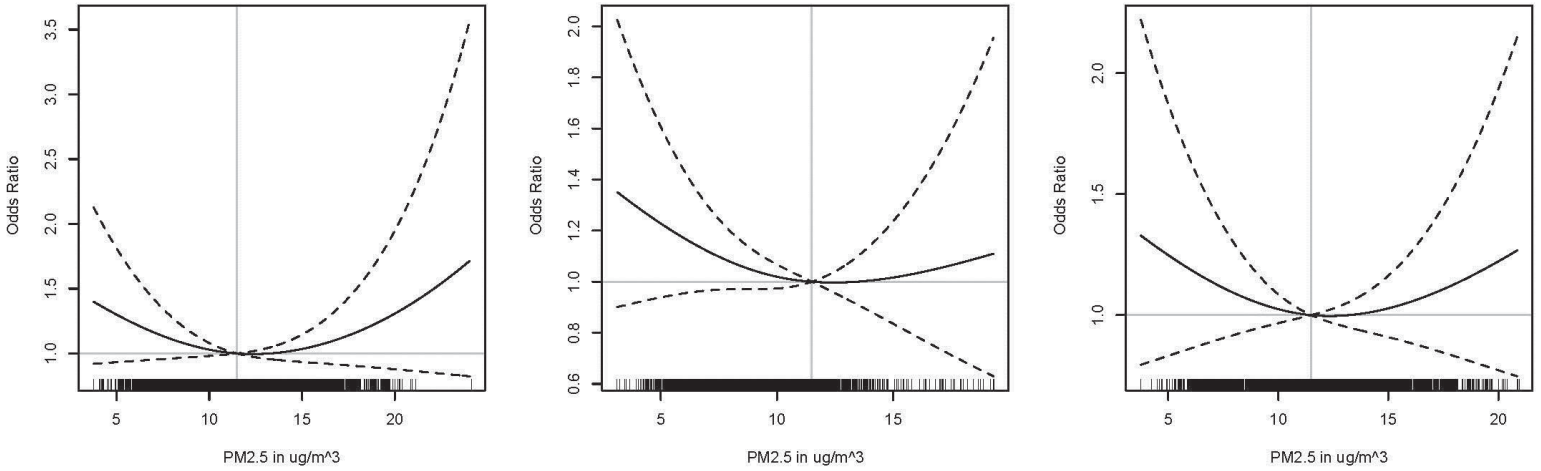

**Appendix Fig. 3** Concentration-response function (solid line) and 95% confidence interval (dashed lines) for the $NO_2$ fused model (top row) and $NO_2$ Satellite model (bottom row) using a natural cubic spline model of 2 degrees of freedom for analysis of all forms of leukemia and for individual sub-types. Columns represent from left to right: all forms of leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, and acute myeloid leukemia. The odds ratios are computed with respect to the reference value of 14.6 parts per billion (the horizontal line represents the null value). This function was derived from an unconditional logistic regression model, adjusted for five year age groups, gender, reporting province, self reported total years of exposure to benzene, self reported total years of exposure to ionizing radiation, total years of smoking, smoking category (never, current, former), total years of education, body mass index, and income category.



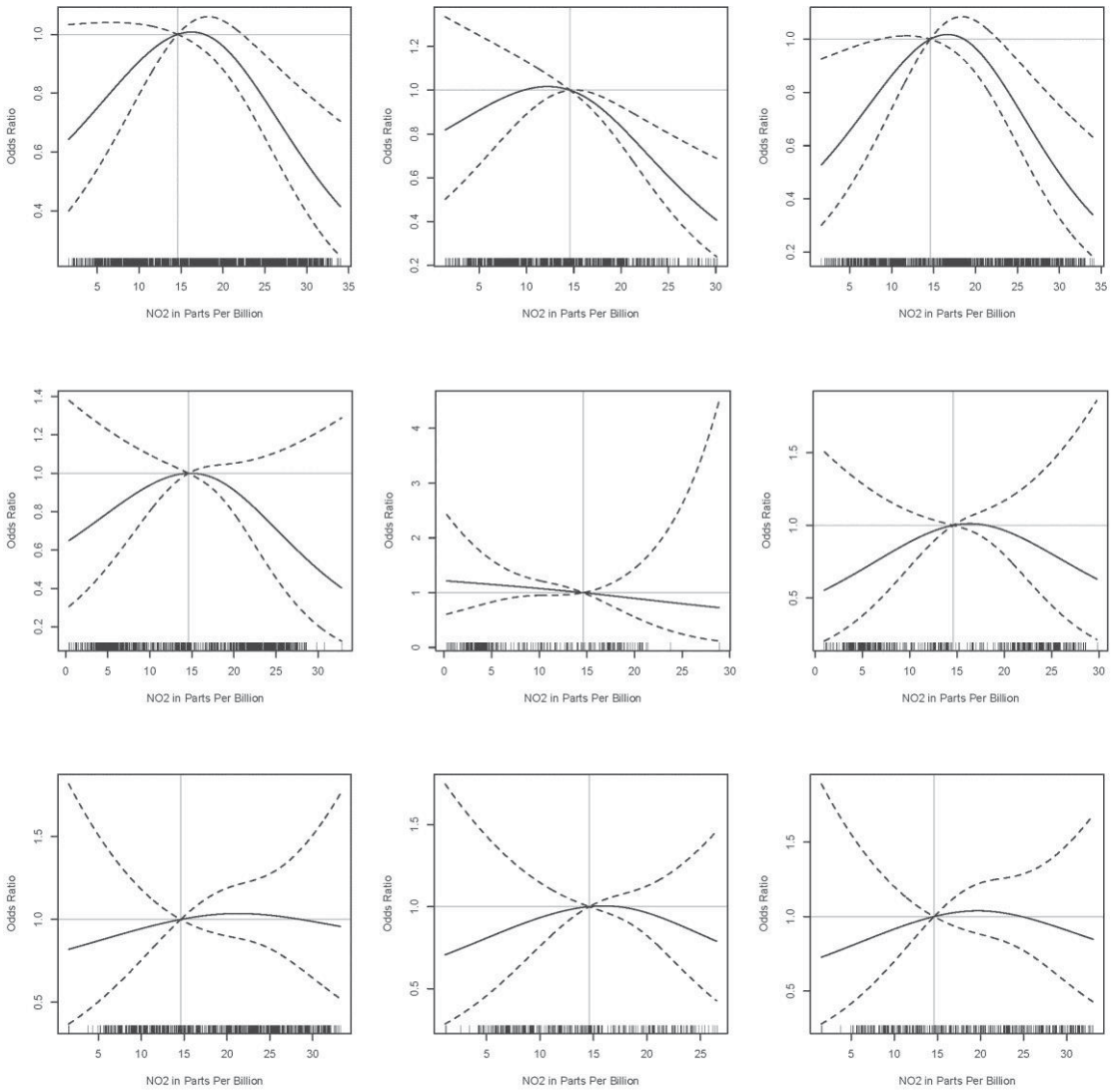

**Appendix Fig. 4** Concentration-response function (solid line) and 95% confidence interval (dashed lines) for the $PM_{2.5}$ fused model (top row) and $PM_{2.5}$ Satellite model (bottom row) using a natural cubic spline model of 2 degrees of freedom for the analysis of all forms of leukemia and for individual subtypes. Columns represent from left to right: all forms of leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, and acute myeloid leukemia. The odds ratios are computed with respect to the reference value of 11.5 $\mu g/m^3$ (the horizontal line represents the null value). This function was derived from an unconditional logistic regression model, adjusted for five year age groups, gender, reporting province, self reported total years of exposure to benzene, self reported total years of exposure to ionizing radiation, total years of smoking, smoking category (never, current, former), total years of education, body mass index, and income category.



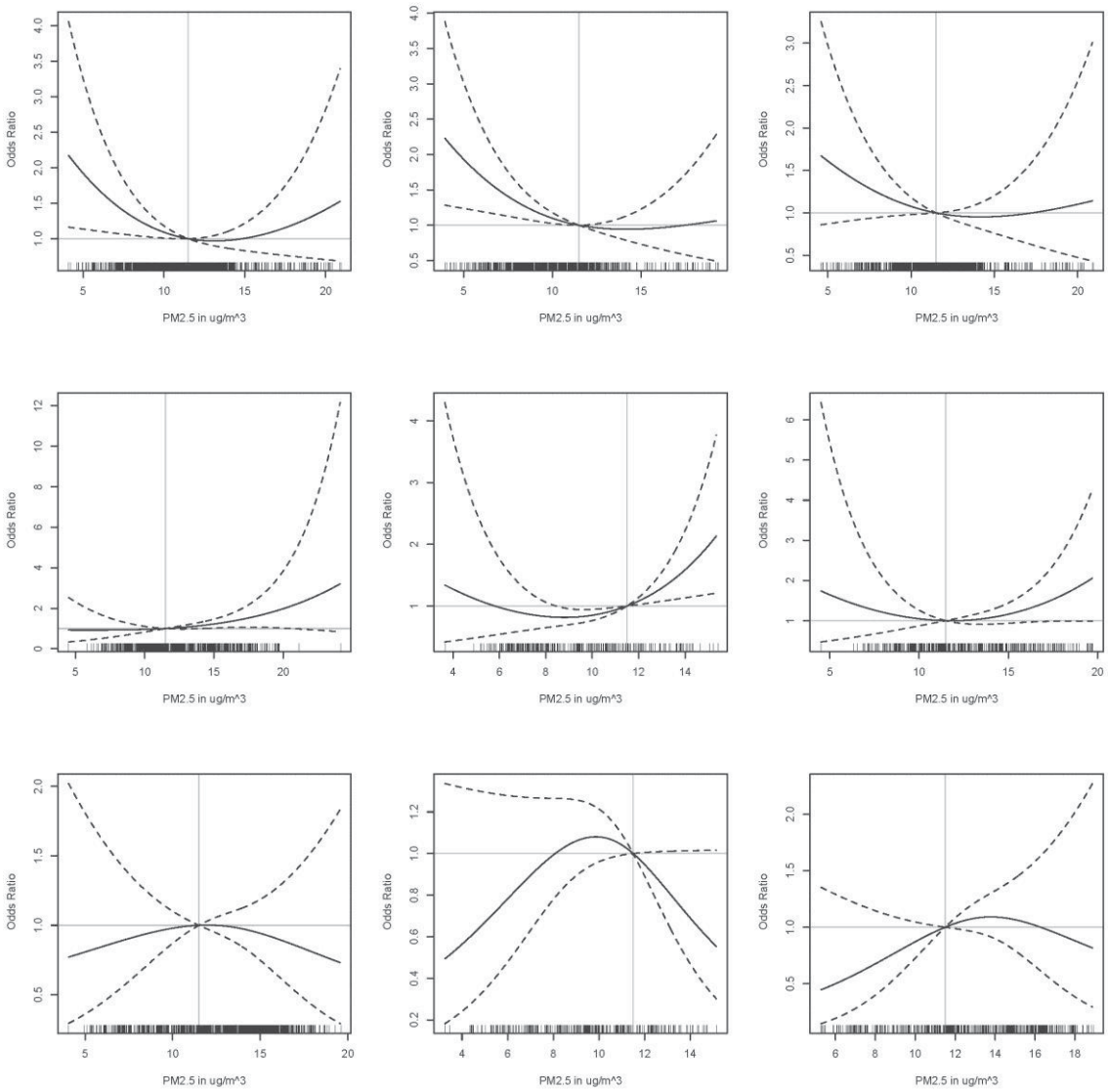

**Appendix Fig. 5** Concentration-response function for the $NO_2$ fused model (solid line) and 95% confidence interval (dashed lines) using a natural cubic spline model of 2 degrees of freedom for the analysis of all forms of leukemia combined during three different time periods (the graphs from left to right: total average exposure, exposure at interview, and 20 years of exposure). The odds ratios are computed with respect to the reference value of 14.6 parts per billion (the horizontal line represents the null value). This function was derived from an unconditional logistic regression model, adjusted for five year age groups, gender, reporting province, self reported total years of exposure to benzene, self reported total years of exposure to ionizing radiation, total years of smoking, smoking category (never, current, former), total years of education, body mass index, and income category.



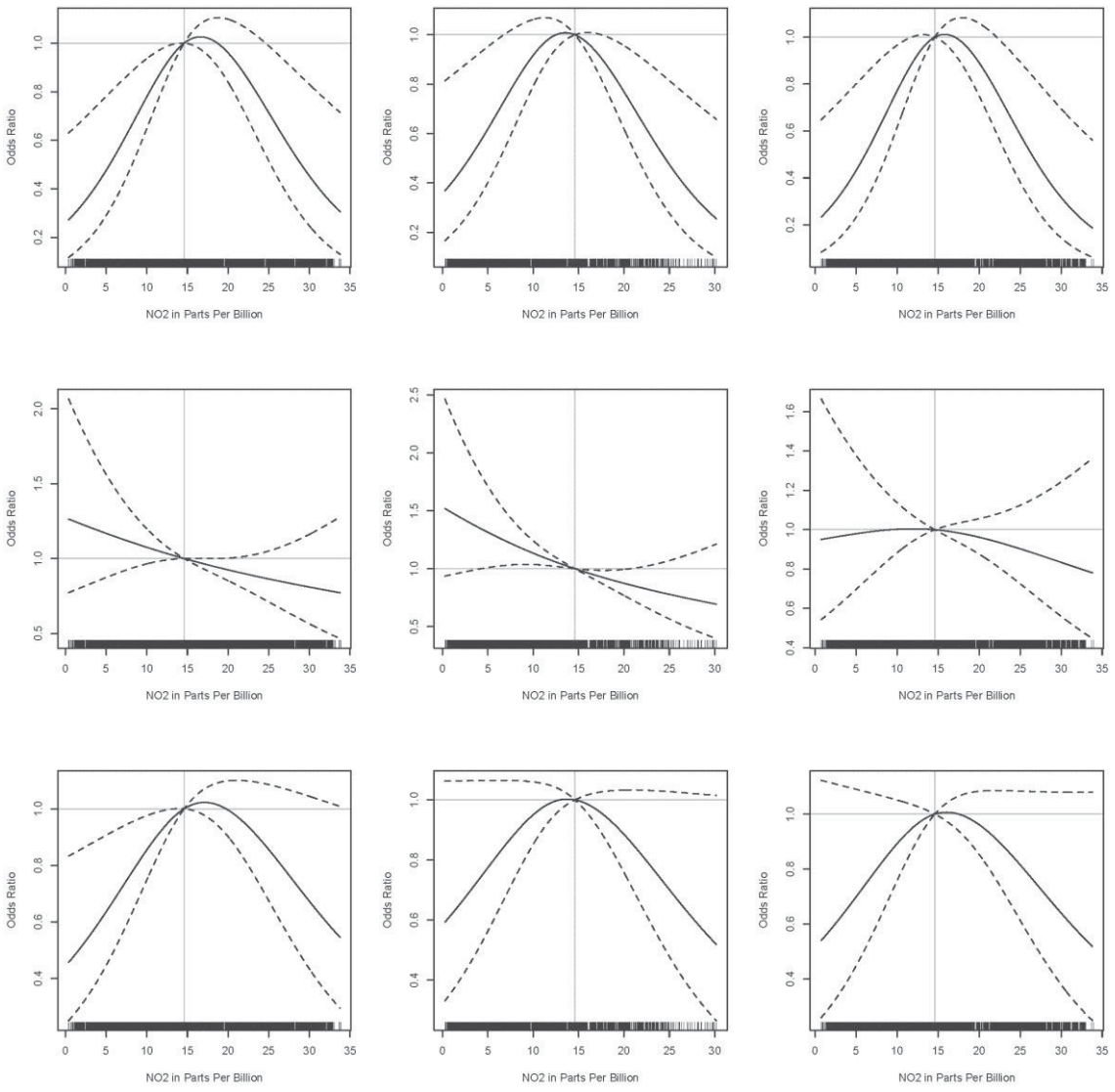

**Appendix Fig. 6** Concentration-response function for the $PM_{2.5}$ fused model (solid line) and 95% confidence interval (dashed lines) using a natural cubic spline model of 2 degrees of freedom for the analysis of all forms of leukemia combined during three different time periods (the graphs from left to right: total average exposure, exposure at interview, and 20 years of exposure). The odds ratios are computed with respect to the reference value of 11.5 $\mu g/m^3$ (the horizontal line represents the null value). This function was derived from an unconditional logistic regression model, adjusted for five year age groups, gender, reporting province, self reported total years of exposure to benzene, self reported total years of exposure to ionizing radiation, total years of smoking, smoking category (never, current, former), total years of education, body mass index, and income category.



