LUNG CANCER AND AMBIENT $PM_{2.5}$ IN CANADA:

A Systematic Review and Meta-analysis

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To obtain additional information, please contact:

Health Canada
Address Locator 0900C2
Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735
E-mail: publications-publications@hc-sc.gc.ca

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Dan Crouse, PhD (Health Effects Institute)

Rebecca Morgan, PhD, MPH (McMaster University)

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ABSTRACT

In Canada, lung cancer is the most commonly diagnosed cancer, with a five-year survival rate under 20%. Fine particulate matter ($PM_{2.5}$) is an important environmental risk factor for lung cancer. Additionally, the International Agency of Research for Cancer (IARC) determined that ambient particulate matter (PM) is a Group 1 carcinogen (2016), Health Canada (2013) concluded that chronic exposure to PM likely causes lung cancer mortality, and the US EPA (2019) concluded that the relationship between long-term exposure to $PM_{2.5}$ and cancer was likely to be causal. Systematic review and meta-analysis methodology was implemented to provide quantitative evidence that long-term exposure to $PM_{2.5}$ is associated with an increased risk of lung cancer specific to Canada. Additional qualitative evidence was provided to characterize other additional factors (such as confounders, effect modifiers, and the shape of the concentration-response curve) that may further contextualize the relationship of interest. Of the 12 Canadian cohort studies identified in the literature search and screening, six (four on lung cancer mortality, two on lung cancer incidence) unique cohorts were selected based on greater length of follow-up and sample size and were included in the final meta-analyses. Mortality and incidence were pooled separately as they represent unique outcomes. The pooled effect estimate for lung cancer mortality was 1.127 (95% CI: 1.085, 1.170) per 10 $\mu g/m^3$ $PM_{2.5}$ exposure and for lung cancer incidence was 1.060 (95% CI: 1.021, 1.100). There was no evidence of heterogeneity or publication bias for either endpoint. In conclusion, long-term exposure to $PM_{2.5}$ is associated with an increased risk of lung cancer even at the relatively low levels experienced in Canada. The results were consistent with other meta-analyses of North American and European studies. Additional studies are needed to further characterize the shape of the association, better understand the effects of adjusting for exposures to other pollutants, and identify any sensitive subgroups.

CHAPTER 1: **INTRODUCTION**

Air pollution is a global health concern. The 2019 Global Burden of Disease Study (GBD) estimated that, collectively, all sources of air pollution are associated with 6.67 million deaths (GBD Risk Factor Collaborators 2020). Specifically, ambient particulate matter with a diameter less than 2.5 micrometres ($PM_{2.5}$) was associated with 4.14 million deaths and is a leading environmental risk factor identified in the 2019 GBD. In a recent evaluation by Health Canada, an estimated 10,000 premature deaths per year were attributed to ambient $PM_{2.5}$ (Health Canada 2021). $PM_{2.5}$ has been extensively studied with respect to sources, composition, health effects, and potential mechanisms of action. Due to its small size, $PM_{2.5}$ is able to penetrate deep into the lungs, pass through the respiratory barrier, and enter systemic circulation (reviewed in Feng et al. 2016). Exposure to ambient $PM_{2.5}$ is associated with cardiorespiratory mortality and morbidity, presenting a risk even at relatively low levels, and newer evidence indicates it may also affect other outcomes, including neurological and reproductive health (Al-Kindi 2020; US EPA 2019; Health Canada 2013). Additionally, evaluation of the concentration-response relationship indicates that there is no clear evidence of a threshold for many health endpoints, including premature mortality (US EPA 2019; Health Canada 2013).

Around the world, concentrations of and the relative contribution of different sources to ambient $PM_{2.5}$ are quite variable, with Canada having comparatively low average annual concentrations of $PM_{2.5}$ (Brauer et al. 2012). Furthermore, ambient levels of $PM_{2.5}$ in Canada decreased from 1990 to the early 2000s (State of the Air 2017). From 2000 to 2010, there was a trend of decreasing $PM_{2.5}$ emissions in Canada attributable to reductions in emissions from agricultural sources; however, since 2010 $PM_{2.5}$ emissions attributable to emissions from dusts and fires have been steadily increasing, outweighing reductions from other sources (ECCC 2020). Understanding the relationship between exposure to ambient $PM_{2.5}$, especially at relatively low levels present in Canada, and adverse health effects is important to support programs and policies dedicated to maintaining or further improving air quality.

Lung cancer is the most commonly diagnosed cancer in Canada. It is mainly diagnosed in adults over 50 years of age, with a higher incidence in men than women, and the five-year survival rate is under 20% (PHAC 2019). Many risk factors for lung cancer have been identified, including some well-known risks such as smoking and environmental tobacco smoke, radon, and asbestos. Outdoor air pollution is also an important environmental risk factor (Canadian Cancer Society 2020). Health Canada (2013) concluded that there was a likely causal relationship between chronic exposure to $PM_{2.5}$ and lung cancer. The International Agency for Research on Cancer (IARC) determined that outdoor air pollution and, more specifically, particulate matter (PM) in outdoor air pollution is carcinogenic to humans (Group 1) (2016). The epidemiological evidence evaluated by IARC indicated that long-term exposure to $PM_{2.5}$ causes lung cancer (Hamra et al. 2014).

The objective of this report is to quantify the relationship between long-term ambient $PM_{2.5}$ exposure and the risk of lung cancer mortality and incidence in Canada. This will be used to support future assessments of the burden of lung cancer associated with ambient $PM_{2.5}$ in the Canadian population. To achieve this, a systematic review and meta-analysis of Canadian cohort studies evaluating this relationship was conducted.

CHAPTER 2: **METHODS**

For this evaluation, the Population, Exposure, Comparator, and Outcomes (PECO) statement is: What is the risk of an incremental increase in exposure to ambient $PM_{2.5}$ on the development of and death due to lung cancer?

2.1. LITERATURE SEARCHES

Two literature search strategies were developed by a health librarian to identify references about $PM_{2.5}$ and lung cancer. The initial search strategies were conducted in Ovid Medline (1946 to September 3, 2019), Ovid Embase (1974 to September 3, 2019), Ovid Global Health (1973 to 2019 Week 34), Ovid CENTRAL (1991 to July 2019), and NLM TOXLINE (1840 to September 3, 2019). No date or language limits were applied. The Medline strategy was peer reviewed using the PRESS Peer review instrument (McGowan et al. 2016). Full strategies, including search terms, are contained in Appendix A.

Following the initial search, handsearching of reference lists of included studies identified relevant articles that had not been captured by this search. It was also identified that these relevant articles were studies of mortality related to $PM_{2.5,}$ including lung cancer mortality as a sub-group analysis; however, "cancer" was not present in any of the fields (e.g., title, abstract, keywords) assessed during the literature search. A supplemental search strategy was therefore developed using broader terms (i.e., not specific to cancer) to identify Canadian publications on the association of incidence and mortality with $PM_{2.5}$. All databases used in the initial search were also used in the supplemental search, and searched up until November 26, 2019. No date or language limits were applied. Results from the initial search strategy were excluded from the supplemental search results to avoid screening duplicate results. Complete dates, database segments, and search terminology can be found in Appendix A.

2.2. SCREENING, DATA EXTRACTION, AND QUALITY ASSESSMENT

To be considered for this meta-analysis, studies were selected that met the following inclusion criteria:

1. was conducted in Canada;
2. was an epidemiological study using a cohort study design;
3. examined long-term exposure to ambient $PM_{2.5}$ with long-term defined as a minimum of 1 year;
4. comparison groups were those exposed to lower levels of ambient $PM_{2.5;}$
5. examined lung cancer as the outcome of interest, which included malignant neoplasms of trachea, bronchus, and lung (ICD-10 codes C33-34 or equivalent ICD-9 codes);
6. measured the lung cancer outcome as either mortality or incidence;
7. provided effect estimates and its confidence interval (CI) per increment of exposure.

The following types of records were excluded:

1. publications in abstract form only, reviews, commentaries, letters, and in vivo or in vitro studies;
2. studies that did not clearly report a quantitative measure of effect estimate [i.e., hazard ratio (HR) or relative risk (RR) with 95% CI] and nor could this be retrieved through contact with study authors;
3. studies not on ambient sources of $PM_{2.5}$ (i.e., occupational studies).

Titles and abstracts of the records identified from the literature searches were independently reviewed by two reviewers. Full-text records were also independently assessed for inclusion by two reviewers. Discrepancies in choice of included studies between the two reviewers were resolved by consensus and/or consultation with a third reviewer when necessary. Data on study characteristics and results of included studies were independently extracted by two reviewers. Fields extracted included cohort name, study period, population size, number of cases, outcome (mortality or incidence), exposure assessment methodology, risk estimate, 95% CI and covariates included in the analysis.

Risk of Bias (RoB) was assessed using criteria proposed by a systematic review conducted using the Navigation Guide (Lam et al. 2016) on air pollution and autism spectrum disorder, and employed in Stieb et al. (2021) with some minor modifications. RoB is an important step in the systematic review process that assesses the validity of included studies and establishes transparency in the evidence synthesis of results (Higgins et al. 2011). Definitions and guidelines for the RoB assessment of cohort studies are presented in Appendix B. The RoB criteria domains included selection bias and generalizability, exposure assessment with regards to modelling and monitoring, confounding, outcome assessment, completeness of outcome data, selective outcome reporting, conflict of interest, and other sources of bias. Two reviewers assessed the RoB for each cohort study independently. Discrepancies between the assessments of the two reviewers were resolved by consensus and/or consultation with a third reviewer when necessary.

2.3. STUDY SELECTION AND DATA ANALYSIS

If multiple included studies considered the same cohort study population, preference was given to the publication with the largest population size and/or level of confounder adjustment. Study effect estimates were standardized to an increment of 10 $\mu g/m^3$ $PM_{2.5}$. The effect estimates were combined using random-effects meta-analysis employing restricted maximum likelihood estimation (REML). In the case where an insufficient number of studies was available ($n \leq 2$), effect estimates were combined using fixed-effects meta-analysis (Borenstein et al. 2009).

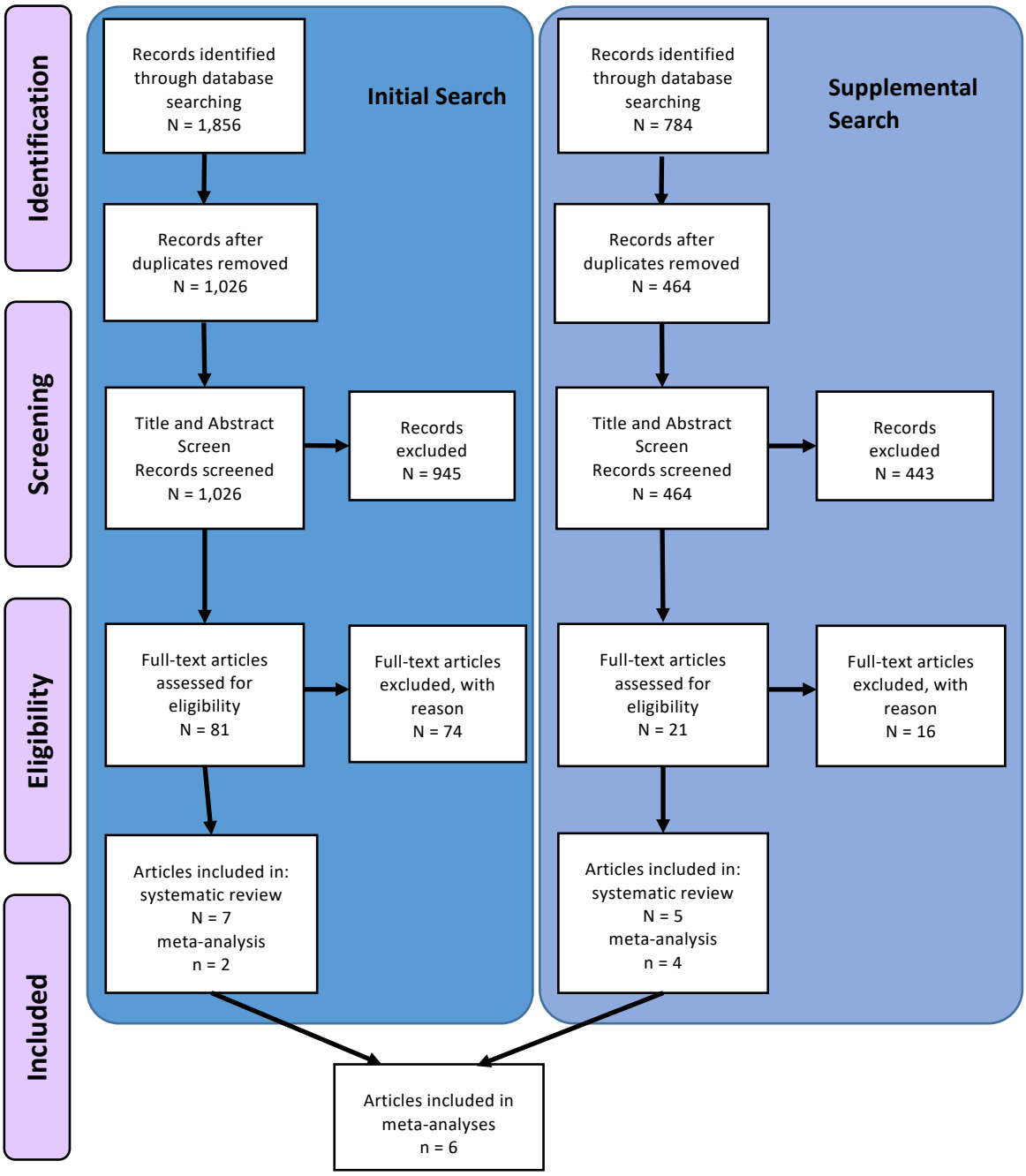
Heterogeneity was evaluated using I^2 statistics, representing the percent of total variance attributable to heterogeneity. Influence diagnostics were conducted using a leave-one-out analysis. I^2 values of 25%, 50%, and 75% correspond to low, moderate, and high levels of heterogeneity, respectively (Borenstein et al. 2009). The use of random-effects meta-analysis incorporates and accounts for heterogeneity among studies. Statistical analysis was conducted using the metafor package (Viechtbauer 2010) in R version 3.6.3 (R Core Team 2013).