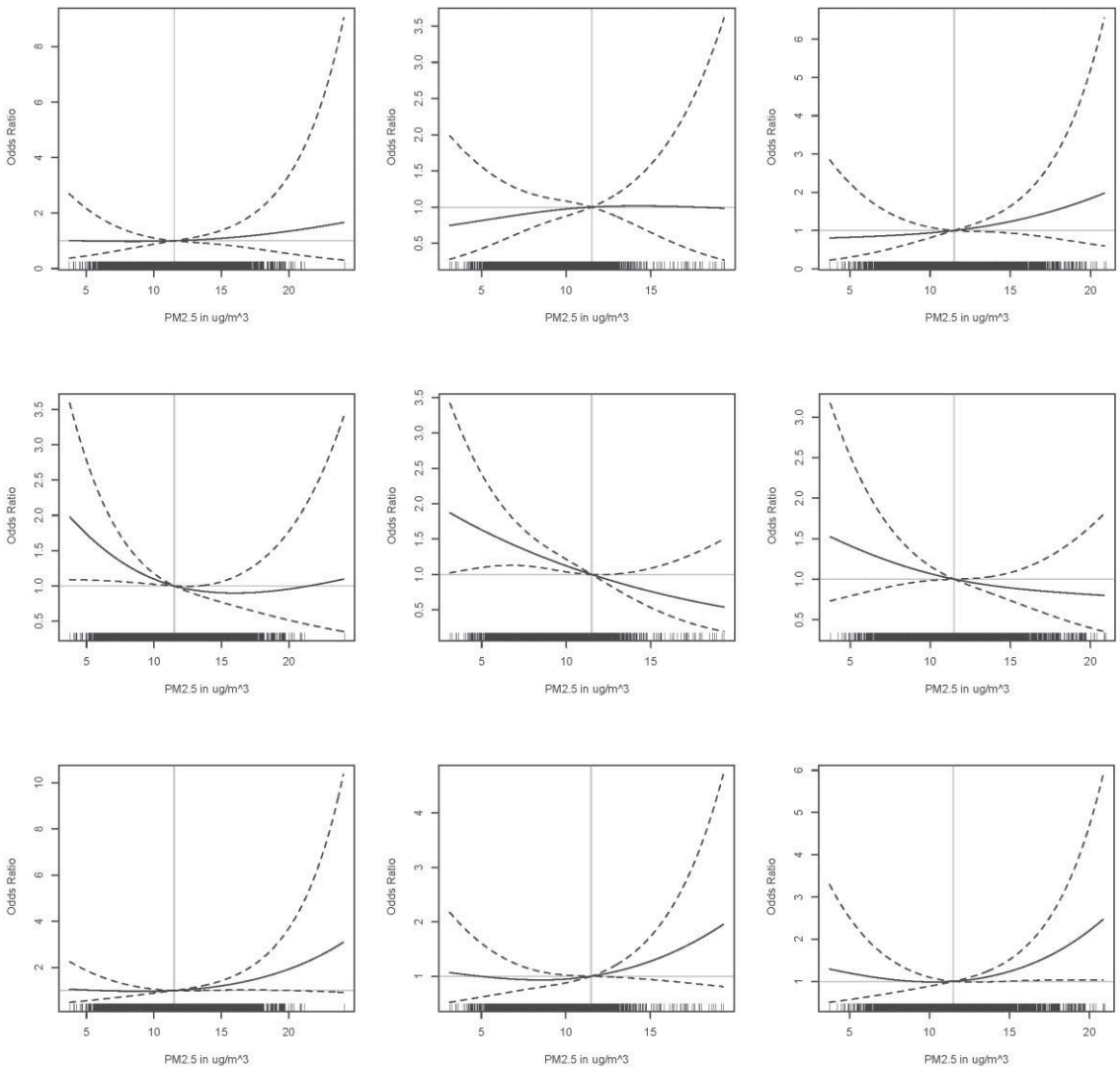

**Appendix Fig. 7** Concentration-response function for the $NO_2$ fused model (solid line) and 95% confidence interval (dashed lines) using a natural cubic spline model of 2 degrees of freedom for the analysis of all forms of leukemia combined during three different time periods (the graphs from left to right: total average exposure, exposure at interview, and 20 years of exposure) and across provinces (the rows of graphs from top to bottom: Ontario, British Columbia, and Alberta). The odds ratios are computed with respect to the reference value of 14.6 parts per billion (the horizontal line represents the null value). This function was derived from an unconditional logistic regression model, adjusted for five year age groups, gender, reporting province, self reported total years of exposure to benzene, self reported total years of exposure to ionizing radiation, total years of smoking, smoking category (never, current, former), total years of education, body mass index, and income category




**Appendix Fig. 8** Concentration-response function for the $PM_{2.5}$ fused model (solid line) and 95% confidence interval (dashed lines) using a natural cubic spline model of 2 degrees of freedom for the analysis of all forms of leukemia combined during three different time periods (the graphs from left to right: total average exposure, exposure at interview, and 20 years of exposure) and across provinces (the rows of graphs from top to bottom: Ontario, British Columbia, and Alberta). The odds ratios are computed with respect to the reference value of 11.5 $\mu g/m^3$ (the horizontal line represents the null value). This function was derived from an unconditional logistic regression model, adjusted for five year age groups, gender, reporting province, self reported total years of exposure to benzene, self reported total years of exposure to ionizing radiation, total years of smoking, smoking category (never, current, former), total years of education, body mass index, and income category.




**Appendix Fig. 9** Concentration-response function for the $NO_2$ fused model (solid line) and 95% confidence interval (dashed lines) using a natural cubic spline model of 2 degrees of freedom for the analysis of all forms of leukemia combined during three different time periods (the graphs from left to right: total average exposure, exposure at interview, and 20 years of exposure) and across sub-types (the rows of graphs from top to bottom: chronic myeloid leukemia, chronic lymphocytic leukemia, and acute myeloid leukemia). The odds ratios are computed with respect to the reference value of 14.6 parts per billion (the horizontal line represents the null value). This function was derived from an unconditional logistic regression model, adjusted for five year age groups, gender, reporting province, self reported total years of exposure to benzene, self reported total years of exposure to ionizing radiation, total years of smoking, smoking category (never, current, former), total years of education, body mass index, and income category**.**




**Appendix Fig. 10** Concentration-response function for the $PM_{2.5}$ fused model (solid line) and 95% confidence interval (dashed lines) using a natural cubic spline model of 2 degrees of freedom for the analysis of all forms of leukemia combined during three different time periods (the graphs from left to right: total average exposure, exposure at interview, and 20 years of exposure) and across sub-types (the rows of graphs from top to bottom: chronic myeloid leukemia, chronic lymphocytic leukemia, and acute myeloid leukemia). The odds ratios are computed with respect to the reference value of 11.5 $\mu g/m^3$ (the horizontal line represents the null value). This function was derived from an unconditional logistic regression model, adjusted for five year age groups, gender, reporting province, self reported total years of exposure to benzene, self reported total years of exposure to ionizing radiation, total years of smoking, smoking category (never, current, former), total years of education, body mass index, and income category.

**Appendix Table 1.** Associations between incidence of all forms of leukemia and NO2 and PM2.5 exposure for four pollutant surfaces in all provinces in Canada (except New Brunswick and Quebec) for total average exposure from 1975 to 1994 and for subjects with 20 years of exposure.

| | Base model† | | Base model (20 years) | | Fully Adjusted Model | | Fully Adjusted Model (20 years) | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted for gender, five year age category, and reporting province | | | | Adjusted for gender, five year age category, reporting province, smoking status, exposure to radiation and benzene, education, body mass index, and income | | | |
| | 1047/1064 Cases | 4923/5029 Controls | 734/1064 Cases | 3504/5029 Controls | 1021/1064 Cases | 4780/5029 Controls | 718/1064 Cases | 3414/5029 Controls |
| **Pollution Surface (percentiles of exposure)‡** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** |
| **$NO_2$ Satellite** | | | | | | | | |
| 0.12 to 0.3 ppb | 69 | 1.05 (1.02 - 1.09) | 53 | 1.06 (1.01 - 1.11) | 68 | 1.06 (1.02 - 1.10) | 53 | 1.07 (1.02 - 1.12) |
| 0.3 to 0.94 ppb | 388 | 1.18 (1.05 - 1.33) | 268 | 1.17 (1.03 - 1.34) | 374 | 1.21 (1.07 - 1.37) | 256 | 1.21 (1.05 - 1.39) |
| 0.94 to 2.09 ppb | 313 | 1.08 (0.96 - 1.21) | 219 | 1.10 (0.96 - 1.27) | 302 | 1.12 (0.99 - 1.27) | 214 | 1.16 (0.99 - 1.34) |
| 2.09 to 3.85 ppb | 198 | 0.69 (0.59 - 0.82) | 141 | 0.72 (0.60 - 0.87) | 189 | 0.73 (0.61 - 0.88) | 136 | 0.76 (0.63 - 0.93) |
| 3.85 to 4.89 ppb | 54 | 0.68 (0.57 - 0.80) | 45 | 0.61 (0.47 - 0.79) | 52 | 0.70 (0.59 - 0.83) | 45 | 0.63 (0.49 - 0.82) |
| **$NO_2$ Fused** | | | | | | | | |
| 1.69 to 4.51 ppb | 60 | 1.09 (1.01 - 1.18) | 39 | 1.09 (1.01 - 1.18) | 59 | 1.10 (1.01 - 1.19) | 39 | 1.11 (1.00 - 1.22) |
| 4.51 to 14.66 ppb | 419 | 1.20 (0.98 - 1.47) | 280 | 1.22 (0.99 - 1.50) | 401 | 1.24 (1.00 - 1.54) | 269 | 1.30 (1.00 - 1.68) |
| 14.66 to 22.75 ppb | 309 | 0.86 (0.79 - 0.95) | 230 | 0.87 (0.79 - 0.95) | 298 | 0.92 (0.84 - 1.01) | 221 | 0.95 (0.84 -1.06) |
| 22.75 to 29.7 ppb | 205 | 0.76 (0.65 - 0.88) | 117 | 0.82 (0.73 - 0.91) | 197 | 0.81 (0.69 - 0.95) | 114 | 0.87 (0.77 - 0.99) |
| 29.7 to 32.52 ppb | 37 | 0.87 (0.81 - 0.94) | 58 | 0.80 (0.70 - 0.90) | 37 | 0.90 (0.83 - 0.97) | 58 | 0.85 (0.73 - 0.98) |
| **$PM_{2.5}$ Satellite** | | | | | | | | |
| 3.3 to 5.3 $\mu g/m^3$ | 69 | 1.18 (0.93 - 1.33) | 49 | 1.10 (0.94 - 1.28) | 69 | 1.17 (0.98 - 1.40) | 49 | 1.12 (0.96 - 1.31) |
| 5.1 to 7.7 $\mu g/m^3$ | 373 | 1.09 (0.92 - 1.28) | 262 | 1.09 (0.92 - 1.29) | 363 | 1.15 (0.97 - 1.37) | 254 | 1.15 (0.93 - 1.42) |
| 7.7 to 9.8 $\mu g/m^3$ | 342 | 0.99 (0.91 - 1.07) | 231 | 0.99 (0.91 - 1.07) | 323 | 1.02 (0.93 - 1.11) | 219 | 1.01 (0.91 - 1.13) |
| 9.8 to 11.8 $\mu g/m^3$ | 193 | 0.93 (0.83 - 1.04) | 117 | 0.95 (0.87 - 1.03) | 188 | 0.95 (0.85 - 1.06) | 117 | 0.96 (0.86 - 1.06) |
| 11.8 to 15.1 $\mu g/m^3$ | 50 | 0.81 (0.61 - 1.07) | 62 | 0.79 (0.57 - 1.08) | 47 | 0.83 (0.63 - 1.10) | 60 | 0.79 (0.55 - 1.15) |
| **$PM_{2.5}$ Fused** | | | | | | | | |
| 5.6 to 8.0 $\mu g/m^3$ | 95 | 0.87 (0.75 - 1.00) | 59 | 0.83 (0.63 - 1.10) | 90 | 0.89 (0.76 - 1.03) | 56 | 0.91 (0.77 - 1.09) |
| 8.0 to 11.5 $\mu g/m^3$ | 425 | 0.88 (0.77 - 1.01 | 308 | 0.93 (0.83 - 1.04) | 405 | 0.91 (0.79 - 1.05) | 294 | 0.92 (0.76 - 1.12) |
| 11.5 to 13.3 $\mu g/m^3$ | 241 | 0.99 (0.95 - 1.04) | 168 | 0.99 (0.91 - 1.15) | 234 | 1.00 (0.96 - 1.05) | 163 | 1.01 (0.95 - 1.07) |
| 13.3 to 15.6 $\mu g/m^3$ | 152 | 1.04 (0.96 - 1.14) | 104 | 1.02 (0.91 - 1.15) | 149 | 1.06 (0.97 - 1.16) | 104 | 1.06 (0.95 - 1.18) |
| 15.6 to 19.2 $\mu g/m^3$ | 109 | 1.17 (0.94 - 1.46) | 78 | 1.09 (0.86 - 1.39) | 106 | 1.20 (0.96 - 1.51) | 77 | 1.17 (0.89 - 1.52) |

† Based on natural spline models with 2 degrees of freedom, unconditional logistic regression models without random effects. ‡ Cut points derived based on the range of concentrations for both cases and controls combined (1st, 10th, median, 75th, 90th, and 99th percentiles); the output represents the OR for each level as concentration changes from the lower percentile to the higher percentile.

**Appendix Table 2**. Associations between incidence of all forms of leukemia and NO2 and PM2.5 exposure for four pollutant surfaces in all provinces in Canada (except New Brunswick and Quebec) for total average exposure from 1975 to 1994 and for exposure at time of interview (1994).

| | Base model† | | Base model (Interview) | | Fully Adjusted Model | | Fully Adjusted Model (Interview) | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted for gender, five year age category, and reporting province | | | | Adjusted for gender, five year age category, reporting province, smoking status, exposure to radiation and benzene, education, body mass index, and income | | | |
| | 1047/1064 Cases | 4923/5029 Controls | 1029/1064 Cases | 4840/5029 Controls | 1021/1064 Cases | 4780/5029 Controls | 1003/1064 Cases | 4700/5029 Controls |
| **Pollution Surface (percentiles of exposure)‡** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** |
| **$NO_2$ Satellite** | | | | | | | | |
| 0.12 to 0.3 ppb | 69 | 1.05 (1.02 - 1.09) | 82 | 1.03 (0.99 - 1.07) | 68 | 1.06 (1.02 - 1.10) | 81 | 1.03 (0.99 - 1.08) |
| 0.3 to 0.94 ppb | 388 | 1.18 (1.05 - 1.33) | 397 | 1.07 (0.96 - 1.20) | 374 | 1.21 (1.07 - 1.37) | 383 | 1.10 (0.98 - 1.23) |
| 0.94 to 2.09 ppb | 313 | 1.08 (0.96 - 1.21) | 274 | 0.99 (0.87 - 1.11) | 302 | 1.12 (0.99 - 1.27) | 270 | 1.03 (0.91 - 1.17) |
| 2.09 to 3.85 ppb | 198 | 0.69 (0.59 - 0.82) | 200 | 0.72 (0.61 - 0.84) | 189 | 0.73 (0.61 - 0.88) | 195 | 0.75 (0.63 - 0.89) |
| 3.85 to 4.89 ppb | 54 | 0.68 (0.57 - 0.80) | 49 | 0.69 (0.56 - 0.84) | 52 | 0.70 (0.59 - 0.83) | 48 | 0.71 (0.57 - 0.87) |
| **$NO_2$ Fused** | | | | | | | | |
| 1.69 to 4.51 ppb | 60 | 1.09 (1.01 - 1.18) | 64 | 1.04 (0.97 - 1.11) | 59 | 1.10 (1.01 - 1.19) | 64 | 1.04 (0.97 - 1.12) |
| 4.51 to 14.66 ppb | 419 | 1.20 (0.98 - 1.47) | 418 | 1.06 (0.87 - 1.30) | 401 | 1.24 (1.00 - 1.54) | 405 | 1.09 (0.8 - 1.35) |
| 14.66 to 22.75 ppb | 309 | 0.86 (0.79 - 0.95) | 288 | 0.84 (0.78 - 0.92) | 298 | 0.92 (0.84 - 1.01) | 281 | 0.89 (0.81 - 0.97) |
| 22.75 to 29.7 ppb | 205 | 0.76 (0.65 - 0.88) | 181 | 0.82 (0.73 - 0.91) | 197 | 0.81 (0.69 - 0.95) | 176 | 0.86 (0.77 - 0.95) |
| 29.7 to 32.52 ppb | 37 | 0.87 (0.81 - 0.94) | 65 | 0.73 (0.61 - 0.87) | 37 | 0.90 (0.83 - 0.97) | 64 | 0.78 (0.65 - 0.94) |
| **$PM_{2.5}$ Satellite** | | | | | | | | |
| 3.3 to 5.3 µg/$m^3$ | 69 | 1.18 (0.93 - 1.33) | 80 | 0.99 (0.84 - 1.17) | 69 | 1.17 (0.98 - 1.40) | 79 | 1.03 (0.87 - 1.23) |
| 5.1 to 7.7 µg/$m^3$ | 373 | 1.09 (0.92 - 1.28) | 365 | 0.96 (0.82 - 1.13) | 363 | 1.15 (0.97 - 1.37) | 357 | 1.01 (0.86 - 1.20) |
| 7.7 to 9.8 µg/$m^3$ | 342 | 0.99 (0.91 - 1.07) | 313 | 0.94 (0.86 - 1.02) | 323 | 1.02 (0.93 - 1.11) | 303 | 0.97 (0.89 - 1.05) |
| 9.8 to 11.8 µg/$m^3$ | 193 | 0.93 (0.83 - 1.04) | 200 | 0.92 (0.82 - 1.02) | 188 | 0.95 (0.85 - 1.06) | 196 | 0.94 (0.84 - 1.05) |
| 11.8 to 15.1 µg/$m^3$ | 50 | 0.81 (0.61 - 1.07) | 47 | 0.84 (0.64 - 1.10) | 47 | 0.83 (0.63 - 1.10) | 45 | 0.86 (0.66 - 1.13) |
| **$PM_{2.5}$ Fused** | | | | | | | | |
| 5.6 to 8.0 µg/$m^3$ | 95 | 0.87 (0.75 - 1.00) | 91 | 0.98 (0.86 - 1.13) | 90 | 0.89 (0.76 - 1.03) | 88 | 1.02 (0.89 - 1.17) |
| 8.0 to 11.5 µg/$m^3$ | 425 | 0.88 (0.77 - 1.01 | 442 | 0.91 (0.78 - 1.07) | 405 | 0.91 (0.79 - 1.05) | 430 | 0.97 (0.82 - 1.14) |
| 11.5 to 13.3 µg/$m^3$ | 241 | 0.99 (0.95 - 1.04) | 248 | 0.92 (0.82 - 1.02) | 234 | 1.00 (0.96 - 1.05) | 242 | 0.94 (0.84 - 1.05) |
| 13.3 to 15.6 µg/$m^3$ | 152 | 1.04 (0.96 - 1.14) | 141 | 0.94 (0.87 - 1.02) | 149 | 1.06 (0.97 - 1.16) | 138 | 0.95 (0.88 - 1.03) |
| 15.6 to 19.2 µg/$m^3$ | 109 | 1.17 (0.94 - 1.46) | 89 | 0.80 (0.56 - 1.14) | 106 | 1.20 (0.96 - 1.51) | 88 | 0.83 (0.58 - 1.18) |

† Based on natural spline models with 2 degrees of freedom, unconditional logistic regression models without random effects. ‡ Cut points derived based on the range of concentrations for both cases and controls combined (1st, 10th, median, 75th, 90th, and 99th percentiles); the output represents the OR for each level as concentration changes from the lower percentile to the higher percentile.

**Appendix Table 3.** Distributions of total average concentrations of $NO_2$ fused surface for all forms of leukemia in Ontario, British Columbia, and Alberta and for chronic and acute myeloid leukemia cases in all provinces (except Quebec and New Brunswick), 1975 to 1994.

| **$NO_2$ Fused (ppb) (Exposed / total subjects)** | **Mean** | **Standard Deviation** | **Minimum** | **$25^{th}$ percentile** | **Median** | **$75^{th}$ percentile** | **Maximum** |
|---|---|---|---|---|---|---|---|
| Ontario | | | | | | | |
| Cases (404/412) | 18.2 | 7.3 | 2.2 | 12.3 | 18.8 | 23.8 | 34.1 |
| Controls (1869/1933) | 19.2 | 7.9 | 1.6 | 13.0 | 19.2 | 25.7 | 33.9 |
| British Columbia | | | | | | | |
| Cases (172/178) | 15.4 | 8.3 | 2.3 | 6.4 | 16.6 | 23.0 | 32.9 |
| Controls (861/870) | 15.9 | 8.5 | 0.4 | 6.7 | 18.2 | 23.6 | 30.7 |
| Alberta | | | | | | | |
| Cases (206/207) | 19.8 | 8.0 | 5.7 | 12.1 | 20.2 | 27.0 | 33.3 |
| Controls (613/618) | 19.8 | 8.2 | 1.5 | 12.2 | 20.7 | 26.6 | 33.1 |
| Chronic myeloid leukemia | | | | | | | |
| Cases (168/168) | 16.5 | 7.2 | 3.7 | 9.8 | 17.1 | 22.9 | 32.9 |
| Acute myeloid leukemia | | | | | | | |
| Cases (300/307) | 16.0 | 7.9 | 1.6 | 9.4 | 15.9 | 22.5 | 32.9 |

**Appendix Table 4.** Distributions of total average concentrations of $PM_{2.5}$ fused surface for all forms of leukemia in Ontario, British Columbia, and Alberta and for chronic and acute myeloid leukemia cases in all provinces (except Quebec and New Brunswick), 1975 to 1994.

| $PM_{2.5}$ Fused ($\mu g/m^3$) (Exposed / total subjects) | Mean | Standard Deviation | Minimum | 25th percentile | Median | 75th percentile | Maximum |
|---|---|---|---|---|---|---|---|
| Ontario | | | | | | | |
| Cases (404/412) | 11.3 | 2.6 | 4.2 | 9.9 | 11.2 | 12.6 | 20.3 |
| Controls (1869/1933) | 11.5 | 2.3 | 4.1 | 10.5 | 11.6 | 12.6 | 21.0 |
| British Columbia | | | | | | | |
| Cases (172/178) | 12.8 | 3.2 | 5.4 | 10.6 | 13.0 | 15.6 | 18.8 |
| Controls (860/870) | 12.9 | 3.2 | 4.1 | 10.8 | 13.4 | 15.5 | 19.6 |
| Alberta | | | | | | | |
| Cases (206/207) | 13.2 | 3.4 | 6.5 | 10.4 | 12.8 | 15.9 | 19.7 |
| Controls (613/618) | 12.6 | 3.2 | 4.5 | 10.4 | 11.9 | 14.9 | 24.2 |
| Chronic myeloid leukemia | | | | | | | |
| Cases (168/168) | 11.8 | 2.8 | 6.5 | 9.9 | 11.5 | 13.7 | 19.2 |
| Acute myeloid leukemia | | | | | | | |
| Cases (300/307) | 11.9 | 3.0 | 5.5 | 9.8 | 11.6 | 13.6 | 19.7 |

**Appendix Table 5. Associations between incidence of all forms of leukemia and $NO_2$ and $PM_{2.5}$ exposure for four pollutant surfaces in Ontario, Canada for total average exposure from 1975 to 1994 and for subjects with 20 years of exposure.**

| | Base model† | | Base model (20 years) | | Fully Adjusted Model | | Fully Adjusted Model (20 years) | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted for gender, five year age category, and reporting province | | | | Adjusted for gender, five year age category, reporting province, smoking status, exposure to radiation and benzene, education, body mass index, and income | | | |
| | 404 / 412 Cases | 1870 / 1933 Controls | 280 / 412 Cases | 1297 / 1933 Controls | 392 / 412 Cases | 1814 / 1933 controls | 274 / 412 Cases | 1256 / 1933 controls |
| **Pollution Surface (percentiles of exposure)‡** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** |
| **$NO_2$ Satellite** | | | | | | | | |
| 0.2 to 0.5 ppb | 38 | 1.17 (1.08 - 1.25) | 30 | 1.16 (1.06 - 1.27) | 37 | 1.17 (1.08 - 1.26) | 29 | 1.18 (1.08 - 1.30) |
| 0.5 to 2.3 ppb | 169 | 1.73 (1.29 - 2.33) | 118 | 1.63 (1.19 - 2.38) | 164 | 1.75 (1.28 - 2.39) | 15 | 1.82 (1.26 - 2.64) |
| 2.3 to 3.8 ppb | 122 | 0.68 (0.58 - 0.81) | 84 | 0.68 (0.57 - 0.82) | 119 | 0.69 (0.58 - 0.82) | 83 | 0.67 (0.43 - 0.71) |
| 3.8 to 4.7 ppb | 44 | 0.57 (0.46 - 0.69) | 28 | 0.58 (0.46 - 0.73) | 42 | 0.57 (0.46 - 0.71) | 28 | 0.56 (0.43 - 0.71) |
| 4.7 to 5 ppb | 11 | 0.79 (0.73 - 0.86) | 11 | 0.80 (0.73 - 0.88) | 11 | 0.80 (0.73 - 0.87) | 11 | 0.79 (0.71 - 0.87) |
| **$NO_2$ Fused** | | | | | | | | |
| 3 to 7.7 ppb | 41 | 1.25 (1.04 - 1.52) | 24 | 1.15 (0.96 - 1.38) | 41 | 1.22 (1.00 - 1.50) | 24 | 1.34 (1.05 - 1.70) |
| 7.7 to 19 ppb | 161 | 1.20 (0.92 - 1.57) | 116 | 1.04 (0.80 - 1.34) | 154 | 1.19 (0.86 - 1.59) | 112 | 1.32 (0.94 - 1.84) |
| 19 to 25.4 ppb | 131 | 1.20 (0.92 - 1.57) | 92 | 0.82 (0.72 - 0.93) | 127 | 1.19 (0.89 - 1.59) | 91 | 0.90 (0.76 - 1.07) |
| 25.4 to 28.8 ppb | 41 | 0.78 (0.69 - 0.88) | 29 | 0.79 (0.69 - 0.89) | 40 | 0.81 (0.71 - 0.92) | 28 | 0.77 (0.66 - 0.90) |
| 28.8 to 32.9 ppb | 21 | 0.71 (0.59 - 0.84) | 16 | 0.74 (0.60 - 0.86) | 21 | 0.74 (0.61 - 0.90) | 16 | 0.63 (0.55 - 0.86) |
| **$PM_{2.5}$ Satellite** | | | | | | | | |
| 4.0 to 7.2 $\mu g/m^3$ | 41 | 0.80 (0.58 - 1.12) | 34 | 0.74 (0.54 -1.02) | 40 | 0.86 (0.60 - 1.22) | 33 | 0.97 (0.63 - 1.47) |
| 7.2 to 10 $\mu g/m^3$ | 177 | 0.86 (0.73 - 1.02) | 117 | 0.81 (0.69 - 0.96) | 171 | 0.89 (0.74 - 1.07) | 114 | 0.94 (0.76 - 1.17) |
| 10 to 11.3 $\mu g/m^3$ | 100 | 0.95 (0.89 - 1.02) | 64 | 0.93 (0.87 - 0.99) | 98 | 0.96 (0.89 - 1.03) | 64 | 0.96 (0.88 - 1.04) |
| 11.3 to 12.1 $\mu g/m^3$ | 39 | 0.97 (0.92 - 1.03) | 29 | 0.96 (0.91 - 1.02) | 37 | 0.97 (0.92 - 1.03) | 27 | 0.97 (0.90 - 1.04) |
| 12.1 to 17.0 $\mu g/m^3$ | 41 | 0.92 (0.53 - 1.61) | 35 | 0.88 (0.51 - 1.53) | 40 | 0.90 (0.51 - 1.60) | 35 | 0.79 (0.39 - 1.60) |
| **$PM_{2.5}$ Fused** | | | | | | | | |
| 5.3 to 8.7 $\mu g/m^3$ | 47 | 0.65 (0.47 - 0.88) | 31 | 0.73 (0.51 - 1.05) | 46 | 0.67 (0.48 - 0.94) | 30 | 0.77 (0.52 - 1.14) |
| 8.7 to 11.6 $\mu g/m^3$ | 183 | 0.80 (0.68 - 0.94) | 129 | 0.83 (0.68 - 1.00) | 177 | 0.82 (0.69 - 0.98) | 126 | 0.86 (0.70 - 1.06) |
| 11.6 to 12.6 $\mu g/m^3$ | 70 | 0.97 (0.93 - 1.01) | 47 | 0.96 (0.91 - 1.01) | 68 | 0.98 (0.93 - 1.02) | 47 | 0.97 (0.92 - 1.03) |
| 12.6 to 13.7 $\mu g/m^3$ | 54 | 0.99 (0.94 - 1.05) | 33 | 0.97 (0.90 - 1.04) | 52 | 1.00 (0.94 - 1.06) | 31 | 0.98 (0.91 - 1.06) |
| 13.7 to 19.3 $\mu g/m^3$ | 43 | 1.35 (0.81 - 2.27) | 33 | 1.05 (0.56 - 1.98) | 42 | 1.36 (0.80 - 2.31) | 33 | 1.11 (0.58 - 2.11) |

† Based on natural spline models with 2 degrees of freedom, unconditional logistic regression models without random effects. ‡ Cut points derived based on the range of concentrations for both cases and controls combined (1st, 10th, median, 75th, 90th, and 99th percentiles); the output represents the OR for each level as concentration changes from the lower percentile to the higher percentile.