CHAPTER 3:
RESULTS

3.1. LITERATURE SEARCH

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the literature search results and screening is provided in Figure 1. The initial literature search identified 1,026 unique records, 81 of which underwent full-text screening, and seven met the criteria for inclusion in the systematic review. The supplemental literature search identified 464 unique records, 21 of which underwent full-text screening, and five met the criteria for inclusion in the systematic review. The reasons studies were excluded during the full-text review included that they were not specific to Canadian cohorts, or they did not assess the association between $PM_{2.5}$ and lung cancer. Of the 12 studies (i.e., seven studies from the initial search and five studies from the supplemental search) that met the inclusion criteria, six studies were included in the meta-analysis. For the meta-analysis, two studies were identified in the initial search and four studies in the supplemental search.

FIGURE 1: PRISMA flowchart



3.2. CANADIAN COHORT STUDIES

Twelve Canadian cohort studies were identified from the literature search and screening process. These 12 studies were based on five cohorts: Canadian Census Health and Environment Cohort (CanCHEC) 1991 (three studies), CanCHEC 2001 (three studies), Canadian National Breast Screening Study (CNBSS) (three studies), Canadian Community Health Survey (CCHS) (one study), and ONtario Population Health and Environment Cohort (ONPHEC) (two studies). Membership in the CanCHEC cohorts, CNBSS, and CCHS is nationwide, while ONPHEC includes only Ontario residents. The cohorts were comprised only of adults (25 to 100 years of age considering all cohorts) and included both men and women, except for CNBSS, which restricted membership to women only. Each of the cohort studies had a minimum of 10 years of follow-up. A table of study characteristics of the 12 Canadian cohort studies is presented in Table 1.

In general, the study authors cited similar reasons for exclusion of participants from each analytical cohort, such as inability to assign $PM_{2.5}$ estimates, diagnosed case before enrolment in the cohort, and not within a pre-determined age limit; for some studies, immigrants were excluded. Although most of the studies considered the full population of the analytical cohort, To et al. (2015) and Weichenthal et al. (2016) restricted analyses to only a portion of the total cohort considered. To et al. (2015) considered only the CNBSS cohort members residing in Ontario, and Weichenthal et al. (2017) considered only the Toronto residents of ONPHEC (approximately 79% of the cohort excluded). Additionally, some of the studies excluded participants for reasons that could possibly introduce bias. Specifically, Weichenthal et al. (2016) considered only Ontario residents in CanCHEC 1991 (about 37% of the national cohort) and further excluded participants who did not live within 5 km of a provincial monitoring site for assessing $PM_{2.5}$ oxidative potential (approximately 80% of the Ontario residents in the cohort excluded). Also, Cakmak et al. (2018) excluded participants who could not be assigned to a spatial synoptic classification (SSC) zone for weather data (approximately 9% of the cohort excluded).

Almost all of the cohort studies used satellite-derived data to estimate $PM_{2.5}$ exposures in the study population, while Weichenthal et al. (2016) used fixed site monitors to assign exposures. Of the 11 cohort studies using satellite-derived $PM_{2.5}$ concentrations, five studies used a 10 × 10 km spatial scale, five studies used a finer scale at 1 × 1 km, and one study evaluated scales of 1 × 1 km, 5 × 5 km, and 10 × 10 km. Eight cohort studies used moving averages to assign a temporal scale to exposure, while three used time-invariant averages.

Eight cohort studies considered lung cancer mortality as the outcome measure of interest, and four studies considered lung cancer incidence. Each of the eight cohort studies on mortality ascertained cases from the Canadian Mortality Database (CMDB). Of the four cohort studies on incidence, two ascertained cases from the Ontario Cancer Registry (OCR), one from the Canadian Cancer Registry (CCR), and one from multiple Ontario administrative databases maintained by the Institute for Clinical Evaluative Sciences (ICES). The majority of cohort studies adjusted indirectly or directly for confounding by smoking, which is considered an important potential confounder; however, two cohort studies did not adjust for smoking (Pinault et al. 2017; Crouse et al. 2020).

TABLE 1: Study Characteristics of Canadian Cohort Studies on Lung Cancer Mortality and Incidence

Author	Study			Study Population			$PM_{2.5}$ Exposure		Lung Cancer	
	Cohort	Location	Period	Demographics	Total	Cases	Method	Definition	Outcome Measure	Confounder Adjustment
Cakmak et al. 2018	CanCHEC 1991	Canada	1991–2011	Exclusions: unable to assign SSC zone (weather data), unable to assign air pollution exposure estimate	2,291,250	53,220	Satellite	10 km^2, 7-year moving average	Mortality; CMDB	Stratified by age (5-year increments) and sex, and adjusted for personal covariates, and **indirectly adjusted for smoking** and obesity
Crouse et al. 2015	CanCHEC 1991	Canada	1991–2006	Exclusions: missing postal code information for > 3 of 7 years of exposure	2,521,525	30,545	Satellite	10 km^2, 7-year moving average, 1-year lag	Mortality; CMDB	Stratified by age and sex, adjusted for personal and contextual covariates, and **indirectly adjusted for smoking** and obesity
Weichenthal et al. 2016	CanCHEC 1991	Ontario	1991–2009	Exclusion: living outside of 5-km provincial monitoring site	193,300	3,200	Fixed site monitor	30 sites, < 5 km from site	Mortality; CMDB	Adjusted for age, sex, Aboriginal ancestry, visible minority status, immigrant status, marital status, highest level of education, employment status, occupational classification, and household income with **indirect adjustment for smoking** and obesity
Crouse et al. 2020	CanCHEC 2001	Canada	2001–2011		2,452,665	21,640	Satellite	1, 5, and 10 km^2, 1-, 3-, and 8-year, 1-year lag	Mortality; CMDB	Stratified by sex and 5-year age groups; adjusted for Aboriginal identity, visible minority status, marital status, highest level of education, employment status, household income adequacy quintiles, community size, community-level marginalization, and airshed
Erickson et al. 2019	CanCHEC 2001	Canada	2001–2011		2,468,180	22,200	Satellite	1 km^2, 3-year moving average, 1-year lag	Mortality; CMDB	Stratified by 5-year age-sex groups; adjusted for individual and ecological covariates, **indirectly adjusted for smoking**, alcohol use, exercise, diet using sample weights (W-matrix)

Author	Study			Study Population			$PM_{2.5}$ Exposure		Lung Cancer	
	Cohort	Location	Period	Demographics	Total	Cases	Method	Definition	Outcome Measure	Confounder Adjustment
Pinault et al. 2017	CanCHEC 2001	Canada	2001–2011	Exclusions: unable to assign air pollution estimates (86,100), not within ages 25–90 (319,000), immigrants (683,100)	2,448,500	23,900	Satellite	1 km^2, 3-year moving average, 1-year lag	Mortality; CMDB	Stratified by age (5-year categories), sex, airshed, and population centre size, and adjusted for visible minority status, Aboriginal identity, marital status, educational attainment, income quintile, and labour force status, and also for the % unemployed (aged 25 and older), % not graduated from high school (aged 25 and older), and % low income status, for CDs
Pinault et al. 2016	CCHS	Canada	Recruited 2000–2008 Followed up until 2011	Exclusions: unable to link to tax file (69,300), not recent immigrant (13,200), not within ages 25–90 (72,000), unable to link to air pollution estimates (3,400)	299,500	2,700	Satellite	1 km^2, 3-year moving average, 1-year lag	Mortality; CMDB	Stratified by age and sex; adjusted for behavioural (**smoking** and BMI, alcohol consumption, fruit and vegetable consumption), SES factors (immigrant status, visible minority status, Aboriginal status, marital status, education, income, employment), and ecological covariates
Villeneuve et al. 2015	CNBSS	Canada	Recruited 1980–1985 Followed up until 2005	Women; aged 40–59 at baseline Mean age (SD): 48.5 (5.6) Exclusions: unable to assign $PM_{2.5}$ (587)	89,248	1,111	Satellite	10 km^2, 9-year time-invariant average	Mortality; CMDB	Adjusted for age at entry, occupation, marital status, attained education, contextual variables derived from census area measures, **smoking**, and BMI

Author	Study			Study Population			$PM_{2.5}$ Exposure		Lung Cancer	
	Cohort	Location	Period	Demographics	Total	Cases	Method	Definition	Outcome Measure	Confounder Adjustment
Bai et al. 2019	ONPHEC	Ontario	2001–2015	Mean age: 53	4,952,022	100,146	Satellite	1 km^2, 3-year moving average, 4-year lag	Incidence; OCR	Stratified by region (living in Toronto or not); adjusted for age, sex, neighbourhood-level covariates (census tract-level recent immigrants (arrived in the 5 years prior to census), unemployment rate, education and annual household income), select comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease, and asthma), neighbourhood deprivation, health care access; **indirectly adjusted for smoking,** BMI, alcohol drinking, and physical activity
Weichenthal et al. 2017	ONPHEC	Toronto	1996–2012	Mean age: 50.7 (14.6)	1,039,128	12,908	Satellite	1-km^2, 3-year moving average, no lag	Incidence; OCR	Stratified by one-year age and sex, adjusted for neighbourhood-level covariates and comorbid diseases, **indirectly adjusted for smoking** and BMI
Tomczak et al. 2016	CNBSS	Canada	Recruited 1980–1985 Followed up until 2004	Women; aged 40–59 at baseline Exclusions: unable to assign $PM_{2.5}$ estimates (587), diagnosed case before enrolment (14)	89,234	932	Satellite	10 km^2, 9-year time-invariant average	Incidence; CCR	Adjusted for age group at entry, occupation, marital status, attained education, BMI, **smoking,** and four contextual variables derived from census area measures
To et al. 2015	CNBSS	Ontario	Recruited 1980–1985 Followed up until 2013	Women; aged 40–59 at baseline Mean age (SD): 48.5 (5.6) Exclusions: unable to assign $PM_{2.5}$ (587)	29,549	781	Satellite	10 km^2, 9-year time-invariant average	Prevalence; provincial administrative database maintainedby ICES, considered incidenceby authorsin cases identifiedafter 1996	Adjusted for age at baseline, education, occupation, marital status, **smoking**, BMI, andfour contextual variables derived from census area measures (mean income, proportion with high school education, percentage oflow income households,and unemployment rate)

Abbreviations: **$PM_{2.5}$**–fine particulate matter; **CanCHEC**–Canadian Census Health and Environment Cohorts; **CNBSS**–Canadian National Breast Screening Study; **CCHS**–Canadian Community Health Survey; **ONPHEC**–ONtario Population Health and Environment Cohort; **CMDB**–Canadian Mortality Database; **CCR**–Canadian Cancer Registry; **ICES**–Institute for Clinical Evaluative Sciences; **OCR**–Ontario Cancer Registry; **SSC**–spatial synoptic classification; **BMI**–body mass index; **SES**–socioeconomic status.

3.3. RISK OF BIAS (ROB)

A heat map summarizing the RoB of the 12 Canadian cohort studies is presented in Table 2. Outcome assessment, selective outcome reporting, and conflict of interest were the most uniformly low RoB domains. Risk of selection bias was rated low or probably low. Exposure assessment and confounding domains varied between low, probably low, and probably high RoB, with probably high RoB indicative of lack of data on residential mobility and lack of direct or indirect smoking data for exposure assessment and confounding domains, respectively. Completeness of outcome data was the only domain that indicated high RoB (for four studies), largely due to shorter lengths of follow-up (< 11 years).

TABLE 2: Heat Map of Risk of Bias (RoB) Assessment of Canadian Cohort Studies

Author	Selection bias	Exposure Assessment	Confounding	Outcome Assessment	Completeness of Outcome Data	Selective Outcome Reporting	Conflict of Interest	Other
Crouse et al. 2015 (CanCHEC 1991)	Low	Probably low	Probably low	Low	Low	Low	Low	Low
To et al. 2015 (CNBSS)	Probably low	Probably high	Low	Low	Low	Low	Low	Probably low
Villeneuve et al. 2015 (CNBSS)	Probably low	Probably high	Low	Low	Low	Low	Low	Probably low
Pinault et al. 2016 (CCHS)	Low	Probably high	Low	Low	High	Low	Low	Low
Tomczak et al. 2016 (CNBSS)	Probably low	Probably high	Low	Low	Low	Low	Low	Probably low
Weichenthal et al. 2016 (CanCHEC 1991)	Low	Probably high	Probably low	Low	Low	Low	Low	Probably low
Pinault et al. 2017 (CanCHEC 2001)	Low	Probably low	Probably high	Low	High	Low	Low	Low
Weichenthal et al. 2017 (ONPHEC)	Probably low	Probably low	Probably low	Low	Low	Low	Low	Low
Cakmak et al. 2018 (CanCHEC 1991)	Low	Probably low	Probably low	Low	Low	Low	Low	Low
Bai et al. 2019 (ONPHEC)	Low	Probably low	Probably low	Low	Low	Low	Low	Low
Erickson et al. 2019 (CanCHEC 2001)	Low	Probably low	Probably low	Low	High	Low	Low	Low
Crouse et al. 2020 (CanCHEC 2001)	Low	Probably low	Probably high	Low	High	Low	Low	Low

Legend: Low
Probably low
Probably high
High

3.4. COHORT STUDY SELECTION

Although lung cancer incidence and mortality have previously been combined in pooled analyses (Gogna et al. 2019a; Huang et al. 2017; Hamra et al. 2014), for the present analysis these outcomes were considered separately. They represent unique outcome measures of lung cancer and therefore have differing benefits and limitations to their use in epidemiologic research (Ellis et al. 2014). With respect to lung cancer mortality, eight studies represented four cohorts (CanCHEC 1991, CanCHEC 2001, CCHS, and CNBSS), and with respect to lung cancer incidence, the four studies represented two cohorts (CNBSS and ONPHEC). A list of studies included in the systematic review but excluded from the meta-analysis, along with rationale, are presented in Appendix C (Table C.1).