**Appendix Table 6. Associations between incidence of all forms of leukemia and $NO_2$ and $PM_{2.5}$ exposure for four pollutant surfaces in Ontario, Canada for total average exposure from 1975 to 1994 and for exposure at time of interview (1994).**

| | Base model† | | Base model (Interview) | | Fully Adjusted Model | | Fully Adjusted Model (Interview) | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted for gender, five year age category, and reporting province | | | | Adjusted for gender, five year age category, reporting province, smoking status, exposure to radiation and benzene, education, body mass index, and income | | | |
| | 404 / 412 Cases | 1870 / 1933 Controls | 397 / 412 Cases | 1845 / 1933 Controls | 392 / 412 Cases | 1814 / 1933 Controls | 385 / 412 Cases | 1789 / 1933 Controls |
| Pollution Surface (percentiles of exposure)‡ | Cases per category | Odds ratio (95% CI) | Cases per category | Odds ratio (95% CI) | Cases per category | Odds ratio (95% CI) | Cases per category | Odds ratio (95% CI) |
| **$NO_2$ Satellite** | | | | | | | | |
| 0.2 to 0.5 ppb | 38 | 1.17 (1.08 - 1.25) | 31 | 1.13 (1.05 - 1.21) | 37 | 1.17 (1.08 - 1.26) | 29 | 1.13 (1.04 - 1.22) |
| 0.5 to 2.3 ppb | 169 | 1.73 (1.29 - 2.33) | 123 | 1.49 (1.12 - 1.99) | 164 | 1.75 (1.28 - 2.39) | 117 | 1.51 (1.11 - 2.04) |
| 2.3 to 3.8 ppb | 122 | 0.68 (0.58 - 0.81) | 81 | 0.69 (0.59 - 0.80) | 119 | 0.69 (0.58 - 0.82) | 78 | 0.70 (0.59 - 0.83) |
| 3.8 to 4.7 ppb | 44 | 0.57 (0.46 - 0.69) | 28 | 0.61 (0.50 - 0.74) | 42 | 0.57 (0.46 - 0.71) | 28 | 0.61 (0.50 - 0.75) |
| 4.7 to 5 ppb | 11 | 0.79 (0.73 - 0.86) | 7 | 0.82 (0.76 - 0.88) | 11 | 0.80 (0.73 - 0.87) | 7 | 0.82 (0.76 - 0.89) |
| **$NO_2$ Fused** | | | | | | | | |
| 3 to 7.7 ppb | 41 | 1.25 (1.04 - 1.52) | 24 | 1.16 (0.95 - 1.40) | 41 | 1.22 (1.00 - 1.50) | 29 | 1.12 (0.92 - 1.13) |
| 7.7 to 19 ppb | 161 | 1.20 (0.92 - 1.57) | 116 | 1.04 (0.81 - 1.34) | 154 | 1.19 (0.86 - 1.59) | 126 | 1.01 (0.77 - 1.33) |
| 19 to 25.4 ppb | 131 | 1.20 (0.92 - 1.57) | 92 | 0.74 (0.64 - 0.86) | 127 | 1.19 (0.89 - 1.59) | 70 | 0.77 (0.66 - 0.89) |
| 25.4 to 28.8 ppb | 41 | 0.78 (0.69 - 0.88) | 29 | 0.81 (0.73 - 0.90) | 40 | 0.81 (0.71 - 0.92) | 29 | 0.83 (0.74 - 0.93) |
| 28.8 to 32.9 ppb | 21 | 0.71 (0.59 - 0.84) | 16 | 0.65 (0.52 - 0.82) | 21 | 0.74 (0.61 - 0.90) | 12 | 0.69 (0.54 - 0.87) |
| **$PM_{2.5}$ Satellite** | | | | | | | | |
| 4.0 to 7.2 µg/$m^3$ | 41 | 0.80 (0.58 - 1.12) | 40 | 0.74 (0.54 - 1.02) | 40 | 0.86 (0.60 - 1.22) | 38 | 0.78 (0.55 - 1.10) |
| 7.2 to 10 µg/$m^3$ | 177 | 0.86 (0.73 - 1.02) | 119 | 0.81 (0.69 - 0.96) | 171 | 0.89 (0.74 - 1.07) | 111 | 0.84 (0.70 - 1.00) |
| 10 to 11.3 µg/$m^3$ | 100 | 0.95 (0.89 - 1.02) | 60 | 0.93 (0.88 - 1.00) | 98 | 0.96 (0.89 - 1.03) | 60 | 0.94 (0.87 - 1.01) |
| 11.3 to 12.1 µg/$m^3$ | 39 | 0.97 (0.92 - 1.03) | 24 | 0.96 (0.91 - 1.02) | 37 | 0.97 (0.92 - 1.03) | 22 | 0.97 (0.91 - 1.02) |
| 12.1 to 17.0 µg/$m^3$ | 41 | 0.92 (0.53 - 1.61) | 37 | 0.87 (0.44 - 1.73) | 40 | 0.90 (0.51 - 1.60) | 37 | 0.88 (0.43 - 1.76) |
| **$PM_{2.5}$ Fused** | | | | | | | | |
| 5.3 to 8.7 µg/$m^3$ | 47 | 0.65 (0.47 - 0.88) | 33 | 0.65 (0.49 - 0.86) | 46 | 0.67 (0.48 - 0.94) | 31 | 0.68 90.50 - 0.92) |
| 8.7 to 11.6 µg/$m^3$ | 183 | 0.80 (0.68 - 0.94) | 141 | 0.71 (0.59 - 0.86) | 177 | 0.82 (0.69 - 0.98) | 133 | 0.74 (0.60 - 0.91) |
| 11.6 to 12.6 µg/$m^3$ | 70 | 0.97 (0.93 - 1.01) | 37 | 0.96 (0.92 - 0.99) | 68 | 0.98 (0.93 - 1.02) | 36 | 0.96 (0.92 - 1.00) |
| 12.6 to 13.7 µg/$m^3$ | 54 | 0.99 (0.94 - 1.05) | 37 | 0.97 (0.91 - 1.03) | 52 | 1.00 (0.94 - 1.06) | 36 | 0.97 (0.91 - 1.03) |
| 13.7 to 19.3 µg/$m^3$ | 43 | 1.35 (0.81 - 2.27) | 31 | 1.12 (0.61 - 2.04) | 42 | 1.36 (0.80 - 2.31) | 31 | 1.09 (0.58 - 2.03) |

† Based on natural spline models with 2 degrees of freedom, unconditional logistic regression models without random effects. ‡ Cut points derived based on the range of concentrations for both cases and controls combined (1st, 10th, median, 75th, 90th, and 99th percentiles); the output represents the OR for each level as concentration changes from the lower percentile to the higher percentile.

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**Appendix Table 7. Associations between incidence of all forms of leukemia and $NO_2$ and $PM_{2.5}$ exposure for four pollutant surfaces in Alberta Canada for total average exposure from 1975 to 1994 and for subjects with 20 years of exposure.**

| | Base model† | | Base model (20 years) | | Fully Adjusted Model | | Fully Adjusted Model (20 years) | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted for gender, five year age category, and reporting province | | | | Adjusted for gender, five year age category, reporting province, smoking status, exposure to radiation and benzene, education, body mass index, and income | | | |
| | 206/ 207 cases | 613/ 618 controls | 141 / 207 cases | 411 / 618 controls | 205 / 207 cases | 605 / 618 controls | 141 / 207 cases | 408 / 618 controls |
| **Pollution Surface (percentiles of exposure)‡** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** |
| **$NO_2$ Satellite** | | | | | | | | |
| 0.3 to 0.5 ppb | 14 | 1.03 (0.89 - 1.18) | 15 | 1.05 (0.81 - 1.36) | 14 | 1.04 (0.89 - 1.20) | 15 | 1.07 (0.81 - 1.42) |
| 0.5 to 1.3 ppb | 89 | 1.06 (0.71 - 1.59) | 55 | 1.05 (0.68 - 1.64) | 89 | 1.10 (0.72 - 1.68) | 55 | 1.10 (0.68 - 1.77) |
| 1.3 to 1.9 ppb | 59 | 0.93 (0.80 - 1.09) | 36 | 0.92 (0.77 - 1.09) | 58 | 0.96 (0.82 - 1.13) | 36 | 0.94 (0.78 - 1.13) |
| 1.9 to 2.4 ppb | 20 | 0.88 (0.68 - 1.15) | 19 | 0.83 (0.57 - 1.19) | 19 | 0.91 (0.69 - 1.19) | 19 | 0.83 (0.56 - 1.22) |
| 2.4 to 2.6 ppb | 20 | 0.94 (0.81 - 1.08) | 15 | 0.92 (0.78 - 1.09) | 20 | 0.95 (0.82 - 1.10) | 15 | 0.92 (0.77 - 1.10) |
| **$NO_2$ Fused** | | | | | | | | |
| 5.5 to 8.8 ppb | 19 | 1.04 (0.85 - 1.29) | 17 | 1.09 (0.89 - 1.32) | 19 | 1.03 (0.83 - 1.28) | 17 | 1.06 (0.84 - 1.34) |
| 8.8 to 20.5 ppb | 85 | 1.09 (0.74 - 1.59) | 58 | 1.12 (0.75 - 1.69) | 85 | 1.06 (0.71 - 1.58) | 58 | 1.12 (0.67 - 1.88) |
| 20.5 to 26.7 ppb | 50 | 0.94 (0.76 - 1.17) | 28 | 0.95 (0.86 - 1.04) | 50 | 0.99 (0.79 - 1.25) | 28 | 0.98 (0.87 - 1.11) |
| 26.7 to 30.6 ppb | 32 | 0.94 (0.75 - 1.16) | 21 | 0.94 (0.85 - 1.04) | 30 | 0.98 (0.78 - 1.23) | 21 | 0.97 (0.87 - 1.09) |
| 30.6 to 32.3 ppb | 14 | 0.97 (0.87 - 1.07) | 12 | 0.97 (0.92 - 1.01) | 14 | 0.99 (0.89 - 1.10) | 12 | 0.98 (0.93 - 1.04) |
| **$PM_{2.5}$ Satellite** | | | | | | | | |
| 4.0 to 6.1 $\mu g/m^3$ | 20 | 0.87 (0.54 - 1.40) | 18 | 0.69 (0.39 - 1.23) | 20 | 0.82 (0.50 - 1.37) | 18 | 0.64 (0.34 - 1.19) |
| 6.1 to 9.0 $\mu g/m^3$ | 76 | 1.04 (0.77 - 1.41) | 47 | 0.92 (0.65 - 1.31) | 75 | 1.08 (0.77 - 1.51) | 47 | 0.92 (0.62 - 1.36) |
| 9.0 to 10.0 $\mu g/m^3$ | 83 | 1.11 (0.93 - 1.31) | 55 | 1.15 (0.92 - 1.44) | 82 | 1.17 (0.97 - 1.41) | 55 | 1.20 (0.94 - 1.51) |
| 10.0 to 10.7 $\mu g/m^3$ | 18 | 1.07 (0.93 - 1.31) | 13 | 1.15 (0.93 - 1.42) | 18 | 1.16 (0.97 - 1.39) | 13 | 1.20 (0.96 - 1.49) |
| 10.7 to 11.5 $\mu g/m^3$ | 5 | 1.14 (0.90 - 1.45) | 5 | 1.21 (0.92 - 1.60) | 5 | 1.23 (0.96 - 1.57) | 5 | 1.27 (0.95 - 1.71) |
| **$PM_{2.5}$ Fused** | | | | | | | | |
| 6.8 to 8.8 $\mu g/m^3$ | 19 | 1.02 (0.75 - 1.38) | 14 | 0.91 (0.70 - 1.18) | 19 | 1.01 (0.73 - 1.38) | 14 | 0.87 (0.66 - 1.15) |
| 8.8 to 12.2 $\mu g/m^3$ | 71 | 1.10 (0.78 - 1.53) | 46 | 0.88 (0.60 - 1.30) | 70 | 1.09 (0.77 - 1.56) | 46 | 0.82 (0.54 - 1.24) |
| 12.2 to 15.2 $\mu g/m^3$ | 53 | 1.18 (1.01 - 1.37) | 35 | 0.92 (0.60 - 1.41) | 53 | 1.21 (1.03 - 1.47) | 35 | 0.87 (0.55 - 1.38) |
| 15.2 to 17.6 $\mu g/m^3$ | 43 | 1.19 (0.95 - 1.50) | 31 | 1.03 (0.95 - 1.12) | 42 | 1.25 (0.98 - 1.58) | 31 | 1.05 (0.95 - 1.15) |
| 17.6 to 19.7 $\mu g/m^3$ | 13 | 1.20 (0.91 - 1.58) | 8 | 1.09 (0.97 - 1.22) | 13 | 1.25 (0.94 - 1.67) | 8 | 1.13 (1.00 - 1.28) |

† Based on natural spline models with 2 degrees of freedom, unconditional logistic regression models without random effects. ‡ Cut points derived based on the range of concentrations for both cases and controls combined (1st, 10th, median, 75th, 90th, and 99th percentiles); the output represents the OR for each level as concentration changes from the lower percentile to the higher percentile.

**Appendix Table 8. Associations between incidence of all forms of leukemia and $NO_2$ and $PM_{2.5}$ exposure for four pollutant surfaces in Alberta, Canada for total average exposure from 1975 to 1994 and for exposure at time of interview.**

| | Base model† | | Base model (Interview) | | Fully Adjusted Model | | Fully Adjusted Model (Interview) | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted for gender, five year age category, and reporting province | | | | Adjusted for gender, five year age category, reporting province, smoking status, exposure to radiation and benzene, education, body mass index, and income | | | |
| | 206/ 207 cases | 613/ 618 controls | 202 / 207 cases | 601 / 618 controls | 205 / 207 cases | 605 / 618 controls | 201 / 207 cases | 593 / 618 controls |
| **Pollution Surface (percentiles of exposure)‡** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** |
| **$NO_2$ Satellite** | | | | | | | | |
| 0.3 to 0.5 ppb | 14 | 1.03 (0.89 - 1.18) | 7 | 1.05 (0.90 - 1.22) | 14 | 1.04 (0.89 - 1.20) | 7 | 1.06 (0.90 - 1.23) |
| 0.5 to 1.3 ppb | 89 | 1.06 (0.71 - 1.59) | 70 | 1.10 (0.72 - 1.69) | 89 | 1.10 (0.72 - 1.68) | 70 | 1.13 (0.72 - 1.77) |
| 1.3 to 1.9 ppb | 59 | 0.93 (0.80 - 1.09) | 34 | 0.89 (0.77 - 1.04) | 58 | 0.96 (0.82 - 1.13) | 34 | 0.92 (0.78 - 1.08) |
| 1.9 to 2.4 ppb | 20 | 0.88 (0.68 - 1.15) | 10 | 0.81 (0.61 - 1.08) | 19 | 0.91 (0.69 - 1.19) | 10 | 0.84 (0.62 - 1.12) |
| 2.4 to 2.6 ppb | 20 | 0.94 (0.81 - 1.08) | 18 | 0.90 (0.78 - 1.04) | 20 | 0.95 (0.82 - 1.10) | 18 | 0.91 (0.78 - 1.06 |
| **$NO_2$ Fused** | | | | | | | | |
| 5.5 to 8.8 ppb | 19 | 1.04 (0.85 - 1.29) | 17 | 1.10 (0.88 - 1.36) | 19 | 1.03 (0.83 - 1.28) | 17 | 1.07 (0.85 - 1.34) |
| 8.8 to 20.5 ppb | 85 | 1.09 (0.74 - 1.59) | 61 | 1.11 (0.73 - 1.69) | 85 | 1.06 (0.71 - 1.58) | 61 | 1.11 (0.71 - 1.74) |
| 20.5 to 26.7 ppb | 50 | 0.94 (0.76 - 1.17) | 28 | 0.86 (0.68 - 1.09) | 50 | 0.99 (0.79 - 1.25) | 28 | 0.92 (0.72 - 1.19) |
| 26.7 to 30.6 ppb | 32 | 0.94 (0.75 - 1.16) | 17 | 0.89 (0.73 - 1.08) | 30 | 0.98 (0.78 - 1.23) | 17 | 0.93 (0.76 - 1.14) |
| 30.6 to 32.3 ppb | 14 | 0.97 (0.87 - 1.07) | 11 | 0.95 (0.87 - 1.03) | 14 | 0.99 (0.89 - 1.10) | 11 | 0.97 (0.89 - 1.06) |
| **$PM_{2.5}$ Satellite** | | | | | | | | |
| 4.0 to 6.1 $\mu g/m^3$ | 20 | 0.87 (0.54 - 1.40) | 16 | 0.79 (0.46 - 1.34) | 20 | 0.82 (0.50 - 1.37) | 15 | 0.82 (0.46 - 1.45) |
| 6.1 to 9.0 $\mu g/m^3$ | 76 | 1.04 (0.77 - 1.41) | 47 | 1.06 (0.76 - 1.48) | 75 | 1.08 (0.77 - 1.51) | 47 | 1.16 (0.80 - 1.68) |
| 9.0 to 10.0 $\mu g/m^3$ | 83 | 1.11 (0.93 - 1.31) | 53 | 1.19 (0.99 - 1.43) | 82 | 1.17 (0.97 - 1.41) | 53 | 1.24 (1.02 - 1.51) |
| 10.0 to 10.7 $\mu g/m^3$ | 18 | 1.07 (0.93 - 1.31) | 16 | 1.18 (0.98 - 1.40) | 18 | 1.16 (0.97 - 1.39) | 16 | 1.21 (1.01 - 1.46) |
| 10.7 to 11.5 $\mu g/m^3$ | 5 | 1.14 (0.90 - 1.45) | 6 | 1.24 (0.98 - 1.57) | 5 | 1.23 (0.96 - 1.57) | 6 | 1.29 (1.01 - 1.65) |
| **$PM_{2.5}$ Fused** | | | | | | | | |
| 6.8 to 8.8 $\mu g/m^3$ | 19 | 1.02 (0.75 - 1.38) | 15 | 0.87 (0.67 - 1.13) | 19 | 1.01 (0.73 - 1.38) | 15 | 0.88 (0.66 - 1.15) |
| 8.8 to 12.2 $\mu g/m^3$ | 71 | 1.10 (0.78 - 1.53) | 43 | 0.90 (0.66 - 1.22) | 70 | 1.09 (0.77 - 1.56) | 43 | 0.91 (0.65 - 1.26) |
| 12.2 to 15.2 $\mu g/m^3$ | 53 | 1.18 (1.01 - 1.37) | 40 | 1.33 (1.08 - 1.64) | 53 | 1.21 (1.03 - 1.47) | 40 | 1.40 (1.11 - 1.76) |
| 15.2 to 17.6 $\mu g/m^3$ | 43 | 1.19 (0.95 - 1.50) | 22 | 1.28 (1.06 - 1.55) | 42 | 1.25 (0.98 - 1.58) | 22 | 1.32 (1.08 - 1.61) |
| 17.6 to 19.7 $\mu g/m^3$ | 13 | 1.20 (0.91 - 1.58) | 11 | 1.39 (1.07 - 1.80) | 13 | 1.25 (0.94 - 1.67) | 11 | 1.44 (1.09 - 1.89) |

† Based on natural spline models with 2 degrees of freedom, unconditional logistic regression models without random effects. ‡ Cut points derived based on the range of concentrations for both cases and controls combined (1st, 10th, median, 75th, 90th, and 99th percentiles); the output represents the OR for each level as concentration changes from the lower percentile to the higher percentile.

**Appendix Table 9. Associations between incidence of all forms of leukemia and $NO_2$ and $PM_{2.5}$ exposure for four pollutant surfaces in BC, Canada for total average exposure from 1975 to 1994 and for subjects with 20 years of exposure.**

| | Base model† | | Base model (20 years) | | Fully Adjusted Model | | Fully Adjusted Model (20 years) | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted for gender, five year age category, and reporting province | | | | Adjusted for gender, five year age category, reporting province, smoking status, exposure to radiation and benzene, education, body mass index, and income | | | |
| | 172 /178 cases | 861 / 869 controls | 105 / 178 cases | 524 / 869 controls | 171 / 178 cases | 830 / 869 controls | 104 /178 cases | 509 / 869 controls |
| **Pollution Surface (percentiles of exposure)‡** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** |
| **$NO_2$ Satellite** | | | | | | | | |
| 0.1 to 0.3 ppb | 12 | 0.91 (0.82 - 1.01) | 8 | 1.03 (0.87 - 1.23) | 12 | 0.95 (0.85 - 1.07) | 8 | 1.20 (0.95 - 1.51) |
| 0.3 to 0.9 ppb | 76 | 0.77 (0.56 - 1.07) | 44 | 1.08 (0.72 - 1.60) | 75 | 0.91 (0.64 - 1.30) | 43 | 1.54 (0.91 - 2.62) |
| 0.9 to 1.5 ppb | 47 | 1.01 (0.89 - 1.15) | 30 | 0.97 (0.78 - 1.19) | 47 | 1.08 (0.94 - 1.24) | 30 | 1.09 (0.85 - 1.40) |
| 1.5 to 1.9 ppb | 12 | 1.08 (0.96 - 1.21) | 9 | 0.97 (0.69 - 1.22) | 12 | 1.10 (0.98 - 1.24) | 9 | 0.87 (0.59 - 1.28) |
| 1.9 to 2.2 ppb | 16 | 1.12 (0.96 - 1.32) | 10 | 0.91 (0.67 - 1.23) | 16 | 1.14 (0.97 - 1.34) | 10 | 0.83 (0.55 - 1.25) |
| **$NO_2$ Fused** | | | | | | | | |
| 1.5 to 4.5 ppb | 17 | 1.10 (0.90 - 1.34) | 9 | 0.99 (0.78 - 1.26) | 17 | 1.17 (0.94 - 1.44) | 9 | 1.25 (0.92 - 1.69) |
| 4.5 to 16.5 ppb | 77 | 1.13 (0.71 - 1.78) | 44 | 0.82 (0.55 - 1.21) | 76 | 1.37 (0.82 - 2.30) | 43 | 1.75 (0.85 - 3.61) |
| 16.5 to 24.1 ppb | 38 | 0.79 (0.60 - 1.04) | 23 | 0.67 (0.55 - 1.21) | 38 | 0.81 (0.65 - 1.06) | 23 | 0.86 (0.53 - 1.40) |
| 24.1 to 25.6 ppb | 33 | 0.83 (0.66 - 1.04) | 18 | 0.90 (0.72 - 1.13) | 33 | 0.83 (0.65 - 1.06) | 18 | 0.93 (0.81 - 1.08) |
| 25.6 to 28.6 ppb | 5 | 0.86 (0.71 - 1.03) | 10 | 0.81 (0.50 - 1.32) | 5 | 0.86 (0.71 - 1.04) | 10 | 0.86 (0.62 - 1.19) |
| **$PM_{2.5}$ Satellite** | | | | | | | | |
| 2.6 to 3.8 $\mu g/m^3$ | 11 | 0.96 (0.70 - 1.33) | 4 | 1.36 (0.88 - 2.10) | 10 | 1.11 (0.79 - 1.55) | 3 | 1.65 (0.99 - 2.75) |
| 3.8 to 6.2 $\mu g/m^3$ | 64 | 1.24 (0.83 - 1.84) | 50 | 1.57 (0.89 - 2.77) | 64 | 1.48 (0.97 - 2.26) | 50 | 2.01 (1.05 - 3.85) |
| 6.2 to 6.7 $\mu g/m^3$ | 43 | 1.13 (1.05 - 1.22) | 28 | 1.03 (0.91 - 1.15) | 43 | 1.14 (1.05 - 1.23) | 28 | 1.03 (0.90 - 1.18) |
| 6.7 to 7.16 $\mu g/m^3$ | 28 | 1.15 (1.05 - 1.25) | 11 | 1.00 (0.86 - 1.15) | 28 | 1.14 (1.05 - 1.25) | 11 | 0.98 (0.82 - 1.17) |
| 7.16 to 8.8 $\mu g/m^3$ | 19 | 1.97 (1.24 - 3.13) | 9 | 0.85 (0.39 - 1.88) | 19 | 1.82 (1.15 - 2.89) | 9 | 0.71 (0.27 - 1.86) |
| **$PM_{2.5}$ Fused** | | | | | | | | |
| 5.4 to 7.9 $\mu g/m^3$ | 15 | 1.02 (0.71 - 1.47) | 7 | 1.27 (0.78 - 2.06) | 14 | 1.12 (0.76 - 1.65) | 6 | 1.48 (0.86 - 2.56) |
| 7.9 to 13.2 $\mu g/m^3$ | 76 | 0.95 (0.64 - 1.41) | 46 | 1.46 (0.68 - 3.10) | 76 | 1.11 (0.72 - 1.70) | 46 | 1.91 (0.81 - 4.48) |
| 13.2 to 15.5 $\mu g/m^3$ | 35 | 0.91 (0.74 - 1.13) | 22 | 0.94 (0.72 - 1.21) | 35 | 0.95 (0.76 - 1.19) | 22 | 0.99 (0.81 - 1.14) |
| 15.5 to 16.4 $\mu g/m^3$ | 27 | 0.95 (0.84 - 1.08) | 16 | 0.95 (0.81 - 1.10) | 27 | 0.96 (0.85 - 1.09) | 16 | 0.96 (0.81 - 1.14) |
| 16.4 to 18.3 $\mu g/m^3$ | 17 | 0.90 (0.66 - 1.21) | 13 | 0.87 (0.60 - 1.27) | 17 | 0.92 (0.67 - 1.25) | 13 | 0.89 (0.59 - 1.53) |

† Based on natural spline models with 2 degrees of freedom, unconditional logistic regression models without random effects. ‡ Cut points derived based on the range of concentrations for both cases and controls combined (1st, 10th, median, 75th, 90th, and 99th percentiles); the output represents the OR for each level as concentration changes from the lower percentile to the higher percentile.

**Appendix Table 10. Associations between incidence of all forms of leukemia and $NO_2$ and $PM_{2.5}$ exposure for four pollutant surfaces in BC, Canada for total average exposure from 1975 to 1994 and for exposure at time of interview.**

| | Base model† | | Base model (Interview) | | Fully Adjusted Model | | Fully Adjusted Model (Interview) | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted for gender, five year age category, and reporting province | | | | Adjusted for gender, five year age category, reporting province, smoking status, exposure to radiation and benzene, education, body mass index, and income | | | |
| | 172 /178 cases | 861 / 869 controls | 170 / 178 cases | 830 / 869 controls | 171 / 178 cases | 830 / 869 controls | 169 /178 cases | 800 / 869 controls |
| **Pollution Surface (percentiles of exposure)‡** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** |
| **$NO_2$ Satellite** | | | | | | | | |
| 0.1 to 0.3 ppb | 12 | 0.91 (0.82 - 1.01) | 19 | 0.88 (0.78 - 1.00) | 12 | 0.95 (0.85 - 1.07) | 19 | 0.92 (0.81 - 1.05) |
| 0.3 to 0.9 ppb | 76 | 0.77 (0.56 - 1.07) | 36 | 0.69 (0.49 - 0.98) | 75 | 0.91 (0.64 - 1.30) | 35 | 0.80 (0.55 - 1.17) |
| 0.9 to 1.5 ppb | 47 | 1.01 (0.89 - 1.15) | 25 | 0.94 (0.81 - 1.08) | 47 | 1.08 (0.94 - 1.24) | 25 | 1.00 (0.86 - 1.16) |
| 1.5 to 1.9 ppb | 12 | 1.08 (0.96 - 1.21) | 10 | 1.02 (0.88 - 1.18) | 12 | 1.10 (0.98 - 1.24) | 10 | 1.05 (0.90 - 1.22) |
| 1.9 to 2.2 ppb | 16 | 1.12 (0.96 - 1.32) | 15 | 1.06 (0.87 - 1.30) | 16 | 1.14 (0.97 - 1.34) | 15 | 1.08 (0.88 - 1.33) |
| **$NO_2$ Fused** | | | | | | | | |
| 1.5 to 4.5 ppb | 17 | 1.10 (0.90 - 1.34) | 11 | 0.98 (0.78 - 1.25) | 17 | 1.17 (0.94 - 1.44) | 11 | 0.99 (0.76 - 1.27) |
| 4.5 to 16.5 ppb | 77 | 1.13 (0.71 - 1.78) | 46 | 0.73 (0.52 - 1.02) | 76 | 1.37 (0.82 - 2.30) | 45 | 0.87 (0.59 - 1.27) |
| 16.5 to 24.1 ppb | 38 | 0.79 (0.60 - 1.04) | 26 | 0.73 (0.36 - 1.46) | 38 | 0.81 (0.65 - 1.06) | 26 | 0.88 (0.43 - 1.81) |
| 24.1 to 25.6 ppb | 33 | 0.83 (0.66 - 1.04) | 18 | 0.82 (0.52 - 1.31) | 33 | 0.83 (0.65 - 1.06) | 18 | 0.93 (0.57 - 1.49) |
| 25.6 to 28.6 ppb | 5 | 0.86 (0.71 - 1.03) | 1 | 0.87 (0.62 - 1.22) | 5 | 0.86 (0.71 - 1.04) | 1 | 0.94 (0.66 - 1.34) |
| **$PM_{2.5}$ Satellite** | | | | | | | | |
| 2.6 to 3.8 $\mu g/m^3$ | 11 | 0.96 (0.70 - 1.33) | 8 | 0.91 (0.67 - 1.24) | 10 | 1.11 (0.79 - 1.55) | 7 | 1.04 (0.74 - 1.45) |
| 3.8 to 6.2 $\mu g/m^3$ | 64 | 1.24 (0.83 - 1.84) | 39 | 0.98 (0.70 - 1.39) | 64 | 1.48 (0.97 - 2.26) | 39 | 1.13 (0.78 - 1.63) |
| 6.2 to 6.7 $\mu g/m^3$ | 43 | 1.13 (1.05 - 1.22) | 32 | 1.04 (0.95 - 1.14) | 43 | 1.14 (1.05 - 1.23) | 32 | 1.03 (0.94 - 1.14) |
| 6.7 to 7.16 $\mu g/m^3$ | 28 | 1.15 (1.05 - 1.25) | 19 | 1.05 (0.94 - 1.17) | 28 | 1.14 (1.05 - 1.25) | 19 | 1.03 (0.92 - 1.16) |
| 7.16 to 8.8 $\mu g/m^3$ | 19 | 1.97 (1.24 - 3.13) | 7 | 1.32 (0.74 - 2.33) | 19 | 1.82 (1.15 - 2.89) | 7 | 1.17 (0.64 - 2.13) |
| **$PM_{2.5}$ Fused** | | | | | | | | |
| 5.4 to 7.9 $\mu g/m^3$ | 15 | 1.02 (0.71 - 1.47) | 7 | 1.22 (0.89 - 1.69) | 14 | 1.12 (0.76 - 1.65) | 6 | 1.32 (0.94 - 1.85) |
| 7.9 to 13.2 $\mu g/m^3$ | 76 | 0.95 (0.64 - 1.41) | 47 | 1.12 (0.72 - 1.72) | 76 | 1.11 (0.72 - 1.70) | 47 | 1.32 (0.83 - 2.09) |
| 13.2 to 15.5 $\mu g/m^3$ | 35 | 0.91 (0.74 - 1.13) | 17 | 0.82 (0.67 - 0.99) | 35 | 0.95 (0.76 - 1.19) | 17 | 0.85 (0.69 - 1.04) |
| 15.5 to 16.4 $\mu g/m^3$ | 27 | 0.95 (0.84 - 1.08) | 25 | 0.84 (0.72 - 0.99) | 27 | 0.96 (0.85 - 1.09) | 25 | 0.86 (0.73 - 1.02) |
| 16.4 to 18.3 $\mu g/m^3$ | 17 | 0.90 (0.66 - 1.21) | 5 | 0.81 (0.66 - 0.99) | 17 | 0.92 (0.67 - 1.25) | 5 | 0.83 (0.67 - 1.03) |