3.4.1. Lung Cancer Mortality

For lung cancer mortality, the CanCHEC 1991 and CanCHEC 2001 cohorts were represented in eight of the studies. For study selection, two studies were excluded due to reductions in study population, as analysis was limited to cohort members residing within a given proximity to a monitor (Weichenthal et al. 2016) or weather station (Cakmak et al. 2018). Two additional studies were excluded due to lack of adjustment (direct or indirect) for potential confounding by smoking (Pinault et al. 2017; Crouse et al. 2020), a key risk factor in lung cancer. Of note, risk estimates with adjustments for smoking were available for each of the Canadian cohorts considered in the meta-analysis. Following the study selection process, four cohort studies from four unique cohorts remained for incorporation into the meta-analysis (study characteristics provided in Table 3):

- Crouse et al. (2015), based on CanCHEC 1991;
- Villeneuve et al. (2015), based on CNBSS;
- Pinault et al. (2016), based on CCHS; and
- Erickson et al. (2019), based on CanCHEC 2001.

Each of the four cohort studies estimated $PM_{2.5}$ exposure based on satellite-derived data. Exposure was estimated on varying geo-spatial scales: two studies estimated exposure on a 1 × 1 km scale (Pinault et al. 2016; Erickson et al. 2019) and two studies on a 10 × 10 km scale (Crouse et al. 2015; Villeneuve et al. 2015). Each of the studies, with the exception of Villeneuve et al. (2015), employed a moving average (either a 3-year or 7-year moving average with a 1-year lag) for the exposure. The number of cases of lung cancer mortality ranged from 1,111 to 30,545 out of a total cohort population ranging from 89,248 to 2,521,525. Two of the studies directly adjusted for smoking (Villeneuve et al. 2015; Pinault et al. 2016), while the other two studies relied on indirect adjustment (Crouse et al. 2015; Erickson et al. 2019). The RoB evaluations for these four studies were similar, mostly low or probably low RoB for the domains; however, Pinault et al. (2016) and Erickson et al. (2019) were evaluated as high RoB for completeness of data, reflecting shorter follow-up periods for the cohort.

TABLE 3: Study Characteristics of Canadian Cohort Studies on Lung Cancer Mortality and $PM_{2.5}$ Exposure included in the Meta-Analysis

Author	Study		Study Population		$PM_{2.5}$ Exposure			Lung Cancer Mortality	
	Cohort	Period	Total	Cases	Method	Scale	Exposure Levels ($\mu g/m^3$)	Effect Estimate (95% CI)	Covariates in Single-Pollutant Model
Crouse et al. 2015	CanCHEC 1991	1991–2006	2,521,525	30,545	Satellite	10 km^2 7-year moving average, 1-year lag	Mean = 8.9 Mean–5th percentile = 5.0	HR per 5 $\mu g/m^3$ = 1.064 (1.040, 1.088) HR per 10 $\mu g/m^3$ = 1.13 (1.081, 1.181)	Stratified by age and sex, adjusted for personal and contextual covariates, and **indirectly adjusted for smoking** and obesity **Personal covariates**: Aboriginal ancestry, visible minority status, highest level of education, employment status, occupational class, immigrant status, marital status, income quintile **Contextual variables**: census division and census tract-census division, % of immigrants, % of adults without high school diploma, % of subjects in lowest income quintile
Erickson et al. 2019	CanCHEC 2001	2001–2011	2,468,180	22,200	Satellite	1 km^2 3-year moving average, 1-year lag	Mean (SD) = 8.40 (2.8)	HR per 10 $\mu g/m^3$ = 1.139 (1.043, 1.245)	Stratified by 5-year age-sex groups, adjusted for individual and ecological covariates, **indirectly adjusted for smoking**, alcohol use, exercise, diet using sample weights (W-matrix) **Individual covariates**: marital status, visible minority, Aboriginal identity, employment, income quintile, education **Ecological covariates**: Can-Marg Index, Community Size, Airshed
Villeneuve et al. 2015	CNBSS	1980–2005	89,248	1,111	Satellite	10 km^2 9-year time-invariant average	Median (SD) = 9.1 (3.4) IQR = 6.0	HR per 10 $\mu g/m^3$ = 0.97 (0.80, 1.18)	Adjusted for age at entry, occupation, marital status, attained education, contextual variables derived from census area measures, **smoking**, and BMI **Contextual variables**: mean income, proportion with high school education, percentage of low income households, and unemployment rate

Author	Study		Study Population		$PM_{2.5}$ Exposure			Lung Cancer Mortality	
	Cohort	Period	Total	Cases	Method	Scale	Exposure Levels ($\mu g/m^3$)	Effect Estimate (95% CI)	Covariates in Single-Pollutant Model
Pinault et al. 2016	CCHS	2000–2011	299,500	2,700	Satellite	1 km^2 3-year moving average, 1-year lag	Mean (SD) = 6.3 (2.5)	HR per 10 $\mu g/m^3$ = 1.167 (0.975, 1.396)	Stratified by age (5-year categories) and sex Adjusted for SES, behavioural, and ecological covariates **SES covariates**: immigrant status, visible minority status, Aboriginal status, marital status, income adequacy quintile, educational attainment, and employment **Behavioural covariates**: alcohol consumption, fruit and vegetable consumption, **smoking**, and BMI **Ecological covariates**: (CD-DA and CD) for % recent immigrants, % completed high school, and % low income household

Abbreviations: **$PM_{2.5}$**–fine particulate matter; **CanCHEC**–Canadian Census Health and Environment Cohorts; **CNBSS**–Canadian National Breast Screening Study; **CCHS**–Canadian Community Health Survey; **SD**–standard deviation; **IQR**–interquartile range; **HR**–hazard ratio; **CI**–confidence interval; **BMI**–body mass index; **SES**–socioeconomic status.

3.4.2. Lung Cancer Incidence

For lung cancer incidence, the four studies represented only two cohorts; thus, two studies were excluded from the meta-analysis. Weichenthal et al. (2017) was excluded as it considered a sub-population of the cohort that was fully represented in Bai et al. (2019). Although Tomzak et al. (2016) considered the full CNBSS cohort in their analysis, the results from To et al. (2015), which considered only Ontario residents in the CNBSS cohort, were selected for inclusion in the present meta-analysis. Despite the smaller population size, To et al. (2015) was chosen as the study authors indicated that lung cancer incidence results in Tomzak et al. (2016) were under re-evaluation (P. Villeneuve, personal communication, Feb 19, 2020).

Following the study selection process, two cohort studies from two unique cohorts remained for incorporation into the meta-analysis (study characteristics provided in Table 4):

- Bai et al. (2019), based on ONPHEC; and
- To et al. (2015), based on CNBSS.

Both included studies were based on Ontario populations and utilized satellite-derived estimates of $PM_{2.5}$. The number of cases was considerably smaller in the study by To et al. (2015), at 781 cases compared with 100,146 cases in Bai et al. (2019), with equally noticeable differences in magnitude of total study populations, at 29,549 and 4,952,022 for To et al. (2015) and Bai et al. (2019), respectively. Furthermore, To et al. (2015) examined the association as an incidence rate ratio (IRR), whereas Bai et al. (2019) modelled the relationship as an HR. However, it is common practice to consider HRs comparable to IRRs (Hernán 2010), which would not pose issues in pooling. To et al. (2015) also directly adjusted for smoking, while Bai et al. (2019) relied on indirect adjustments. Both studies had a follow-up period of at least 15 years. The RoB evaluations were similar for both studies, mainly low and probably low for the domains; however, To et al. (2015) was evaluated as probably high RoB for exposure assessment, as residential mobility was not accounted for in the study.

TABLE 4: Study Characteristics of Canadian Cohort Studies on Lung Cancer Incidence and $PM_{2.5}$ Exposure included in the Meta-Analysis

Author	Study		Study Population		$PM_{2.5}$ Exposure			Lung Cancer Mortality	
	Cohort	Period	Total	Cases	Method	Scale	Exposure Levels ($\mu g/m^3$)	Effect Estimate (95% CI)	Covariates in Single-Pollutant Model
To et al. 2015	CNBSS; Ontario	Recruited 1980–1985 Followed up until 2013	29,549	781	Satellite	10 km^2, 9-year time-invariant average	**Those with disease:** Mean (SD) = 12.70 (2.39) IQR = 3.40 **Those without:** Mean (SD) = 12.47 (2.40) IQR = 3.90	IRR per 10 $\mu g/m^3$ = 1.03 (0.72, 1.45)	Adjusted for age at baseline, education, occupation, marital status, **smoking**, BMI, and four contextual variables derived from census area measures (mean income, proportion with high school education, percentage of low income households, and unemployment rate)
Bai et al. 2019	ONPHEC; Ontario	2001–2015	4,952,022	100,146	Satellite	1 km^2, 3-yr moving average, 4-yr lag	Mean = 10.8 IQR = 5.3	HR per 5.3 $\mu g/m^3$ = 1.03 (1.01, 1.05) HR per 10 $\mu g/m^3$ = 1.06 (1.02, 1.10)	Stratified by region (living in Toronto or not); adjusted for age, sex, neighbourhood-level covariates (census tract-level recent immigrants [arrived in the 5 years prior to census], unemployment rate, education, and annual household income), select comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease, and asthma), neighbourhood deprivation, health care access; **indirectly adjusted for smoking**, BMI, alcohol drinking, and physical activity

Abbreviations: **$PM_{2.5}$**–fine particulate matter; **CNBSS**–Canadian National Breast Screening Study; **ONPHEC**–ONtario Population Health and Environment Cohort; **IQR**–interquartile range; **SD**–standard deviation; **IRR**–incidence rate ratio; **HR**–hazard ratio; **CI**–confidence interval; **BMI**–body mass index.

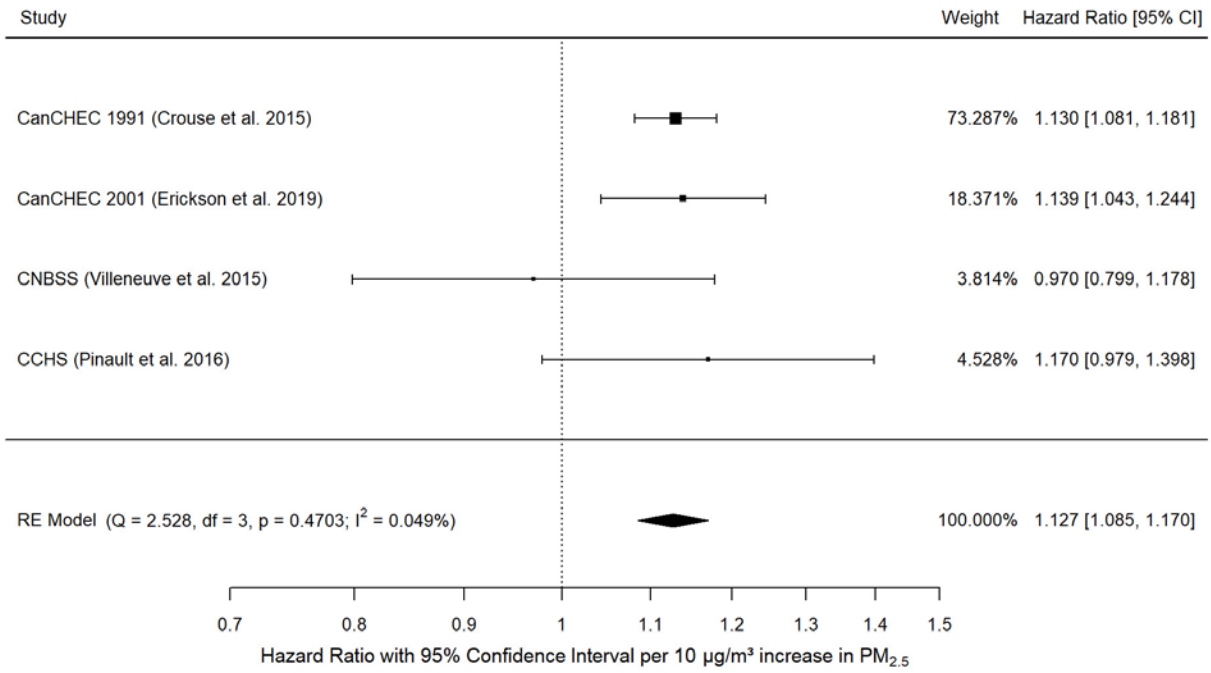
3.5. META-ANALYSIS

3.5.1. Lung Cancer Mortality

Meta-Analysis

The forest plot and results of the random-effects meta-analysis for lung cancer mortality are presented in Figure 2. The pooled risk estimate was 1.127 (95% CI: 1.085, 1.170) per 10 µg/m^3 $PM_{2.5}$ exposure. There was no evidence of heterogeneity (I^2 = 0.049%, *p*-value = 0.4703). Of note, over 90% of the weighting was attributed to the studies based on CanCHEC 1991 and 2001, given their much larger population sizes.