† Based on natural spline models with 2 degrees of freedom, unconditional logistic regression models without random effects. ‡ Cut points derived based on the range of concentrations for both cases and controls combined (1st, 10th, median, 75th, 90th, and 99th percentiles); the output represents the OR for each level as concentration changes from the lower percentile to the higher percentile.

**Appendix Table 11. Associations between incidence of acute myeloid leukemia (AML) and $NO_2$ and $PM_{2.5}$ exposure for four pollutant surfaces in all provinces in Canada (except New Brunswick and Quebec) for total average exposure from 1975 to 1994 and for subjects with 20 years of exposure.**

| | Base Model† | | Base Model (20 years) | | Fully Adjusted Model | | Fully Adjusted Model (20 years) | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted for gender, five year age category, and reporting province | | | | Adjusted for gender, five year age category, reporting province, smoking status, exposure to radiation and benzene, education, body mass index, and income | | | |
| | 300/307 Cases | 4923/5029 Controls | 192/307 Cases | 3504 / 5029 Controls | 292/307 Cases | 4780/5029 Controls | 188/307 Cases | 3414/5029 Controls |
| **Pollution Surface (percentiles of exposure)‡** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** |
| **$NO_2$ Satellite** | | | | | | | | |
| 0.05 to 0.15 ppb | 20 | 1.12 (1.04 - 1.21) | 3 | 1.08 (0.99 - 1.17) | 19 | 1.12 (1.04 - 1.21) | 3 | 1.10 (1.01 - 1.20) |
| 0.15 to 0.49 ppb | 98 | 1.36 (1.11 - 1.66) | 56 | 1.24 (0.98 - 1.58) | 95 | 1.37 (1.12 - 1.69) | 54 | 1.31 (1.02 - 1.69) |
| 0.49 to 1.11 ppb | 107 | 1.27 (1.02 - 1.57) | 55 | 1.16 (0.90 - 1.51) | 105 | 1.30 (1.04 - 1.63) | 55 | 1.25 (0.94 - 1.65) |
| 1.11 to 2.06 ppb | 51 | 0.64 (0.47 - 0.87) | 42 | 0.65 (0.45 - 0.93) | 49 | 0.67 (0.49 - 0.92) | 40 | 0.67 (0.45 - 0.98) |
| 2.06 to 2.66 ppb | 17 | 0.57 (0.41 - 0.78) | 6 | 0.56 (0.36 - 0.87) | 17 | 0.58 (0.42 - 0.82) | 6 | 0.55 (0.35 - 0.87) |
| **$NO_2$ Fused** | | | | | | | | |
| 0.9 to 2.7 ppb | 13 | 1.22 (1.06 - 1.39) | 5 | 1.16 (1.01 - 1.33) | 13 | 1.23 (1.06 - 1.42) | 5 | 1.20 (1.00 - 1.45) |
| 2.7 to 8.8 ppb | 115 | 1.67 (1.15 - 2.43) | 48 | 1.39 (0.98 - 1.97) | 110 | 1.76 (1.17 - 2.63) | 47 | 1.60 (0.98 - 2.60) |
| 8.8 to 12.8 ppb | 97 | 0.87 (0.74 - 1.02) | 23 | 0.62 (0.42 - 0.91) | 94 | 0.94 (0.69 - 0.98) | 21 | 0.75 (0.48 - 1.16) |
| 12.8 to 15.8 ppb | 42 | 0.78 (0.66 - 0.92) | 25 | 0.86 (0.77 - 0.96) | 42 | 0.82 (0.69 - 0.98) | 25 | 0.88 (0.78 - 1.00) |
| 15.8 to 17.4 ppb | 29 | 0.69 (0.55 - 0.88) | 17 | 0.85 (0.76 - 0.96) | 29 | 0.74 (0.58 - 0.95) | 17 | 0.88 (0.77 - 1.00) |
| **$PM_{2.5}$ Satellite** | | | | | | | | |
| 3.2 to 5.3 µg/m$^3$ | 31 | 1.14 (0.82 - 1.56) | 21 | 0.95 (0.78 - 1.15) | 29 | 1.21 (0.86 - 1.68) | 21 | 1.08 (0.83 - 1.40) |
| 5.3 to 8.1 µg/m$^3$ | 117 | 1.17 (0.87 - 1.58) | 72 | 0.94 (0.71 - 1.25) | 114 | 1.26 (0.92 - 1.72) | 69 | 1.17 (0.80 - 1.73) |
| 8.1 to 9.8 µg/m$^3$ | 70 | 1.08 (0.97 - 1.22) | 59 | 1.01 (0.88 - 1.17) | 69 | 1.13 (1.00 - 1.28) | 59 | 1.15 (0.95 - 1.39) |
| 9.8 to 11.5 µg/m$^3$ | 44 | 1.08 (0.95 - 1.24) | 13 | 1.07 (0.90 - 1.27) | 44 | 1.12 (0.98 - 1.29) | 13 | 1.15 (0.93 - 1.43) |
| 11.5 to 15.6 µg/m$^3$ | 33 | 1.18 (0.76 - 1.84) | 25 | 1.20 (0.80 - 1.79) | 31 | 1.26 (0.80 - 1.99) | 24 | 1.25 (0.76 - 2.08) |
| **$PM_{2.5}$ Fused** | | | | | | | | |
| 5.6 to 8.0 µg/m$^3$ | 26 | 0.92 (0.71 - 1.20) | 33 | 0.88 (0.65 - 1.18) | 23 | 0.98 (0.74 - 1.29) | 31 | 0.94 (0.68 - 1.30) |
| 8.0 to 11.7 µg/m$^3$ | 133 | 0.98 (0.76 - 1.27) | 74 | 0.92 (0.66 - 1.29) | 131 | 1.06 (0.81 - 1.40) | 73 | 1.02 (0.71 - 1.47) |
| 11.7 to 13.6 µg/m$^3$ | 67 | 1.06 (0.98 - 1.15) | 24 | 1.05 (0.96 - 1.16) | 66 | 1.10 (1.01 - 1.19) | 24 | 1.09 (0.99 - 1.21) |
| 13.6 to 15.9 µg/m$^3$ | 38 | 1.15 (0.99 - 1.33) | 33 | 1.32 (0.97 - 1.80) | 37 | 1.18 (1.01 - 1.38) | 32 | 1.40 (1.01 - 1.93) |
| 15.9 to 19.1 µg/m$^3$ | 29 | 1.32 (0.96 - 1.82) | 23 | 1.27 (0.96 - 1.68) | 28 | 1.36 (0.97 - 1.90) | 23 | 1.31 (0.97 - 1.75) |

† Based on natural spline models with 2 degrees of freedom, unconditional logistic regression models without random effects. ‡ Cut points derived based on the range of concentrations for both cases and controls combined (1st, 10th, median, 75th, 90th, and 99th percentiles); the output represents the OR for each level as concentration changes from the lower percentile to the higher percentile.

**Appendix Table 12. Associations between incidence of acute myeloid leukemia (AML) and $NO_2$ and $PM_{2.5}$ exposure for four pollutant surfaces in all provinces in Canada (except New Brunswick and Quebec) for total average exposure from 1975 to 1994 and for exposure at time of interview.**

| | Base Model† | | Base model (Interview) | | Fully Adjusted Model | | Fully Adjusted Model (Interview) | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted for gender, five year age category, and reporting province | | | | Adjusted for gender, five year age category, reporting province, smoking status, exposure to radiation and benzene, education, body mass index, and income | | | |
| | 300/307 Cases | 4923/5029 Controls | 292/307 Cases | 4840 / 5029 Controls | 292/307 Cases | 4780/5029 Controls | 284/307 Cases | 4700/5029 Controls |
| **Pollution Surface (percentiles of exposure)‡** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** |
| **$NO_2$ Satellite** | | | | | | | | |
| 0.05 to 0.15 ppb | 20 | 1.12 (1.04 - 1.21) | 5 | 1.08 (1.00 - 1.16) | 19 | 1.12 (1.04 - 1.21) | 5 | 1.09 (1.01 - 1.18) |
| 0.15 to 0.49 ppb | 98 | 1.36 (1.11 - 1.66) | 83 | 1.23 (1.01 - 1.50) | 95 | 1.37 (1.12 - 1.69) | 79 | 1.26 (1.03 - 1.55) |
| 0.49 to 1.11 ppb | 107 | 1.27 (1.02 - 1.57) | 84 | 1.13 (0.92 -1.39) | 105 | 1.30 (1.04 - 1.63) | 83 | 1.18 (0.94 - 1.47) |
| 1.11 to 2.06 ppb | 51 | 0.64 (0.47 - 0.87) | 42 | 0.66 (0.49 - 0.89) | 49 | 0.67 (0.49 - 0.92) | 42 | 0.68 (0.49 - 0.94) |
| 2.06 to 2.66 ppb | 17 | 0.57 (0.41 - 0.78) | 27 | 0.62 (0.45 - 0.85) | 17 | 0.58 (0.42 - 0.82) | 25 | 0.63 (0.45 - 0.88) |
| **$NO_2$ Fused** | | | | | | | | |
| 0.9 to 2.7 ppb | 13 | 1.22 (1.06 - 1.39) | 7 | 1.14 (1.01 - 1.29) | 13 | 1.23 (1.06 - 1.42) | 7 | 1.14 (1.00 - 1.31) |
| 2.7 to 8.8 ppb | 115 | 1.67 (1.15 - 2.43) | 87 | 1.32 (0.94 - 1.86) | 110 | 1.76 (1.17 - 2.63) | 84 | 1.39 (0.96 - 2.02) |
| 8.8 to 12.8 ppb | 97 | 0.87 (0.74 - 1.02) | 41 | 0.87 (0.75 - 1.01) | 94 | 0.94 (0.69 - 0.98) | 39 | 0.93 (0.79 - 1.09) |
| 12.8 to 15.8 ppb | 42 | 0.78 (0.66 - 0.92) | 50 | 0.77 (0.64 - 0.93) | 42 | 0.82 (0.69 - 0.98) | 48 | 0.82 (0.67 - 1.00) |
| 15.8 to 17.4 ppb | 29 | 0.69 (0.55 - 0.88) | 16 | 0.66 (0.49 - 0.89) | 29 | 0.74 (0.58 - 0.95) | 15 | 0.71 (0.52 - 0.98) |
| **$PM_{2.5}$ Satellite** | | | | | | | | |
| 3.2 to 5.3 $\mu g/m^3$ | 31 | 1.14 (0.82 - 1.56) | 27 | 0.93 (0.72 - 1.21) | 29 | 1.21 (0.86 - 1.68) | 26 | 0.99 (0.75 - 1.29) |
| 5.3 to 8.1 $\mu g/m^3$ | 117 | 1.17 (0.87 - 1.58) | 113 | 0.94 (0.71 -1.25) | 114 | 1.26 (0.92 - 1.72) | 109 | 1.02 (0.76 - 1.37) |
| 8.1 to 9.8 $\mu g/m^3$ | 70 | 1.08 (0.97 - 1.22) | 66 | 1.01 (0.88 - 1.16) | 69 | 1.13 (1.00 - 1.28) | 65 | 1.07 (0.93 - 1.24) |
| 9.8 to 11.5 $\mu g/m^3$ | 44 | 1.08 (0.95 - 1.24) | 47 | 1.05 (0.92 - 1.21) | 44 | 1.12 (0.98 - 1.29) | 47 | 1.10 (0.95 - 1.26) |
| 11.5 to 15.6 $\mu g/m^3$ | 33 | 1.18 (0.76 - 1.84) | 32 | 1.21 (0.79 - 1.85) | 31 | 1.26 (0.80 - 1.99) | 30 | 1.31 (0.85 - 2.01) |
| **$PM_{2.5}$ Fused** | | | | | | | | |
| 5.6 to 8.0 $\mu g/m^3$ | 26 | 0.92 (0.71 - 1.20) | 56 | 0.92 (0.80 - 1.07) | 23 | 0.98 (0.74 - 1.29) | 52 | 0.96 (0.82 - 1.12) |
| 8.0 to 11.7 $\mu g/m^3$ | 133 | 0.98 (0.76 - 1.27) | 142 | 0.87 (0.61 - 1.24) | 131 | 1.06 (0.81 - 1.40) | 140 | 0.98 (0.67 - 1.42) |
| 11.7 to 13.6 $\mu g/m^3$ | 67 | 1.06 (0.98 - 1.15) | 57 | 1.05 (0.95 - 1.16) | 66 | 1.10 (1.01 - 1.19) | 56 | 1.09 (0.98 - 1.21) |
| 13.6 to 15.9 $\mu g/m^3$ | 38 | 1.15 (0.99 - 1.33) | 21 | 1.06 (0.98 - 1.14) | 37 | 1.18 (1.01 - 1.38) | 21 | 1.07 (0.99 - 1.16) |
| 15.9 to 19.1 $\mu g/m^3$ | 29 | 1.32 (0.96 - 1.82) | 7 | 1.39 (0.91 - 2.11) | 28 | 1.36 (0.97 - 1.90) | 6 | 1.44 (0.93 - 2.24) |

† Based on natural spline models with 2 degrees of freedom, unconditional logistic regression models without random effects. ‡ Cut points derived based on the range of concentrations for both cases and controls combined (1st, 10th, median, 75th, 90th, and 99th percentiles); the output represents the OR for each level as concentration changes from the lower percentile to the higher percentile.