FIGURE 2: Forest Plot for Lung Cancer Mortality Cohort Studies

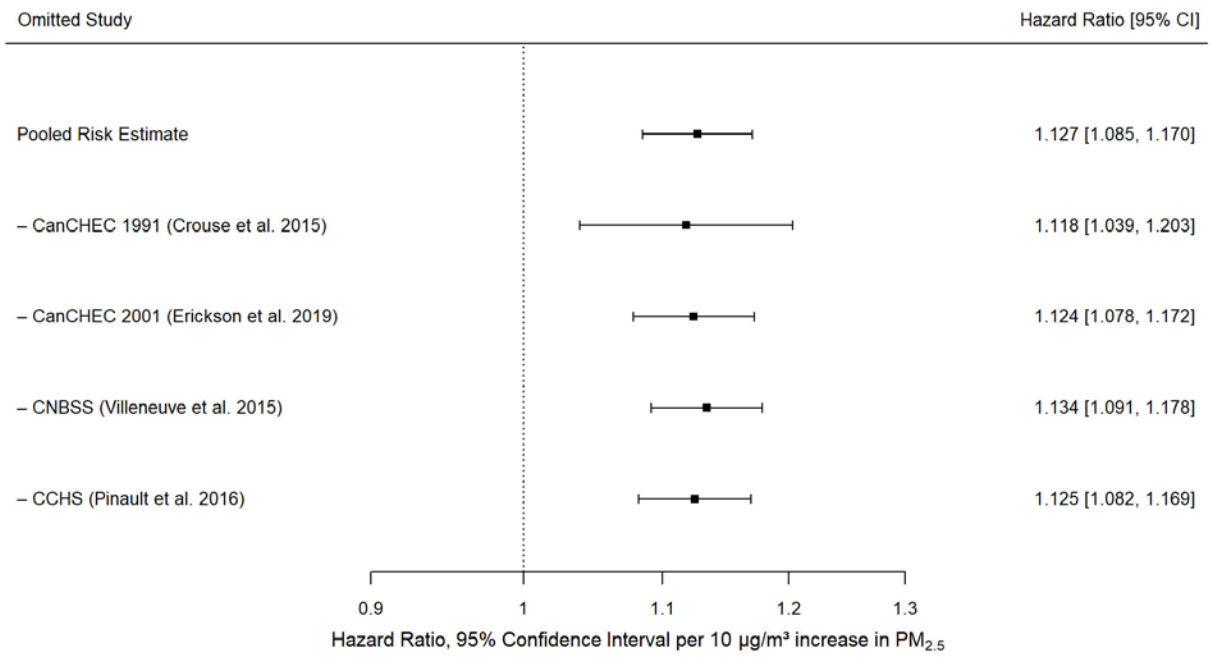


Abbreviations: **CanCHEC**–Canadian Census Health and Environment Cohorts; **CNBSS**–Canadian National Breast Screening Study; **CCHS**–Canadian Community Health Survey; **$PM_{2.5}$**–fine particulate matter; **RE**–random effects; **CI**–confidence interval.
Hazard ratios are presented per 10 µg/m^3 increase in $PM_{2.5}$ exposure.

Influence Diagnostics

The results of the leave-one-out analysis are presented in Figure 3. The leave-one-out analysis identified that omitting one study would lead to pooled risk estimates ranging from 1.118 to 1.134, and each of the leave-one-out pooled risk estimates remained statistically significant with no evidence of heterogeneity.

FIGURE 3: Forest Plot of Leave-One-Out Analysis for Lung Cancer Mortality Cohort Studies



Abbreviations: **CanCHEC**–Canadian Census Health and Environment Cohorts; **CNBSS**–Canadian National Breast Screening Study; **CCHS**–Canadian Community Health Survey; **$PM_{2.5}$**–fine particulate matter; **CI**–confidence interval.

Hazard ratios are presented per 10 µg/m³ increase in $PM_{2.5}$ exposure.

Sensitivity Analysis

As a sensitivity analysis, the excluded studies were individually substituted into the meta-analysis (Table 5) in place of the included study of the same cohort used in the main analysis. The pooled risk estimates ranged from 1.118 to 1.135 and they remained statistically significant, and no evidence of heterogeneity was observed.

TABLE 5: Sensitivity Analysis for Lung Cancer Mortality

Analysis	Pooled Hazard Ratio (95% CI)	Heterogeneity
Base analysis	1.127 (1.085, 1.170)	I^2 = 0.049%, p = 0.4703
Substitute Cakmak et al. 2018 for Crouse et al. 2015 (CanCHEC 1991)	1.135 (1.060, 1.216)	I^2 = 0.000%, p = 0.2894
Substitute Crouse et al. 2020 for Erickson et al. 2019 (CanCHEC 2001)	1.118 (1.078, 1.161)	I^2 = 0.330%, p = 0.4413
Substitute Pinault et al. 2017 for Erickson et al. 2019 (CanCHEC 2001)	1.132 (1.091, 1.175)	I^2 = 0.031%, p = 0.4004

Abbreviations: **CanCHEC**–Canadian Census Health and Environment Cohorts; **$PM_{2.5}$**–fine particulate matter; **CI**–confidence interval.

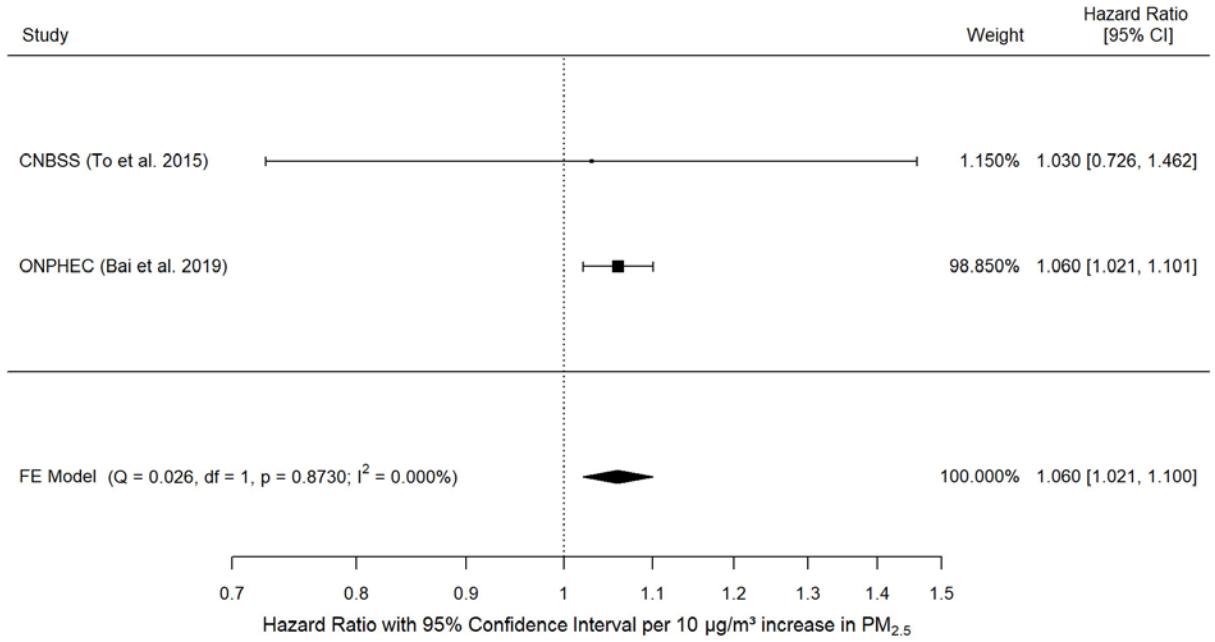
Hazard ratios are presented per 10 µg/m³ increase in $PM_{2.5}$ exposure.

3.5.2. Lung Cancer Incidence

Meta-Analysis

The forest plot of the fixed-effects meta-analysis for lung cancer incidence is presented in Figure 4. The pooled risk estimate was 1.060 (95% CI: 1.021, 1.100) per 10 µg/m^3 $PM_{2.5}$. There was no evidence of heterogeneity. Of note, almost 99% of the weighting was attributed to Bai et al. (2019) owing to its much larger cohort size.

FIGURE 4: Forest Plot for Lung Cancer Incidence Cohort Studies



Abbreviations: **CNBSS**–Canadian National Breast Screening Study; **ONPHEC**–ONtario Population Health and Environment Cohort; **$PM_{2.5}$**–fine particulate matter; **FE**–fixed effects; **CI**–confidence interval.

Hazard ratios are presented per 10 µg/m^3 increase in $PM_{2.5}$ exposure.

3.6. QUALITATIVE SYNTHESIS

A number of the studies additionally examined other key areas of interest, namely the effect of other pollutants or oxidative potential of $PM_{2.5}$ on the relationship between $PM_{2.5}$ and lung cancer, and the shape of the curve of the relationship. Although such analyses cannot be quantitatively synthesized in the meta-analysis, they provide additional context for understanding the association of interest. A qualitative synthesis of these additional analyses is presented in the following sections.

3.6.1. Multipollutant Models and Oxidative Potential

From the literature search, five of the cohort studies evaluated the potential impact of other air pollutants or the oxidative potential of $PM_{2.5}$ on the association between $PM_{2.5}$ and lung cancer. Summaries of these additional analyses are presented in Appendix D (Table D.1).

Using the CanCHEC 1991 cohort, Crouse et al. (2015) observed that when adjusting for O_3 and NO_2, the $PM_{2.5}$ risk estimate for lung cancer mortality slightly decreased in the multipollutant analysis compared with $PM_{2.5}$ alone (1.059 vs. 1.064 per 5 μg/m^3 increase in $PM_{2.5}$) in the models that also indirectly adjusted for smoking and obesity. However, in the models that did not account for smoking and obesity, a slight increase in the $PM_{2.5}$ risk estimate was noted for the multipollutant model (1.031 vs. 1.038 per 5 μg/m^3 increase in $PM_{2.5}$). Considering the CanCHEC 1991 cohort with a longer follow-up period, Cakmak et al. (2018) reported an increase in the risk estimate for lung cancer mortality when $PM_{2.5}$ was adjusted for O_3 compared to $PM_{2.5}$ in the single pollutant model (1.26 vs. 1.49 per 10 μg/m^3 increase in $PM_{2.5}$); models were indirectly adjusted for smoking and obesity. From the CanCHEC 2001 cohort, Crouse et al. (2020) reported an increase in risk estimate for $PM_{2.5}$ and lung cancer mortality when the models adjusted for O_3 or combined oxidant capacity of O_3 and NO_2 (1.15 vs. 1.26 or 1.24 per 10 μg/m^3 increase in $PM_{2.5}$), although a decrease in risk estimate was noted when adjusting for NO_2 (1.15 vs. 1.09 per 10 μg/m^3 increase in $PM_{2.5}$); these models did not account for smoking or obesity. This pattern was consistent regardless of whether exposures were considered as a 3-year or 8-year moving average. In an analysis of the Toronto members of the ONPHEC cohort, Weichenthal et al. (2017) also reported a small decrease in the association between lung cancer incidence and $PM_{2.5}$ when the model was adjusted for NO_2 (1.03 vs. 1.02 per 3.2 μg/m^3 increase in $PM_{2.5}$); these models did not account for smoking or obesity.

Crouse et al. (2020) evaluated effect modification by O_3, and noted the associations between $PM_{2.5}$ and lung cancer mortality were greatest in areas with low O_3. This observation suggested possible differential biological responses to $PM_{2.5}$ in low O_3 regions, or possible chemical interactions between $PM_{2.5}$ and O_3 in the atmosphere altering the biological activity of the particles. To investigate the impact of oxidative burden of $PM_{2.5}$ on cause-specific mortality, Weichenthal et al. (2016) measured the oxidative potential of regional $PM_{2.5}$ samples based on depletion of glutathione (OP^{GSH}) or ascorbic acid (OP^{AA}), and derived an exposure metric by multiplying the oxidative potential and $PM_{2.5}$ mass concentrations. Considering the Ontario members of the CanCHEC 1991 cohort, Weichenthal et al. (2016) reported an increase in risk estimate for lung cancer mortality and $PM_{2.5}$ when considering the glutathione-based oxidative burden (1.050 per IQR increase in $PM_{2.5}$ vs. 1.117 per IQR increase in $PM_{2.5}$*OP^{GSH}); however, no association was observed for the ascorbate-based oxidative burden (0.970 per IQR increase in $PM_{2.5}$*OP^{AA}).

3.6.2. Shape of the $PM_{2.5}$–Lung Cancer Relationship

From the literature search, three cohort studies were identified that evaluated the shape of the relationship between $PM_{2.5}$ and lung cancer mortality or incidence. Summaries of these additional analyses are presented in Appendix D (Table D.2).