**Appendix Table 13. Associations between incidence of chronic myeloid leukemia (CML) and $NO_2$ and $PM_{2.5}$ exposure for four pollutant surfaces in all provinces in Canada (except New Brunswick and Quebec) for total average exposure from 1975 to 1994 and for exposure at time of interview.**

| | Base Model† | | Base model (Interview) | | Fully adjusted model | | Fully adjusted model (Interview) | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted for gender, five year age category, and reporting province | | | | Adjusted for gender, five year age category, reporting province, smoking status, exposure to radiation and benzene, education, body mass index, and income | | | |
| | 168 / 168 Cases | 4923 / 5029 Controls | 165 / 168 Cases | 4840 / 5029 Controls | 164 / 168 Cases | 4780 / 5029 Controls | 161 / 168 Cases | 4700 / 5029 Controls |
| **Pollution Surface (percentiles of exposure)‡** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** |
| **$NO_2$ Satellite** | | | | | | | | |
| 0.05 to 0.15 ppb | 5 | 1.16 (1.05 - 1.27) | 4 | 1.32 (1.06 - 1.65) | 5 | 1.15 (1.04 - 1.27) | 4 | 1.33 (1.05 - 1.69) |
| 0.15 to 0.49 ppb | 57 | 1.48 (1.13 - 1.92) | 63 | 1.64 (1.08 - 2.50) | 56 | 1.47 (1.12 - 1.92) | 63 | 1.65 (1.04 - 2.61) |
| 0.49 to 1.1 ppb | 59 | 1.38 (1.04 - 1.83) | 64 | 0.93 (0.77 - 1.13) | 58 | 1.34 (1.00 - 1.79) | 64 | 0.91 (0.74 - 1.12) |
| 1.1 to 2.4 ppb | 37 | 0.62 (0.41 - 0.92) | 24 | 0.60 (0.43 - 0.82) | 36 | 0.57 (0.37 - 0.87) | 24 | 0.57 (0.41 - 0.79) |
| 2.4 to 2.6 ppb | 9 | 0.52 (0.34 - 0.80) | 9 | 0.24 (0.10 - 0.57) | 8 | 0.49 (0.31 - 0.77) | 8 | 0.22 (0.09 - 0.53) |
| **$NO_2$ Fused** | | | | | | | | |
| 0.82 to 2.29 ppb | 4 | 1.41 (1.15 - 1.74) | 8 | 1.10 (1.00 - 1.21) | 4 | 1.37 (1.11 - 1.69) | 8 | 1.10 (1.00 - 1.22) |
| 2.29 to 7.7 ppb | 66 | 2.31 (1.31 - 3.93) | 60 | 1.30 (1.00 - 1.68) | 64 | 2.11 (1.22 - 3.66) | 58 | 1.29 (0.99 - 1.69) |
| 7.7 to 12.1 ppb | 56 | 0.81 (0.64 - 1.01) | 50 | 1.19 (0.91 - 1.57) | 55 | 0.79 (0.62 - 1.01) | 50 | 1.16 (0.87 - 1.54) |
| 12.1 to 15.7 ppb | 35 | 0.67 (0.53 - 0.86) | 36 | 0.64 (0.43 - 0.96) | 34 | 0.68 (0.53 - 0.87) | 35 | 0.58 (0.38 - 0.89) |
| 15.7 to 17.3 ppb | 6 | 0.56 (0.40 - 0.79) | 9 | 0.59 (0.38 - 0.89) | 6 | 0.57 (0.40 - 0.80) | 8 | 0.54 (0.35 - 0.85) |
| **$PM_{2.5}$ Satellite** | | | | | | | | |
| 3.2 to 5 µg/$m^3$ | 6 | 2.44 (1.44 - 4.12) | 8 | 1.30 (1.08 - 1.55) | 6 | 2.35 (1.39 - 3.96) | 8 | 1.27 (1.06 - 1.53) |
| 5 to 7.6 µg/$m^3$ | 63 | 2.33 (1.38 - 3.94) | 59 | 1.90 (1.16 - 3.09) | 63 | 2.23 (1.32 - 3.77) | 57 | 1.78 (1.07 - 2.96) |
| 7.6 to 9.7 µg/$m^3$ | 56 | 1.08 (0.85 - 1.36) | 59 | 0.82 (0.67 - 1.00) | 53 | 1.06 (0.83 - 1.35) | 59 | 0.78 (0.62 - 0.97) |
| 9.7 to 11.4 µg/$m^3$ | 30 | 0.73 (0.55 - 0.98) | 31 | 0.65 (0.50 - 0.85) | 29 | 0.73 (0.54 - 0.99) | 29 | 0.63 (0.47 - 0.84) |
| 11.4 to 15.2 µg/$m^3$ | 13 | 0.28 (0.11 - 0.69) | 8 | 0.49 (0.32 - 0.76) | 13 | 0.28 (0.11 - 0.72) | 8 | 0.48 (0.30 - 0.75) |
| **$PM_{2.5}$ Fused** | | | | | | | | |
| 5.6 to 7.8 µg/$m^3$ | 12 | 0.97 (0.70 - 1.34) | 7 | 1.86 (1.17 - 2.95) | 12 | 0.94 (0.68 - 1.31) | 7 | 1.81 (1.14 - 2.87) |
| 7.8 to 11.5 µg/$m^3$ | 72 | 1.00 (0.70 - 1.42) | 59 | 1.79 (1.12 - 2.85) | 70 | 0.96 (0.67 - 1.38) | 59 | 1.73 (1.09 - 2.77) |
| 11.5 to 13.2 µg/$m^3$ | 35 | 1.02 (0.92 - 1.13) | 56 | 1.03 (0.83 - 1.29) | 33 | 1.02 (0.92 - 1.13) | 53 | 1.02 (0.81 - 1.28) |
| 13.2 to 16.7 µg/$m^3$ | 41 | 1.09 (0.78 - 1.54) | 29 | 0.79 (0.60 - 1.03) | 41 | 1.11 (0.79 - 1.57) | 28 | 0.78 (0.59 - 1.03) |
| 16.7 to 19.1 µg/$m^3$ | 7 | 1.09 (0.76 - 1.57) | 13 | 0.39 (0.17 - 0.87) | 7 | 1.12 (0.77 - 1.62) | 13 | 0.39 (0.17 - 0.89) |

† Based on natural spline models with 2 degrees of freedom, unconditional logistic regression models without random effects. ‡ Cut points derived based on the range of concentrations for both cases and controls combined (1st, 10th, median, 75th, 90th, and 99th percentiles); the output represents the OR for each level as concentration changes from the lower percentile to the higher percentile.

**Appendix Table 14. Associations between incidence of chronic myeloid leukemia (CML) and $NO_2$ and $PM_{2.5}$ exposure for four pollutant surfaces in all provinces in Canada (except New Brunswick and Quebec) for total average exposure from 1975 to 1994 and for subjects with 20 years of exposure.**

| | Base Model† | | Base Model (20 years) | | Fully Adjusted Model | | Fully Adjusted Model (20 years) | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted for gender, five year age category, and reporting province | | | | Adjusted for gender, five year age category, reporting province, smoking status, exposure to radiation and benzene, education, body mass index, and income | | | |
| | 168 / 168 Cases | 4923 / 5029 Controls | 104 / 168 Cases | 3504 / 5029 controls | 164 / 168 Cases | 4780 / 5029 Controls | 103 / 168 Cases | 3414 / 5029 Controls |
| **Pollution Surface (percentiles of exposure)‡** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** |
| **$NO_2$ Satellite** | | | | | | | | |
| 0.05 to 0.15 ppb | 5 | 1.16 (1.05 - 1.27) | 4 | 1.10 (0.99 - 1.23) | 5 | 1.15 (1.04 - 1.27) | 4 | 1.11 (0.99 - 1.24) |
| 0.15 to 0.49 ppb | 57 | 1.48 (1.13 - 1.92) | 39 | 1.32 (0.97 - 1.80) | 56 | 1.47 (1.12 - 1.92) | 39 | 1.34 (0.97 - 1.85) |
| 0.49 to 1.1 ppb | 59 | 1.38 (1.04 - 1.83) | 26 | 1.22 (0.87 - 1.69) | 58 | 1.34 (1.00 - 1.79) | 26 | 1.24 (0.88 - 1.74) |
| 1.1 to 2.4 ppb | 37 | 0.62 (0.41 - 0.92) | 33 | 0.39 (0.17 - 0.90) | 36 | 0.57 (0.37 - 0.87) | 33 | 0.39 (0.17 - 0.92) |
| 2.4 to 2.6 ppb | 9 | 0.52 (0.34 - 0.80) | 1 | 0.73 (0.56 - 0.95) | 8 | 0.49 (0.31 - 0.77) | 1 | 0.72 (0.55 - 0.95) |
| **$NO_2$ Fused** | | | | | | | | |
| 0.82 to 2.29 ppb | 4 | 1.41 (1.15 - 1.74) | 3 | 1.32 (1.09 - 1.60) | 4 | 1.37 (1.11 - 1.69) | 3 | 1.43 (1.11 - 1.86) |
| 2.29 to 7.7 ppb | 66 | 2.31 (1.31 - 3.93) | 40 | 1.89 (1.17 - 3.07) | 64 | 2.11 (1.22 - 3.66) | 40 | 2.34 (1.20 - 4.53) |
| 7.7 to 12.1 ppb | 56 | 0.81 (0.64 - 1.01) | 35 | 0.75 (0.57 - 0.98) | 55 | 0.79 (0.62 - 1.01) | 34 | 0.73 (0.53 - 1.01) |
| 12.1 to 15.7 ppb | 35 | 0.67 (0.53 - 0.86) | 26 | 0.47 (0.29 - 0.75) | 34 | 0.68 (0.53 - 0.87) | 26 | 0.41 (0.23 - 0.71) |
| 15.7 to 17.3 ppb | 6 | 0.56 (0.40 - 0.79) | 0 | 0.76 (0.65 - 0.90) | 6 | 0.57 (0.40 - 0.80) | 0 | 0.72 (0.59 - 0.88) |
| **$PM_{2.5}$ Satellite** | | | | | | | | |
| 3.2 to 5 µg/$m^3$ | 6 | 2.44 (1.44 - 4.12) | 4 | 1.86 (1.17 - 2.96) | 6 | 2.35 (1.39 - 3.96) | 4 | 1.96 (1.10 - 3.48) |
| 5 to 7.6 µg/$m^3$ | 63 | 2.33 (1.38 - 3.94) | 44 | 1.78 (1.12 - 2.84) | 63 | 2.23 (1.32 - 3.77) | 44 | 1.94 (1.08 - 3.48) |
| 7.6 to 9.7 µg/$m^3$ | 56 | 1.08 (0.85 - 1.36) | 27 | 1.03 (0.82 - 1.28) | 53 | 1.06 (0.83 - 1.35) | 26 | 1.11 (0.84 - 1.47) |
| 9.7 to 11.4 µg/$m^3$ | 30 | 0.73 (0.55 - 0.98) | 18 | 0.79 (0.60 - 1.03) | 29 | 0.73 (0.54 - 0.99) | 18 | 0.85 (0.62 - 1.16) |
| 11.4 to 15.2 µg/$m^3$ | 13 | 0.28 (0.11 - 0.69) | 11 | 0.43 (0.21 - 0.89) | 13 | 0.28 (0.11 - 0.72) | 11 | 0.50 (0.21 - 1.16) |
| **$PM_{2.5}$ Fused** | | | | | | | | |
| 5.6 to 7.8 µg/$m^3$ | 12 | 0.97 (0.70 - 1.34) | 10 | 1.02 (0.67 - 1.53) | 12 | 0.94 (0.68 - 1.31) | 10 | 1.04 (0.68 - 1.59) |
| 7.8 to 11.5 µg/$m^3$ | 72 | 1.00 (0.70 - 1.42) | 36 | 1.08 (0.69 - 1.70) | 70 | 0.96 (0.67 - 1.38) | 36 | 1.13 (0.71 - 1.79) |
| 11.5 to 13.2 µg/$m^3$ | 35 | 1.02 (0.92 - 1.13) | 21 | 1.07 (0.95 - 1.21) | 33 | 1.02 (0.92 - 1.13) | 20 | 1.09 (0.96 - 1.23) |
| 13.2 to 16.7 µg/$m^3$ | 41 | 1.09 (0.78 - 1.54) | 21 | 1.24 (0.79 - 1.94) | 41 | 1.11 (0.79 - 1.57) | 21 | 1.29 (0.82 - 2.03) |
| 16.7 to 19.1 µg/$m^3$ | 7 | 1.09 (0.76 - 1.57) | 16 | 1.15 (0.80 - 1.65) | 7 | 1.12 (0.77 - 1.62) | 16 | 1.17 (0.82 - 1.69) |

† Based on natural spline models with 2 degrees of freedom, unconditional logistic regression models without random effects. ‡ Cut points derived based on the range of concentrations for both cases and controls combined (1st, 10th, median, 75th, 90th, and 99th percentiles); the output represents the OR for each level as concentration changes from the lower percentile to the higher percentile.