Using the CNBSS cohort, Tomczak et al. (2016) observed a supralinear relationship between lung cancer incidence and $PM_{2.5}$ exposure, based on natural cubic spline functions with three degrees of freedom with the fully adjusted model (including both smoking and BMI). At low concentrations of $PM_{2.5}$, the relationship was positive and steep, and plateaued after 12 $\mu g/m^3$ $PM_{2.5}$, and the exposure-response relationship did not indicate a threshold. Pinault et al. (2017) and Bai et al. (2019) evaluated the exposure-response relationship using the Shape Constrained Health Impact Function (SCHIF), a method that fits different shapes of association based on sigmoidal functions. Both studies reported sublinear associations with $PM_{2.5}$. From the CanCHEC 2001 cohort, Pinault et al. (2017) observed that the exposure-response relationship for lung cancer mortality was shallow at < 5 $\mu g/m^3$ $PM_{2.5}$, steepest at 5–10 $\mu g/m^3$ $PM_{2.5}$, and moderate at levels > 10 $\mu g/m^3$ $PM_{2.5}$. Based on the ONPHEC, Bai et al. (2019) observed a threshold at 10 $\mu g/m^3$ $PM_{2.5}$ in the association between $PM_{2.5}$ exposure and lung cancer incidence. Neither Pinault et al. (2017) nor Bai et al. (2019) included adjustments for behavioural risk factors (e.g., smoking and obesity) in the shape analysis.

CHAPTER 4: **DISCUSSION**

The objective of this report was to quantify the relationship between long-term ambient $PM_{2.5}$ exposure and risk of lung cancer mortality and incidence in Canada. This was achieved by conducting a systematic review of the evidence on the relationship between long-term exposure to ambient $PM_{2.5}$ and the risk of lung cancer in the Canadian population. Based on meta-analyses of Canadian cohort studies, long-term exposure to $PM_{2.5}$ was associated with an increased risk of lung cancer mortality and incidence. There was a stronger association for mortality [pooled estimate: 1.127 (95% CI: 1.085, 1.170)] compared to incidence [pooled estimate: 1.060 (95% CI: 1.021, 1.100)] per 10 $\mu g/m^3$ $PM_{2.5}$. However, a larger number of studies considered lung cancer mortality (eight studies identified in literature search, four included in meta-analysis) than incidence (four studies identified in literature search, two included in meta-analysis), and none of the studies reported on both incidence and mortality from the same cohort. There was no indication of heterogeneity in the pooled estimate for lung cancer mortality (I^2 = 0.049%, *p*-value = 0.4703) or incidence (I^2 = 0.000%, *p*-value = 0.8730). Sensitivity analysis resulted in similar pooled risk estimates as the main pooled estimate and no evidence of heterogeneity, indicating robustness in the meta-analysis. However, measures of heterogeneity should be interpreted with caution when based on a small number of studies. Potential confounding of the relationship between ambient $PM_{2.5}$ and lung cancer was considered in each of the primary studies included in the meta-analysis. Specifically, each of the risk estimates included in the two meta-analyses directly or indirectly adjusted for smoking, and included covariates for age, sex, employment status, income, and education.

Since only a small number of studies were included in the meta-analyses, statistical methods for evaluation of publication bias (e.g., Begg's and Egger's tests and funnel plots) were not considered to be relevant. In addition, the authors of this report are unaware of any relevant work that was not included in this systematic review and meta-analysis. For lung cancer mortality, the pooled estimate was robust to the influence analysis. The leave-one-out approach produced a range of effect estimates of 1.118–1.134 per 10 $\mu g/m^3$ $PM_{2.5}$, indicating that exclusion of a given primary study did not greatly influence the pooled estimate compared with the main analysis. In comparison, for lung cancer incidence, the meta-analysis was dominated by Bai et al. (2019), which had a study size two orders of magnitude larger than To et al. (2015).

To account for the possible role of other ambient air pollutants in the association between $PM_{2.5}$ and health effects, a subset of studies evaluated multipollutant models as additional analyses. A stronger association was noted between $PM_{2.5}$ and lung cancer mortality when adjusting for O_3 or total oxidant capacity of O_3 and NO_2 (Cakmak et al. 2018; Crouse et al. 2020). In comparison, adjusting for NO_2 resulted in weaker associations for $PM_{2.5}$ and lung cancer mortality (Crouse et al. 2020) and incidence (Weichenthal et al. 2017). Further research is needed to better understand the role of the oxidant gases in the relationship between $PM_{2.5}$ and lung cancer risks. Similarly, additional studies are necessary to evaluate the possible role of the oxidative potential of $PM_{2.5}$ on the association with lung cancer.

The association between ambient $PM_{2.5}$ and lung cancer risk has been the focus of several other meta-analyses. Often, these evaluations have included other countries and regions that have higher levels of air pollution than are present in Canada and, as such, the results may not be directly comparable to the present analysis. However, when considering other systematic reviews with meta-analysis that limited included studies to regions with similar $PM_{2.5}$ exposures to those in Canada (i.e., North America and Europe), the results of the present meta-analysis are consistent with these other reports (Ghazipura et al. 2019; Gogna et al. 2019a, Huang et al. 2017; Cui et al. 2015; Hamra et al. 2014; Chen et al. 2008). General findings and characteristics of these systematic reviews with meta-analysis are presented in Appendix E (Table E.1).

Previous meta-analyses of North American studies of the association between $PM_{2.5}$ and lung cancer mortality have predominantly included studies conducted in the US and reported nearly identical pooled risk estimates, ranging from 1.14–1.15 per 10 $\mu g/m^3$ $PM_{2.5}$ (Huang et al. 2017; Cui et al. 2015; Chen et al. 2008). Pooled analysis of European studies of lung cancer mortality included fewer primary studies (compared with the North American analyses) and the results were variable ranging from 1.05–1.23 per 10 $\mu g/m^3$ $PM_{2.5}$ (Huang et al. 2017; Chen et al. 2008). For lung cancer incidence, Huang et al. (2017) reported pooled estimates of 1.06 and 1.03 per 10 $\mu g/m^3$ $PM_{2.5}$, for North America and Europe, respectively. However, a stronger association of 1.25 per 10 $\mu g/m^3$ $PM_{2.5}$ for lung cancer incidence was reported by Ghazipura et al. (2019). This pooled estimate is greater than observed in the present estimate limited to Canadian studies, which may be attributable to inclusion of North American and European studies in the pooled estimate, as well as inclusion of both case-control and cohort studies. Additionally, some of the pooled analyses combined lung cancer mortality and incidence, and reported associations with $PM_{2.5}$ that ranged from 1.09–1.11 for North America (Gogna et al. 2019a; Huang et al. 2017; Hamra et al. 2014) and 1.03 for Europe (Huang et al. 2017; Hamra et al. 2014).

Of these previous meta-analyses, Gogna et al. (2019a) also limited included studies to those conducted in Canada. Compared with the present meta-analyses, Gogna et al. (2019a) combined lung cancer mortality and incidence, and included both case-control and cohort studies in the pooled estimate. Despite these differences and a more recent literature search in the present analysis (November 2019 compared with August 2018), the primary studies by Crouse et al. (2015), Villeneuve et al. (2015), and Pinault et al. (2016) were included in both pooled estimates. Neither of the primary studies of lung cancer incidence utilized in the present analysis were included in Gogna et al. (2019a). Based on a pooled risk estimate of 1.09 per 10 $\mu g/m^3$ $PM_{2.5}$, Gogna et al. (2019a) estimated that, for 2015, 6.9% of lung cancer cases in Canada were attributable to $PM_{2.5}$.

The results of the present analyses did not indicate the presence of heterogeneity in the pooled risk estimates (I^2 = 0.049%, *p*-value = 0.4703 for mortality; I^2 = 0.000%, *p*-value = 0.8730 for incidence). The lack of heterogeneity in the meta-analyses was not unexpected for several reasons. Each of the studies employed a cohort design and was conducted in the same population, with mortality studies considering the Canadian population and incidence studies considering the population of Ontario. As such, the baseline characteristics of the cohort populations were largely comparable, with the exception of CNBSS. Compared with the more nationally representative cohorts of CanCHEC and CCHS, CNBSS includes only women who were mostly white, married, and of higher SES (Villeneuve et al. 2015). Of the cohort studies included in the meta-analysis, Villeneuve et al. (2015) was the only study to not report a positive association between $PM_{2.5}$ exposure and lung cancer mortality; however, the lung cancer mortality rate is lower in women than in men, as the age-standardized mortality rates per 100,000 for lung cancer in Canada in 2020 are 42.5 and 53.4 for females and males, respectively (Brenner et al. 2020). For the meta-analyses, the most fully adjusted models including direct or indirect adjustment for smoking were selected, accounting for this key risk factor of lung cancer (Wipfli and Samet 2016). For lung cancer mortality, case ascertainment was identical for each of the cohort studies relying on the CMDB. Lastly, the exposure assessments were highly consistent between the cohort studies. Each study relied on satellite-derived $PM_{2.5}$ exposure estimates, and mean and median concentrations ranged from 6–9 $\mu g/m^3$ $PM_{2.5}$, reflective of the relative stability in ambient $PM_{2.5}$ levels in Canada for the past two decades (ECCC 2018). Crouse et al. (2020) observed that the associations for $PM_{2.5}$ and lung cancer mortality were stronger when exposure was estimated at finer spatial scales, and that the associations were less sensitive to alterations of the temporal scale, indicating that localized sources and $PM_{2.5}$ components may be relevant considerations for lung cancer.

The main strength of this meta-analysis is the use of Canadian studies, including large population-based cohort studies, to derive a pooled risk estimate that is representative of the population of interest. By only considering cohort studies, this analysis addressed the temporality of the association between long-term exposure to $PM_{2.5}$ and lung cancer. Additionally, lung cancer mortality and incidence were evaluated separately, with mortality having approximately twice the magnitude of association as incidence; however, this is based on a small number of studies. The most persuasive evidence that the magnitude of association differs for incidence and mortality would come from analysis of both outcomes in multiple cohorts. Both outcomes were evaluated in only one of the cohorts (CNBSS) included in the present analysis. Lastly, each of the studies included in the meta-analyses included adjustment for smoking, accounting for this key confounder.

This meta-analysis has some limitations and uncertainties. Each of the cohort studies assigned exposure based on place of residence, which does not account for daily activities or travel to other areas, both of which are anticipated to influence an individual's exposure to air pollutants. The meta-analysis of lung cancer mortality included both the CanCHEC 1991 (Crouse et al. 2015) and CanCHEC 2001 (Erickson et al. 2019) cohorts. The populations of these cohorts are not entirely unique as 2.6 million of the CanCHEC 1991 participants (~16%) are also included in the 2001 cohort (M. Tjepkema, personal communication, Feb 12, 2021). A few of the studies had comparatively shorter follow-up periods of less than 11 years in length (Pinault et al. 2016; Pinault et al. 2017; Erickson et al. 2019; Crouse et al. 2020), potentially reducing the study's ability to detect an association. However, of the studies with shorter follow-up periods, three of the four studies observed significant associations and the magnitude of the risk estimates were comparable to those from the studies with longer follow-up periods. The data available in the cohort studies were insufficient to conduct analyses to evaluate any sensitive subgroups (e.g., sex, SES status). Additionally, nearly all the cohorts considered were nationally representative, which was preferable for the objectives of this analysis; however, the available studies were not sufficient to identify any regional variability in the observed association between $PM_{2.5}$ and lung cancer, as the risk may not be uniform across the country. None of the studies considered potential confounding by radon exposure, which is estimated to be associated with 6.9% of lung cancer cases in Canada (Gogna et al. 2019b), similar to the burden attributable to $PM_{2.5}$ (Gogna et al. 2019a). The pooled risk estimates derived in the present evaluation assume a linear relationship between $PM_{2.5}$ exposure and lung cancer mortality or incidence. A small number of studies have evaluated the shape of the relationship (Tomczak et al. 2016; Pinault et al. 2017; Bai et al. 2019), and indicated the relationship may not be linear, and Bai et al. (2019) suggested a possible threshold may exist. Additionally, there was some evidence that the relationship between $PM_{2.5}$ and lung cancer may be influenced by other pollutants and not accounting for these may result in over or underestimating the association. Lastly, the meta-analysis for lung cancer incidence relied solely on two studies, and the pooled estimate was dominated by the larger study. Further studies of lung cancer incidence, preferably on a national scale, are necessary to increase the confidence in and generalizability of the pooled estimate.

CHAPTER 5: **CONCLUSION**

Based on this systematic review with meta-analysis, ambient $PM_{2.5}$ exposure, even at the relatively low levels experienced in Canada, is associated with an increased risk of lung cancer mortality and incidence. The pooled risk estimates derived here from Canadian cohort studies can be used to assess the burden of lung cancer associated with ambient $PM_{2.5}$ in Canada. The results were consistent with other meta-analyses of North American and European studies. Additional studies are needed to further characterize the shape of the association, understand the effects of adjusting for exposures to other pollutants, and identify any sensitive subgroups.

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APPENDICES

ANNEXE A : INITIAL AND SUPPLEMENTAL SEARCH

A.1. Initial Search

Medline

Database(s): **Ovid MEDLINE(R) ALL** 1946 to September 03, 2019
Search Strategy:

#	Searches
1	exp lung neoplasms/
2	Tracheal Neoplasms/
3	((lung* or pulmonary or respiratory or bronch* or alveola* or trache*) adj4 (neoplas* or cancer* or adenocarcinom* or carcinom* or chondosarcoma* or blastoma* or hemangioma* or malignan* or sarcoma* or tumor* or tumour* or squamous or oat cell or small cell or SCLC)).tw,kw,kf.
4	(pancoast* adj3 (syndrome* or tumor* or tumour*)).tw,kw,kf.
5	((ICD or classif*) adj5 ("C33" or "C34" or "C34.0" or "C34.1" or "C34.2" or "C34.3" or "C34.8" or "C34.9")).tw,kw,kf.
6	or/1-5 [Lung or Tracheal Cancer]
7	("pm2.5" or "pm 2.5" or pmfine or finepm or pm fine or fine pm or fine particle* or fine particulate*).tw,kw,kf.
8	(("2.5" adj3 (mum or micro m or micromet* or micro meter* or micro metre* or micron*)) or "2.5mum" or "2.5micro m").tw,kw,kf.
9	7 or 8 [Fine PM]
10	6 and 9

Embase

Database(s): **Embase** 1974 to 2019 September 03
Search Strategy:

#	Searches
1	exp lung cancer/
2	exp trachea cancer/
3	((lung* or pulmonary or respiratory or bronch* or alveola* or trache*) adj4 (neoplas* or cancer* or adenocarcinom* or carcinom* or chondosarcoma* or blastoma* or hemangioma* or malignan* or sarcoma* or tumor* or tumour* or squamous or oat cell or small cell or SCLC)).tw,kw.
4	(pancoast* adj3 (syndrome* or tumor* or tumour*)).tw,kw.
5	((ICD or classif*) adj5 ("C33" or "C34" or "C34.0" or "C34.1" or "C34.2" or "C34.3" or "C34.8" or "C34.9")).tw,kw.
6	or/1-5 [Lung or Tracheal Cancer]
7	("pm2.5" or "pm 2.5" or pmfine or finepm or pm fine or fine pm or fine particle* or fine particulate*).tw,kw.
8	(("2.5" adj3 (mum or micro m or micromet* or micro meter* or micro metre* or micron*)) or "2.5mum" or "2.5micro m").tw,kw.
9	7 or 8 [Fine PM]
10	6 and 9

Global Health

Database(s): **Global Health** 1973 to 2019 Week 34
Search Strategy:

#	Searches
1	exp lung cancer/
2	((lung* or pulmonary or respiratory or bronch* or alveola* or trache*) adj4 (neoplas* or cancer* or adenocarcinom* or carcinom* or chondosarcoma* or blastoma* or hemangioma* or malignan* or sarcoma* or tumor* or tumour* or squamous or oat cell or small cell or SCLC)).tw.
3	(pancoast* adj3 (syndrome* or tumor* or tumour*)).tw.
4	((ICD or classif*) adj5 ("C33" or "C34" or "C34.0" or "C34.1" or "C34.2" or "C34.3" or "C34.8" or "C34.9")).tw.
5	or/1-4 [Lung or Tracheal Cancer]
6	("pm2.5" or "pm 2.5" or pmfine or finepm or pm fine or fine pm or fine particle* or fine particulate*).tw.
7	(("2.5" adj3 (mum or micro m or micromet* or micro meter* or micro metre* or micron*)) or "2.5mum" or "2.5micro m").tw.
8	6 or 7 [Fine PM]
9	5 and 8

Cochrane CENTRAL Register of Controlled Trials

Database(s): **EBM Reviews–Cochrane Central Register of Controlled Trials** July 2019
Search Strategy:

#	Searches
1	exp lung neoplasms/
2	tracheal neoplasms/
3	((lung* or pulmonary or respiratory or bronch* or alveola* or trache*) adj4 (neoplas* or cancer* or adenocarcinom* or carcinom* or chondosarcoma* or blastoma* or hemangioma* or malignan* or sarcoma* or tumor* or tumour* or squamous or oat cell or small cell or SCLC)).tw,kw.
4	(pancoast* adj3 (syndrome* or tumor* or tumour*)).tw,kw.
5	((ICD or classif*) adj5 ("C33" or "C34" or "C34.0" or "C34.1" or "C34.2" or "C34.3" or "C34.8" or "C34.9")).tw,kw.
6	or/1-5 [Lung or Tracheal Cancer]
7	("pm2.5" or "pm 2.5" or pmfine or finepm or pm fine or fine pm or fine particle* or fine particulate*).tw,kw.
8	(("2.5" adj3 (mum or micro m or micromet* or micro meter* or micro metre* or micron*)) or "2.5mum" or "2.5micro m").tw,kw.
9	7 or 8 [Fine PM]
10	6 and 9

Toxline

Search	Database	Query
# 8	toxline	(#4 AND #7) AND NOT PubMed [org] AND NOT pubdart [org]
# 7	toxline	(#5 OR #6) AND NOT PubMed [org] AND NOT pubdart [org]
# 6	toxline	(("2 5" AND (mum OR "micro m" OR "micrometre" OR "micrometres" OR "micro meter" OR "micro meters" OR "micro metre" OR "micro metres" OR micron OR microns)) OR "2 5mum" OR "2 5micro m") AND NOT PubMed [org] AND NOT pubdart [org]
# 5	toxline	("pm2 5" OR "pm 2 5" OR pmfine OR finepm OR (pm OR 1320-67-8 [rn]) fine OR fine (pm OR 1320-67-8 [rn]) OR "fine particle" OR "fine particles" OR "fine particulate" OR "fine particulates") AND NOT PubMed [org] AND NOT pubdart [org]
# 4	toxline	((#1 AND #2) OR #3) AND NOT PubMed [org] AND NOT pubdart [org]
# 3	toxline	("pancoast syndrome" OR "pancoast tumor" OR "pancoast tumors" OR "pancoast tumour" OR "pancoast tumours") AND NOT PubMed [org] AND NOT pubdart [org]
# 2	toxline	(neoplasm OR neoplasms OR neoplastic OR cancer OR cancers OR cancerous OR adenocarcinoma OR adenocarcinomas OR carcinoma OR carcinomas OR chondosarcoma OR chondosarcomas OR blastoma OR blastomas OR hemangioma OR hemangiomas OR malignant OR malignancy OR malignancies OR sarcoma OR sarcomas OR tumor OR tumors OR tumour OR tumours OR squamous OR "oat cell" OR "oat cells" OR "small cell" OR "small cells" OR sclc) AND NOT PubMed [org] AND NOT pubdart [org]
# 1	toxline	(lung OR pulmonary OR respiratory OR bronchia OR bronchi OR bronchial OR bronchiole OR bronchus OR alveola OR alveolas OR alveolar OR trachea OR trachea OR tracheal) AND NOT PubMed [org] AND NOT pubdart [org]

A.2. Supplemental Search

Medline

Database(s): **Ovid MEDLINE(R) ALL** 1946 to November 26, 2019
Search Strategy:

#	Searches
1	exp lung neoplasms/
2	Tracheal Neoplasms/
3	((lung* or pulmonary or respiratory or bronch* or alveola* or trache*) adj4 (neoplas* or cancer* or adenocarcinom* or carcinom* or chondosarcoma* or blastoma* or hemangioma* or malignan* or sarcoma* or tumor* or tumour* or squamous or oat cell or small cell or SCLC)).tw,kw,kf.
4	(pancoast* adj3 (syndrome* or tumor* or tumour*)).tw,kw,kf.
5	((ICD or classif*) adj5 ("C33" or "C34" or "C34.0" or "C34.1" or "C34.2" or "C34.3" or "C34.8" or "C34.9")).tw,kw,kf.
6	or/1-5 [Lung or Tracheal Cancer]
7	("pm2.5" or "pm 2.5" or pmfine or finepm or pm fine or fine pm or fine particle* or fine particulate*).tw,kw,kf.
8	(("2.5" adj3 (mum or micro m or micromet* or micro meter* or micro metre* or micron*)) or "2.5mum" or "2.5micro m").tw,kw,kf.
9	7 or 8 [Fine PM]
10	6 and 9
11	(19* or 200* or 2010* or 2011* or 2012* or 2013* or 2015* or 2016* or 2017* or 2018* or 2019 01* or 2019 02* or 2019 03* or 2019 04* or 2019 05* or 2019 06* or 2019 07* or 2019 08* or "2019 09 01" or "2019 09 02" or "2019 09 03" or 2019 jan* or 2019 feb* or 2019 mar* or 2019 apr* or 2019 may* or 2019 jun* or 2019 jul* or 2019 aug* or "2019 sep 01" or "2019 sep 02" or "2019 sep 03" or 201901* or 201902* or 201903* or 201904* or 201905* or 201906* or 201907* or 201908* or "20190901" or "20190902" or "20190903").dt,dp.
12	10 and 11 [Previous search results: PM2.5 + Lung Cancer]
13	exp Canada/ or (canada* or canadia* or canadien* or Ottawa* or british columbia* or colombie britannique* or vancouver* or alberta* or edmonton* or calgar* or saskatchewan* or regina* or saskatoon* or manitoba* or winnipeg* or ontari* or toronto* or quebec* or montreal* or new brunswick* or nouveau brunswick* or fredericton* or nova scotia* or nouvelle ecosse* or halifax* or haligonian* or prince edward island* or ile du prince edouard* or pei or charlottetown* or Newfoundland* or terre neuve* or labrador* or nfld or yukon* or whitehorse* or northwest territor* or territoires du nord ouest* or nwt or yellowknife* or nunavut* or iqaluit*).tw.
14	exp Epidemiology/ or exp Epidemiologic Methods/
15	(biosurveill* or epidemiolog* or inciden* or prevalen* or morbid* or mortal* or ((communit* or population* or resident or residents or famil* or public*) adj4 (assess* or sampl* or monitor* or follow* or study or studies* or survey* or rate* or report*))).tw,kw,kf.
16	exp "Outcome Assessment (Health Care)"/
17	or/14-16 [Incidence, Mortality]
18	9 and 13 and 17
19	18 not 12

Embase

Database(s): **Embase** 1974 to 2019 November 26
Search Strategy:

#	Searches
1	exp lung cancer/
2	exp trachea cancer/
3	((lung* or pulmonary or respiratory or bronch* or alveola* or trache*) adj4 (neoplas* or cancer* or adenocarcinom* or carcinom* or chondosarcoma* or blastoma* or hemangioma* or malignan* or sarcoma* or tumor* or tumour* or squamous or oat cell or small cell or SCLC)).tw,kw.
4	(pancoast* adj3 (syndrome* or tumor* or tumour*)).tw,kw.
5	((ICD or classif*) adj5 ("C33" or "C34" or "C34.0" or "C34.1" or "C34.2" or "C34.3" or "C34.8" or "C34.9")).tw,kw.
6	or/1-5 [Lung or Tracheal Cancer]
7	("pm2.5" or "pm 2.5" or pmfine or finepm or pm fine or fine pm or fine particle* or fine particulate*).tw,kw.
8	(("2.5" adj3 (mum or micro m or micromet* or micro meter* or micro metre* or micron*)) or "2.5mum" or "2.5micro m").tw,kw.
9	7 or 8 [Fine PM]
10	6 and 9
11	(19* or 200* or 2010* or 2011* or 2012* or 2013* or 2015* or 2016* or 2017* or 2018* or 201901* or 201902* or 201903* or 201904* or 201905* or 201906* or 201907* or 201908* or "20190901" or "20190902" or "20190903").dc,dd.
12	10 and 11 [Previous search results: PM2.5 + Lung Cancer]
13	exp Canada/ or Canadian/ or Canadian Aboriginal/ or (canada* or canadia* or canadien* or Ottawa* or british columbia* or colombie britannique* or vancouver* or alberta* or edmonton* or calgar* or saskatchewan* or regina* or saskatoon* or manitoba* or winnipeg* or ontari* or toronto* or quebec* or montreal* or new brunswick* or nouveau brunswick* or fredericton* or nova scotia* or nouvelle ecosse* or halifax* or haligonian* or prince edward island* or ile du prince edouard* or pei or charlottetown* or Newfoundland* or terre neuve* or labrador* or nfld or yukon* or whitehorse* or northwest territor* or territoires du nord ouest* or nwt or yellowknife* or nunavut* or iqaluit*).tw.
14	exp epidemiological data/ or exp epidemiology/
15	public health problem/
16	(biosurveill* or epidemiolog* or inciden* or prevalen* or morbid* or mortal* or ((communit* or population* or resident or residents or famil* or public*) adj4 (assess* or sampl* or monitor* or follow* or study or studies* or survey* or rate* or report*))).tw,kw.
17	follow up/ or outcome assessment/ or cause of death/
18	or/14-17 [Incidence, Mortality]
19	9 and 13 and 18
20	19 not 12

Global Health

Database(s): **Global Health** 1973 to 2019 Week 47
Search Strategy:

#	Searches
1	exp lung cancer/
2	((lung* or pulmonary or respiratory or bronch* or alveola* or trache*) adj4 (neoplas* or cancer* or adenocarcinom* or carcinom* or chondosarcoma* or blastoma* or hemangioma* or malignan* or sarcoma* or tumor* or tumour* or squamous or oat cell or small cell or SCLC)).tw.
3	(pancoast* adj3 (syndrome* or tumor* or tumour*)).tw.
4	((ICD or classif*) adj5 ("C33" or "C34" or "C34.0" or "C34.1" or "C34.2" or "C34.3" or "C34.8" or "C34.9")).tw.
5	or/1-4 [Lung or Tracheal Cancer]
6	("pm2.5" or "pm 2.5" or pmfine or finepm or pm fine or fine pm or fine particle* or fine particulate*).tw.
7	(("2.5" adj3 (mum or micro m or micromet* or micro meter* or micro metre* or micron*)) or "2.5mum" or "2.5micro m").tw.
8	6 or 7 [Fine PM]
9	5 and 8
10	(19* or 200* or 2010* or 2011* or 2012* or 2013* or 2015* or 2016* or 2017* or 2018* or 201901* or 201902* or 201903* or 201904* or 201905* or 201906* or 201907* or 201908* or "20190904").up.
11	9 and 10 [Previous search results: PM2.5 + Lung Cancer]
12	exp Canada/ or (canada* or canadia* or canadien* or Ottawa* or british columbia* or colombie britannique* or vancouver* or alberta* or edmonton* or calgar* or saskatchewan* or regina* or saskatoon* or manitoba* or winnipeg* or ontari* or toronto* or quebec* or montreal* or new brunswick* or nouveau brunswick* or fredericton* or nova scotia* or nouvelle ecosse* or halifax* or haligonian* or prince edward island* or ile du prince edouard* or pei or charlottetown* or Newfoundland* or terre neuve* or labrador* or nfld or yukon* or whitehorse* or northwest territor* or territoires du nord ouest* or nwt or yellowknife* or nunavut* or iqaluit*).tw.
13	exp epidemiology/
14	(biosurveill* or epidemiolog* or inciden* or prevalen* or morbid* or mortal* or ((communit* or population* or resident or residents or famil* or public*) adj4 (assess* or sampl* or monitor* or follow* or study or studies* or survey* or rate* or report*))).tw.
15	follow up/ or "causes of death"/
16	or/13-15 [Incidence, Mortality]
17	8 and 12 and 16
18	17 not 11