**Appendix Table 15. Associations between incidence of chronic lymphocytic leukemia (CLL) and $NO_2$ and $PM_{2.5}$ exposure for four pollutant surfaces in all provinces in Canada (except New Brunswick and Quebec) for total average exposure from 1975 to 1994 and for exposure at time of interview.**

| | Base Model† | | Base Model (Interview) | | Fully Adjusted Model | | Fully Adjusted Model (Interview) | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted for gender, five year age category, and reporting province | | | | Adjusted for gender, five year age category, reporting province, smoking status, exposure to radiation and benzene, education, body mass index, and income | | | |
| | 402/410 Cases | 4923 / 5029 Controls | 395/410 Cases | 4840 /5029 Controls | 392 /410 Cases | 4780 /5029 Controls | 385 /410 Cases | 4700 /5029 Controls |
| **Pollution Surface (percentiles of exposure)‡** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** |
| **$NO_2$ Satellite** | | | | | | | | |
| 0.05 to 0.15 ppb | 32 | 1.02 (0.95 - 1.08) | 37 | 0.99 (0.92 - 1.05) | 32 | 1.02 (0.96 - 1.09) | 37 | 0.99 (0.93 - 1.06) |
| 0.15 to 0.49 ppb | 160 | 1.04 (0.88 - 1.24) | 168 | 0.96 (0.80 - 1.14) | 155 | 1.06 (0.89 - 1.27) | 163 | 0.97 (0.81 - 1.16) |
| 0.49 to 1.1 ppb | 110 | 0.95 (0.79 - 1.14) | 97 | 0.85 (0.71 - 1.02) | 108 | 0.99 (0.82 - 1.20) | 95 | 0.89 (0.74 - 1.08) |
| 1.1 to 2.4 ppb | 77 | 0.68 (0.51 - 0.90) | 75 | 0.68 (0.51 - 0.89) | 76 | 0.74 (0.56 - 0.99) | 73 | 0.74 (0.55 - 0.98) |
| 2.4 to 2.6 ppb | 18 | 0.70 (0.52 - 0.94) | 13 | 0.74 (0.55 - 1.00) | 17 | 0.75 (0.56 - 1.02) | 13 | 0.79 (0.58 - 1.06) |
| **$NO_2$ Fused** | | | | | | | | |
| 0.82 to 2.29 ppb | 18 | 0.95 (0.84 -1.07) | 23 | 0.92 (0.81 - 1.05) | 18 | 0.95 (0.84 - 1.08) | 23 | 0.92 (0.81 - 1.05) |
| 2.29 to 7.7 ppb | 172 | 0.85 (0.62 - 1.16) | 174 | 0.79 (0.60 - 1.05) | 169 | 0.86 (0.62 - 1.20) | 171 | 0.81 (0.60 - 1.08) |
| 7.7 to 12.1 ppb | 116 | 0.87 (0.76 - 1.00) | 101 | 0.83 (0.73 - 0.94) | 113 | 0.93 (0.81 - 1.08) | 98 | 0.88 (0.77 - 1.01) |
| 12.1 to 15.7 ppb | 51 | 0.92 (0.80 - 1.06) | 63 | 0.88 (0.75 - 1.03) | 48 | 0.97 (0.84 - 1.13) | 60 | 0.93 (0.79 - 1.10) |
| 15.7 to 17.3 ppb | 37 | 0.91 (0.75 - 1.11) | 26 | 0.86 (0.66 - 1.11) | 36 | 0.98 (0.80 - 1.20) | 25 | 0.93 (0.72 - 1.21) |
| **$PM_{2.5}$ Satellite** | | | | | | | | |
| 3.2 to 5 $\mu g/m^3$ | 21 | 1.00 (0.77 - 1.28) | 24 | 0.90 (0.73 - 1.11) | 21 | 1.02 (0.79 - 1.31) | 24 | 0.92 (0.74 - 1.14) |
| 5 to 7.6 $\mu g/m^3$ | 140 | 0.93 (0.72 - 1.20) | 135 | 0.73 (0.58 - 0.91) | 138 | 0.96 (0.74 - 1.26) | 133 | 0.78 (0.61 - 0.99) |
| 7.6 to 9.7 $\mu g/m^3$ | 146 | 0.85 (0.75 - 0.97) | 143 | 0.79 (0.65 - 0.97) | 141 | 0.89 (0.78 - 1.02) | 138 | 0.83 (0.68 - 1.00) |
| 9.7 to 11.4 $\mu g/m^3$ | 67 | 0.83 (0.70 - 0.97) | 66 | 0.85 (0.73 - 1.00) | 65 | 0.86 (0.73 - 1.01) | 64 | 0.88 (0.75 - 1.03) |
| 11.4 to 14.7 $\mu g/m^3$ | 21 | 0.62 (0.38 - 1.01) | 19 | 0.62 (0.35 - 1.10) | 20 | 0.68 (0.42 - 1.09) | 18 | 0.68 (0.39 - 1.18) |
| **$PM_{2.5}$ Fused** | | | | | | | | |
| 5.6 to 7.8 $\mu g/m^3$ | 36 | 0.80 (0.66 - 0.97 | 36 | 0.86 (0.70 - 1.05) | 36 | 0.80 (0.66 - 0.98) | 36 | 0.85 (0.69 - 1.04) |
| 7.8 to 11.5 $\mu g/m^3$ | 183 | 0.76 (0.61 - 0.94) | 189 | 0.76 (0.64 - 0.90) | 179 | 0.76 (0.61 - 0.95) | 184 | 0.78 (0.65 - 0.92) |
| 11.5 to 13.2 $\mu g/m^3$ | 79 | 0.93 (0.87 - 0.99) | 89 | 0.87 (0.75 - 1.01) | 75 | 0.94 (0.88 - 1.00) | 87 | 0.89 (0.77 - 1.03) |
| 13.2 to 16.7 $\mu g/m^3$ | 75 | 0.96 (0.76 - 1.22) | 49 | 0.75 (0.47 - 1.19) | 75 | 0.98 (0.78 - 1.24) | 47 | 0.80 (0.51 - 1.27) |
| 16.7 to 19.1 $\mu g/m^3$ | 18 | 1.04 (0.81 - 1.32) | 26 | 0.82 (0.55 - 1.20) | 16 | 1.06 (0.83 - 1.35) | 25 | 0.86 (0.59 - 1.26) |

† Based on natural spline models with 2 degrees of freedom, unconditional logistic regression models without random effects. ‡ Cut points derived based on the range of concentrations for both cases and controls combined (1st, 10th, median, 75th, 90th, and 99th percentiles); the output represents the OR for each level as concentration changes from the lower percentile to the higher percentile.

**Appendix Table 16. Associations between incidence of chronic lymphocytic leukemia (CLL) and $NO_2$ and $PM_{2.5}$ exposure for four pollutant surfaces in all provinces in Canada (except New Brunswick and Quebec) for total average exposure from 1975 to 1994 and for subjects with 20 years of exposure.**

| | Base Model† | | Base Model (20 years) | | Fully Adjusted Model | | Fully Adjusted Model (20 years) | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted for gender, five year age category, and reporting province | | | | Adjusted for gender, five year age category, reporting province, smoking status, exposure to radiation and benzene, education, body mass index, and income | | | |
| | 402/410 Cases | 4923 / 5029 Controls | 308 / 410 Cases | 3504 / 5029 Controls | 392 /410 Cases | 4780 /5029 Controls | 300 / 410 Cases | 3414 / 5029 Controls |
| **Pollution Surface (percentiles of exposure)‡** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** | **Cases per category** | **Odds ratio (95% CI)** |
| **$NO_2$ Satellite** | | | | | | | | |
| 0.05 to 0.15 ppb | 32 | 1.02 (0.95 - 1.08) | 20 | 1.04 (0.97 - 1.12) | 32 | 1.02 (0.96 - 1.09) | 20 | 1.05 (0.98 - 1.13) |
| 0.15 to 0.49 ppb | 160 | 1.04 (0.88 - 1.24) | 117 | 1.13 (0.93 - 1.38) | 155 | 1.06 (0.89 - 1.27) | 113 | 1.16 (0.95 - 1.43) |
| 0.49 to 1.1 ppb | 110 | 0.95 (0.79 - 1.14) | 88 | 1.07 (0.87 - 1.32) | 108 | 0.99 (0.82 - 1.20) | 86 | 1.11 (0.89 - 1.39) |
| 1.1 to 2.4 ppb | 77 | 0.68 (0.51 - 0.90) | 75 | 0.56 (0.34 - 0.93) | 76 | 0.74 (0.56 - 0.99) | 74 | 0.61 (0.36 - 1.02) |
| 2.4 to 2.6 ppb | 18 | 0.70 (0.52 - 0.94) | 5 | 0.83 (0.71 - 0.98) | 17 | 0.75 (0.56 - 1.02) | 5 | 0.84 (0.71 - 0.99) |
| **$NO_2$ Fused** | | | | | | | | |
| 0.82 to 2.29 ppb | 18 | 0.95 (0.84 -1.07) | 11 | 0.93 (0.83 - 1.05) | 18 | 0.95 (0.84 - 1.08) | 11 | 1.02 (0.89 - 1.18) |
| 2.29 to 7.7 ppb | 172 | 0.85 (0.62 - 1.16) | 126 | 0.79 (0.59 - 1.06) | 169 | 0.86 (0.62 - 1.20) | 123 | 1.06 (0.82 - 1.16) |
| 7.7 to 12.1 ppb | 116 | 0.87 (0.76 - 1.00) | 97 | 0.80 (0.68 - 0.94) | 113 | 0.93 (0.81 - 1.08) | 94 | 0.97 (0.82 - 1.16) |
| 12.1 to 15.7 ppb | 51 | 0.92 (0.80 - 1.06) | 55 | 0.83 (0.63 - 1.10) | 48 | 0.97 (0.84 - 1.13) | 53 | 0.93 (0.70 - 1.24) |
| 15.7 to 17.3 ppb | 37 | 0.91 (0.75 - 1.11) | 11 | 0.94 (0.86 - 1.04) | 36 | 0.98 (0.80 - 1.20) | 11 | 0.97 (0.88 - 1.07) |
| **$PM_{2.5}$ Satellite** | | | | | | | | |
| 3.2 to 5 $\mu g/m^3$ | 21 | 1.00 (0.77 - 1.28) | 14 | 1.15 (0.84 - 1.57) | 21 | 1.02 (0.79 - 1.31) | 14 | 1.18 (0.86 - 1.61) |
| 5 to 7.6 $\mu g/m^3$ | 140 | 0.93 (0.72 - 1.20) | 107 | 1.07 (0.78 - 1.47) | 138 | 0.96 (0.74 - 1.26) | 105 | 1.12 (0.81 - 1.55) |
| 7.6 to 9.7 $\mu g/m^3$ | 146 | 0.85 (0.75 - 0.97) | 114 | 0.88 (0.76 - 1.03) | 141 | 0.89 (0.78 - 1.02) | 109 | 0.93 (0.79 - 1.09) |
| 9.7 to 11.4 $\mu g/m^3$ | 67 | 0.83 (0.70 - 0.97) | 50 | 0.81 (0.67 - 0.98) | 65 | 0.86 (0.73 - 1.01) | 50 | 0.85 (0.71 - 1.03) |
| 11.4 to 14.7 $\mu g/m^3$ | 21 | 0.62 (0.38 - 1.01) | 19 | 0.58 (0.34 - 0.98) | 20 | 0.68 (0.42 - 1.09) | 18 | 0.65 (0.39 - 1.06) |
| **$PM_{2.5}$ Fused** | | | | | | | | |
| 5.6 to 7.8 $\mu g/m^3$ | 36 | 0.80 (0.66 - 0.97 | 50 | 0.87 (0.69 - 1.11) | 36 | 0.80 (0.66 - 0.98) | 50 | 0.88 (0.69 - 1.13) |
| 7.8 to 11.5 $\mu g/m^3$ | 183 | 0.76 (0.61 - 0.94) | 138 | 0.83 (0.64 - 1.07) | 179 | 0.76 (0.61 - 0.95) | 133 | 0.85 (0.65 - 1.11) |
| 11.5 to 13.2 $\mu g/m^3$ | 79 | 0.93 (0.87 - 0.99) | 42 | 0.93 (0.86 - 1.01) | 75 | 0.94 (0.88 - 1.00) | 40 | 0.95 (0.88 - 1.03) |
| 13.2 to 16.7 $\mu g/m^3$ | 75 | 0.96 (0.76 - 1.22) | 44 | 0.89 (0.66 - 1.21) | 75 | 0.98 (0.78 - 1.24) | 44 | 0.94 (0.69 - 1.28) |
| 16.7 to 19.1 $\mu g/m^3$ | 18 | 1.04 (0.81 - 1.32) | 29 | 0.95 (0.75 - 1.21) | 16 | 1.06 (0.83 - 1.35) | 28 | 0.98 (0.77 - 1.25) |

† Based on natural spline models with 2 degrees of freedom, unconditional logistic regression models without random effects. ‡ Cut points derived based on the range of concentrations for both cases and controls combined (1st, 10th, median, 75th, 90th, and 99th percentiles); the output represents the OR for each level as concentration changes from the lower percentile to the higher percentile.

# Chapter 6 ~ Discussion and Conclusion

## 6.1 Discussion

I defined two objectives for my thesis and these were met with: 1) a structured review of the peer-reviewed literature in order to identify epidemiological investigations that reported on the incidence or mortality of leukemia and exposure to ambient air pollution; and 2) an analysis of a population-based case-control study to determine whether the incidence of leukemia, diagnosed in adults in eight Canadian provinces between 1994 and 1997, was associated with exposure to ambient air pollution.

In my structured review of the literature, I identified 17 case-control studies and four cohort studies. I found that in children there is a suggestion that exposure to traffic-related air pollution (as measured by $NO_2$ or $NO_x$) may be associated with the incidence of leukemia, but the lack of studies make it difficult to draw any conclusions. The available studies were limited by small numbers of cases, specificity of type of leukemia, potential misclassification of exposures, low and unreported response rates, and possible confounding due to not including essential risk factors. In addition, only five studies were used to investigate leukemia in adults. Thus, it was not possible to conclude whether air pollution is associated with the incidence of leukemia in children or in adults.

For my second objective, I investigated the associations between the incidence of adult leukemia and air pollution. I analyzed a case-control study that included 1,064 incident cases of adult leukemia and 5,029 controls diagnosed between 1994 and 1997 in all Canadian provinces except Quebec and New Brunswick. Using estimates of ambient pollution from satellite estimates and remote-sensing stations across Canada, I assigned subjects' past exposure to $NO_2$ and $PM_{2.5}$ for the time period between 1975 and 1994. In the analyses, I used two metrics of exposure: $NO_2$ (adjusted with annual average $NO_2$ measurements from the fixed-site monitoring network between 1975-1994) and "Fused $PM_{2.5}$" that was adjusted for secular changes in annual average $PM_{2.5}$. We used ordinary

logistic regression to estimate odds ratios. The odds ratios were derived using a natural cubic spline function on 2 degrees of freedom and were computed with respect to the median concentration of both cases and controls. I adjusted for five year age groups, gender, reporting province, self reported total years of exposure to benzene, self reported total years of exposure to ionizing radiation, total years of smoking, smoking category (never, current, former), total years of education, body mass index, and income category.

For the $PM_{2.5}$ fused surfaces I found a concentration-response function that was consistent with a linear function with a slight increase in risk of all forms of leukemia as concentrations increased. This was consistent across all provinces and for each of the subtypes of leukemia. I found that the concentration-response function for chronic lymphocytic leukemia was also linear for the $PM_{2.5}$ fused surface. The response functions for acute myeloid leukemia and chronic myeloid leukemia, however, were similar to the analysis of all forms of leukemia combined.

For the estimates of ambient concentrations to $NO_2$ and incidence of all forms of leukemia combined, a non-linear, 'n-shaped' concentration-response function was found. We found that as concentrations of $NO_2$ increased to about the median, the odds ratio increased, but at concentrations greater than the median the odds ratio decreased for risk of all forms of leukemia. The n-shaped curve for $NO_2$ appears to be related to urban-rural differences in which we observed an increasing trend in rural areas but a decreasing trend in urban ones. I found response functions for acute myeloid leukemia and chronic myeloid leukemia that were consistent with the analysis of all forms of leukemia combined, but I found a decreasing linear trend for chronic lymphocytic leukemia.

My study had the advantages of being population-based, including subjects from both rural and urban areas nationwide, and having 20-year residential histories of subjects. However, several limitations including potential under-ascertainment of leukemia cases and low response rates appear to have had an effect on the results.

Although my results for $NO_2$, which could be a chance finding, suggest a positive association at low concentrations and a protective effect at high concentrations, and there was no obvious biological explanation for a protective effect, it would appear that there may be some form of selection effect biasing the results. I found a null association for $PM_{2.5}$, however if there was a true effect the potential bias may have led to attenuation of the results. Additionally, these differences may be related to under-ascertainment of incident cases of leukemia in persons of lower socioeconomic status and/or relatively low response rates of cases and controls.

## 6.2 Conclusion

In conclusion, I met both the objectives I set out to address for my thesis. I reviewed the literature and conducted a case-control study to investigate the effects that air pollution has on incidence of leukemia in adults. I found that there is a dearth of information on adult leukemia and associations with air pollution, providing strong justification for my study. The results of my case-control study appear to indicate a null association, but cannot rule out if there was indeed selection bias that attenuated the odds ratios. Thus, due to the limited number of studies and potential biases in my case-control study, it is not possible to conclude with confidence whether there is an association between ambient air pollution and leukemia.

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