Cochrane CENTRAL Register of Controlled Trials

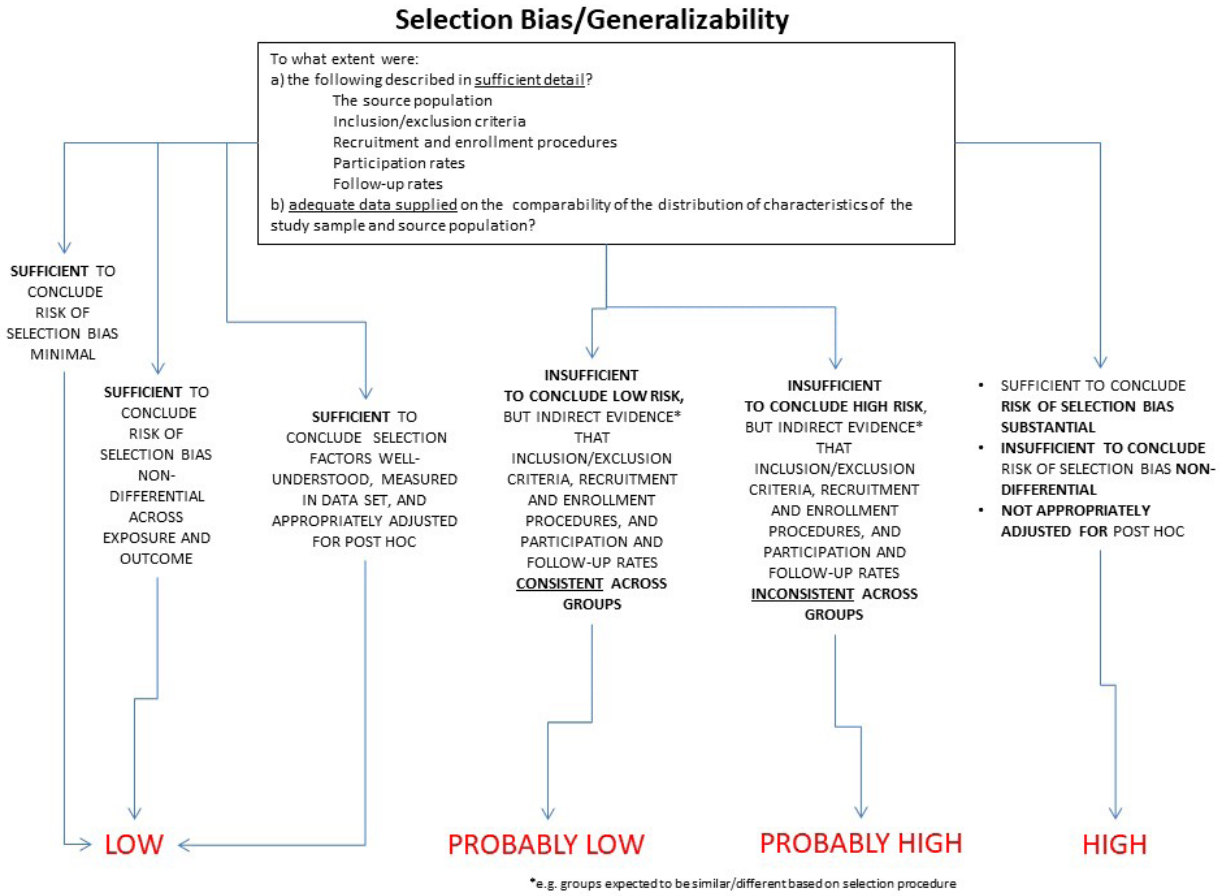
Database(s): **EBM Reviews–Cochrane Central Register of Controlled Trials** October 2019
Search Strategy:

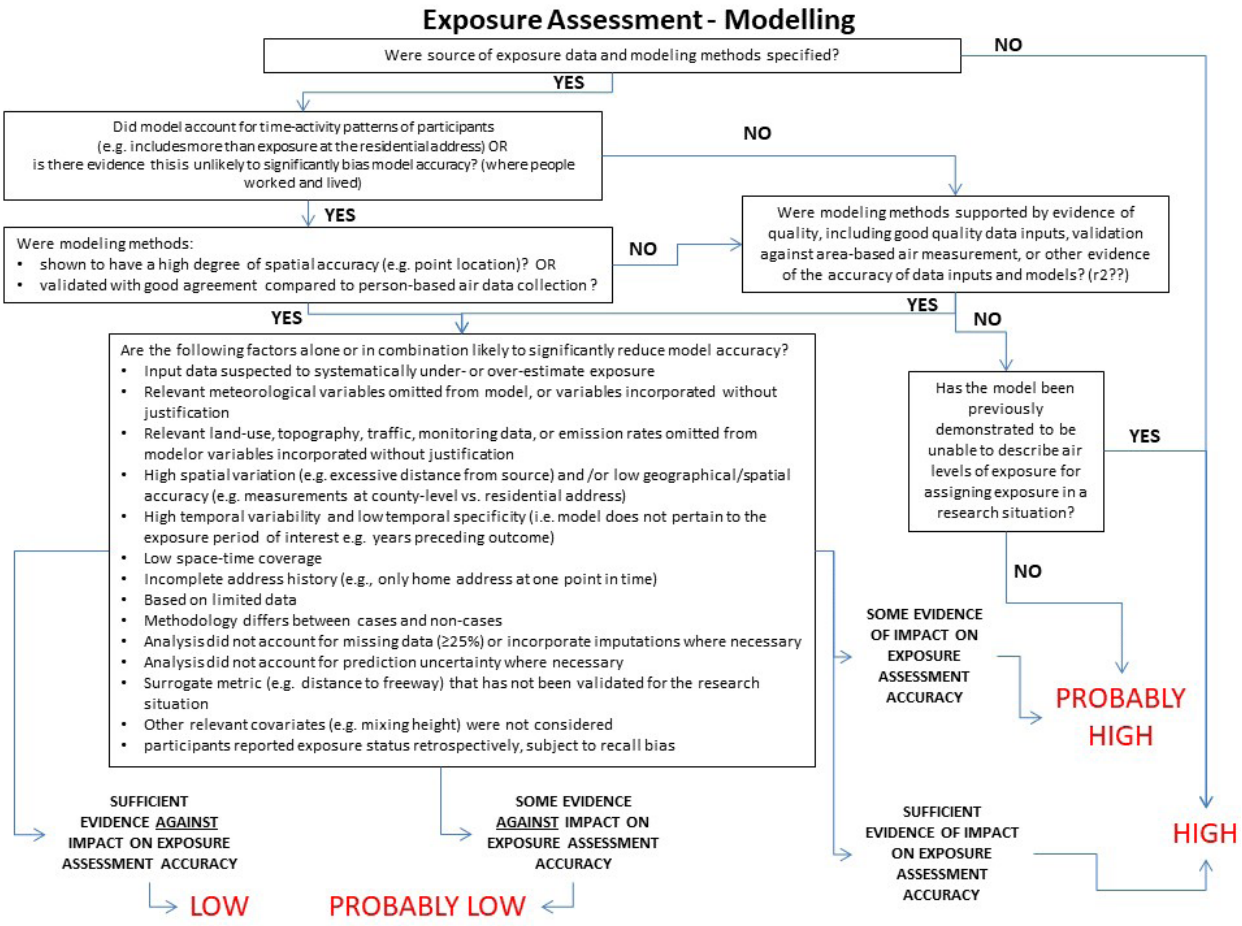
#	Searches
1	exp lung neoplasms/
2	tracheal neoplasms/
3	((lung* or pulmonary or respiratory or bronch* or alveola* or trache*) adj4 (neoplas* or cancer* or adenocarcinom* or carcinom* or chondosarcoma* or blastoma* or hemangioma* or malignan* or sarcoma* or tumor* or tumour* or squamous or oat cell or small cell or SCLC)).tw,kw.
4	(pancoast* adj3 (syndrome* or tumor* or tumour*)).tw,kw.
5	((ICD or classif*) adj5 ("C33" or "C34" or "C34.0" or "C34.1" or "C34.2" or "C34.3" or "C34.8" or "C34.9")).tw,kw.
6	or/1-5 [Lung or Tracheal Cancer]
7	("pm2.5" or "pm 2.5" or pmfine or finepm or pm fine or fine pm or fine particle* or fine particulate*).tw,kw.
8	(("2.5" adj3 (mum or micro m or micromet* or micro meter* or micro metre* or micron*)) or "2.5mum" or "2.5micro m").tw,kw.
9	7 or 8 [Fine PM]
10	6 and 9
11	(19* or 200* or 2010* or 2011* or 2012* or 2013* or 2015* or 2016* or 2017* or 2018* or 201901* or 201902* or 201903* or 201904* or 201905* or 201906* or 201907* or 201908*).up.
12	10 and 11 [Previous search results: PM2.5 + Lung Cancer]
13	exp Canada/ or (canada* or canadia* or canadien* or Ottawa* or british columbia* or colombie britannique* or vancouver* or alberta* or edmonton* or calgar* or saskatchewan* or regina* or saskatoon* or manitoba* or winnipeg* or ontari* or toronto* or quebec* or montreal* or new brunswick* or nouveau brunswick* or fredericton* or nova scotia* or nouvelle ecosse* or halifax* or haligonian* or prince edward island* or ile du prince edouard* or pei or charlottetown* or Newfoundland* or terre neuve* or labrador* or nfld or yukon* or whitehorse* or northwest territor* or territoires du nord ouest* or nwt or yellowknife* or nunavut* or iqaluit*).tw.
14	exp Epidemiology/ or exp Epidemiologic Methods/
15	(biosurveill* or epidemiolog* or inciden* or prevalen* or morbid* or mortal* or ((communit* or population* or resident or residents or famil* or public*) adj4 (assess* or sampl* or monitor* or follow* or study or studies* or survey* or rate* or report*))).tw,kw.
16	exp "Outcome Assessment (Health Care)"/
17	or/14-16 [Incidence, Mortality]
18	9 and 13 and 17
19	18 not 12

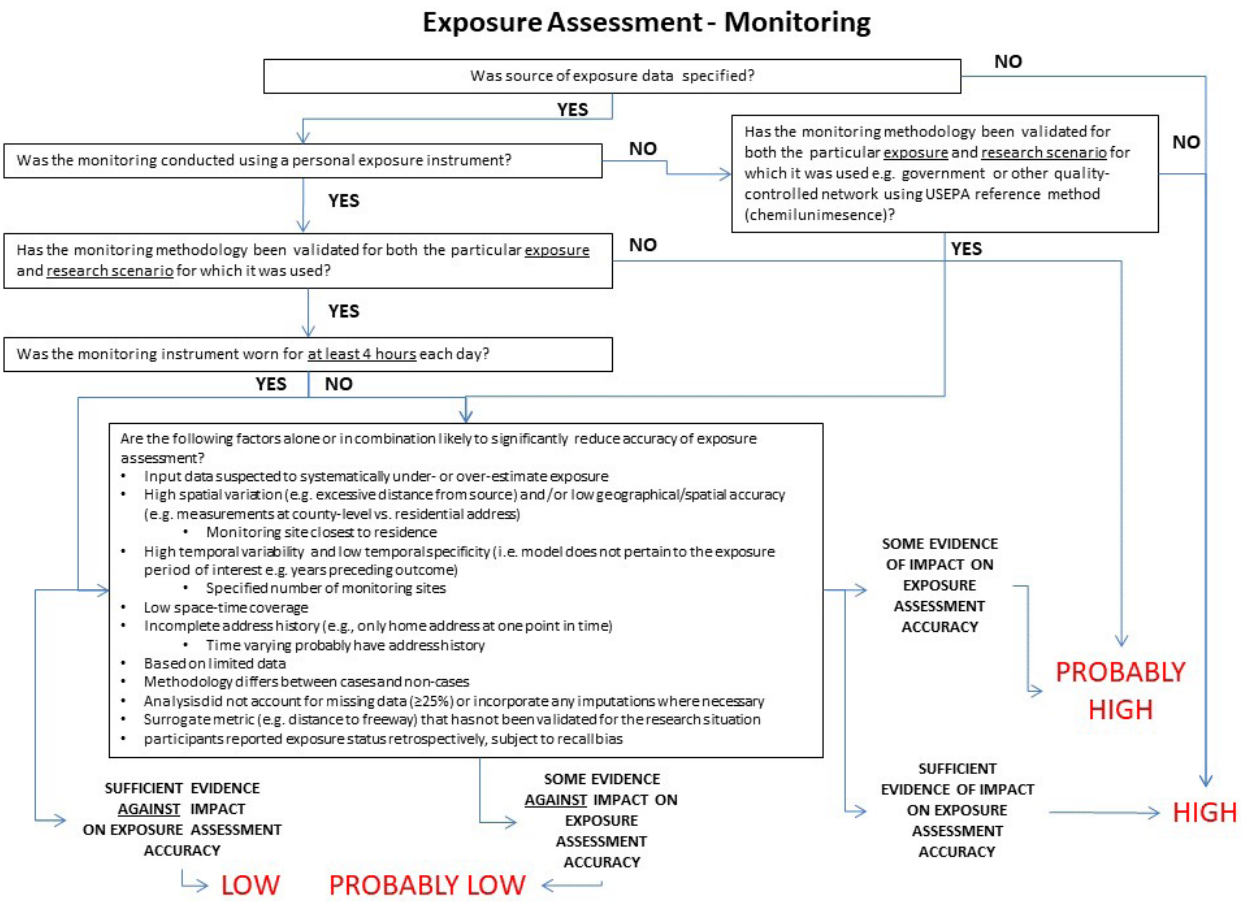
Toxline

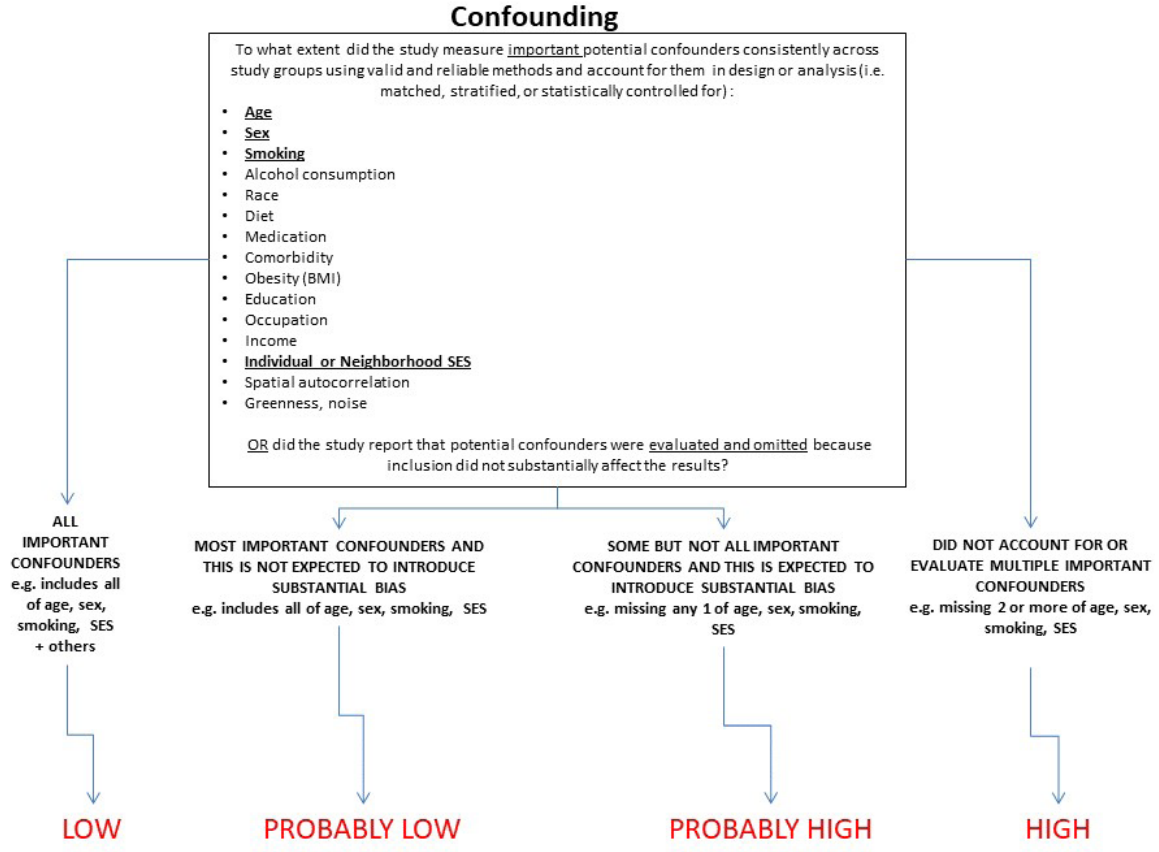
Search	Database	Query
# 6	toxline	(#4 AND NOT #5) AND NOT PubMed [org] AND NOT pubdart [org]
# 5	toxline	("pancoast syndrome" OR "pancoast tumor" OR "pancoast tumors" OR "pancoast tumour" OR "pancoast tumours" OR ((neoplasm OR neoplasms OR neoplastic OR cancer OR cancers OR cancerous OR adenocarcinoma OR adenocarcinomas OR carcinoma OR carcinomas OR chondosarcoma OR chondosarcomas OR blastoma OR blastomas OR hemangioma OR hemangiomas OR malignant OR malignancy OR malignancies OR sarcoma OR sarcomas OR tumor OR tumors OR tumour OR tumours OR squamous OR "oat cell" OR "oat cells" OR "small cell" OR "small cells" OR sclc) OR (lung OR pulmonary OR respiratory OR bronchia OR bronchi OR bronchial OR bronchiole OR bronchus OR alveola OR alveolas OR alveolar OR trachea OR trachea OR tracheal)) AND NOT PubMed [org] AND NOT pubdart [org] AND AND 1900:2018 [year]
# 4	toxline	((#1 OR #2) AND #3) AND NOT PubMed [org] AND NOT pubdart [org]
# 3	toxline	(canada OR canadian OR canadien OR canadienne) AND NOT PubMed [org] AND NOT pubdart [org]
# 2	toxline	((("2 5" AND (mum OR "micro m" OR "micrometre" OR "micrometres" OR "micro meter" OR "micro meters" OR "micro metre" OR "micro metres" OR micron OR microns)) OR "2 5mum" OR "2 5micro m") AND NOT pubmed [org] AND NOT pubdart [org]) AND NOT PubMed [org] AND NOT pubdart [org]
# 1	toxline	(("pm2 5" OR "pm 2 5" OR pmfine OR finepm OR ((pm OR 1320-67-8 [rn]) OR 1320-67-8 [rn]) fine OR fine ((pm OR 1320-67-8 [rn]) OR 1320-67-8 [rn]) OR "fine particle" OR "fine particles" OR "fine particulate" OR "fine particulates") AND NOT pubmed [org] AND NOT pubdart [org])

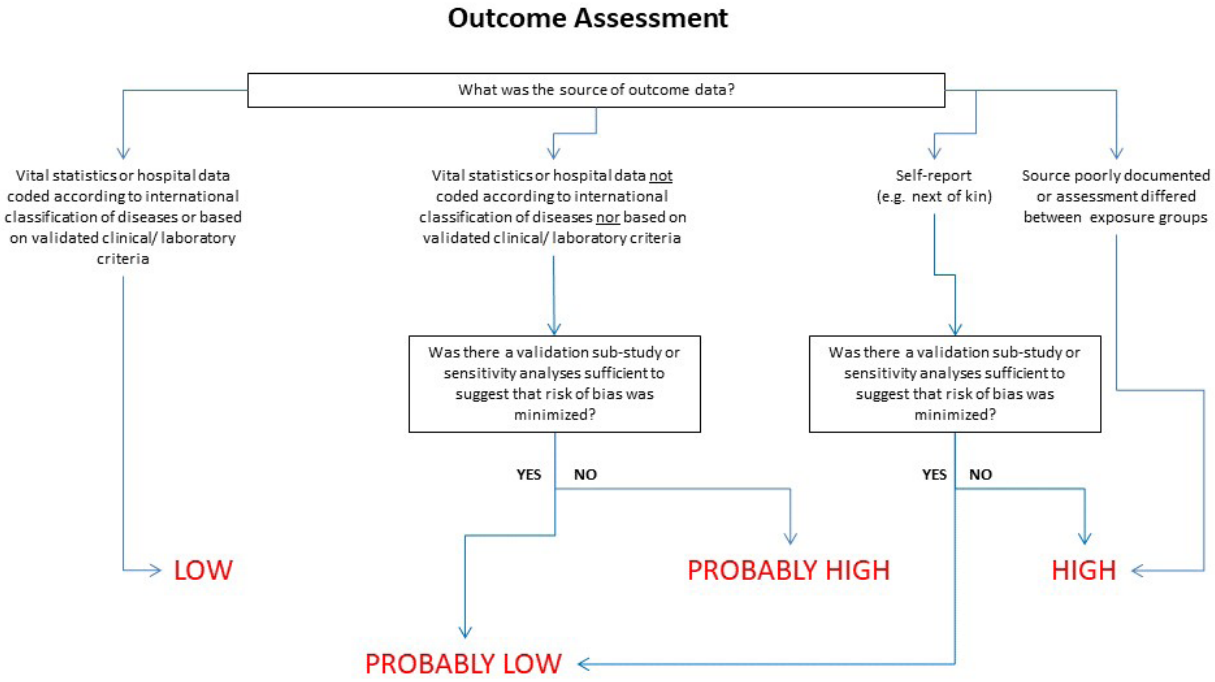
ANNEXE B : ROB GUIDELINES

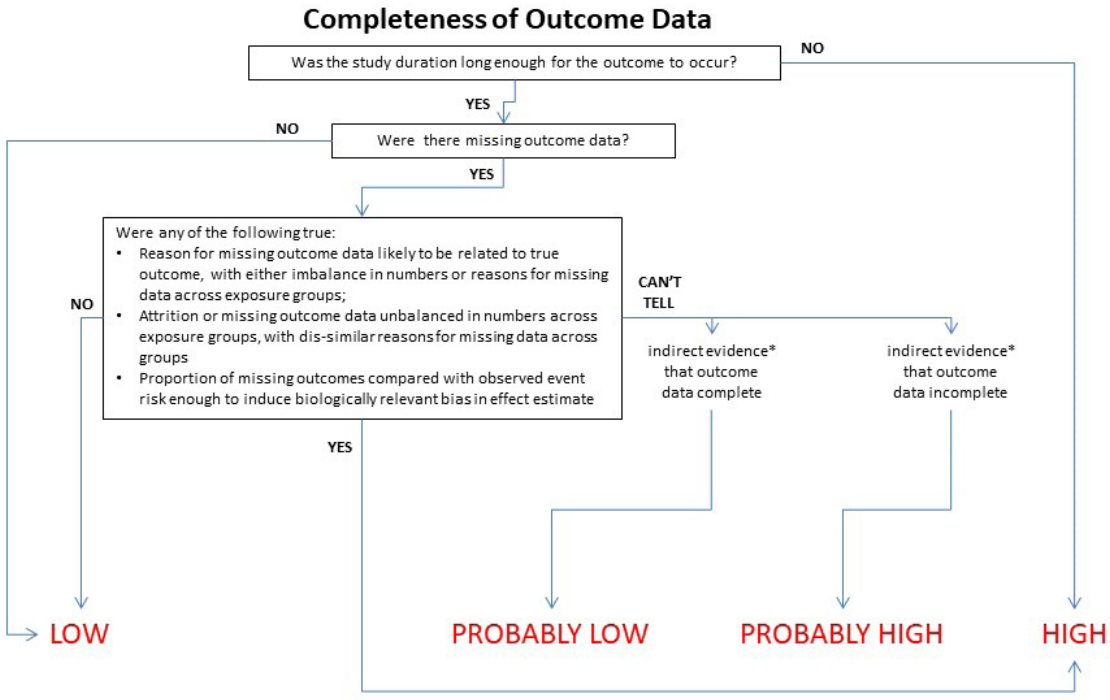



Exposure Assessment - Modelling
Were source of exposure data and modeling methods specified?
NO
YES
Did model account for time-activity patterns of participants (e.g. includes more than exposure at the residential address) OR is there evidence this is unlikely to significantly bias model accuracy? (where people worked and lived)
NO
YES
Were modeling methods:
• shown to have a high degree of spatial accuracy (e.g. point location)? OR
• validated with good agreement compared to person-based air data collection ?
NO
Were modeling methods supported by evidence of quality, including good quality data inputs, validation against area-based air measurement, or other evidence of the accuracy of data inputs and models? (r2??)
YES
NO
YES
Are the following factors alone or in combination likely to significantly reduce model accuracy?
• Input data suspected to systematically under- or over-estimate exposure
• Relevant meteorological variables omitted from model, or variables incorporated without justification
• Relevant land-use, topography, traffic, monitoring data, or emission rates omitted from model or variables incorporated without justification
• High spatial variation (e.g. excessive distance from source) and /or low geographical/spatial accuracy (e.g. measurements at county-level vs. residential address)
• High temporal variability and low temporal specificity (i.e. model does not pertain to the exposure period of interest e.g. years preceding outcome)
• Low space-time coverage
• Incomplete address history (e.g., only home address at one point in time)
• Based on limited data
• Methodology differs between cases and non-cases
• Analysis did not account for missing data (≥25%) or incorporate imputations where necessary
• Analysis did not account for prediction uncertainty where necessary
• Surrogate metric (e.g. distance to freeway) that has not been validated for the research situation
• Other relevant covariates (e.g. mixing height) were not considered
• participants reported exposure status retrospectively, subject to recall bias
Has the model been previously demonstrated to be unable to describe air levels of exposure for assigning exposure in a research situation?
YES
NO
SOME EVIDENCE OF IMPACT ON EXPOSURE ASSESSMENT ACCURACY
PROBABLY HIGH
SUFFICIENT EVIDENCE AGAINST IMPACT ON EXPOSURE ASSESSMENT ACCURACY
LOW
SOME EVIDENCE AGAINST IMPACT ON EXPOSURE ASSESSMENT ACCURACY
PROBABLY LOW
SUFFICIENT EVIDENCE OF IMPACT ON EXPOSURE ASSESSMENT ACCURACY
HIGH

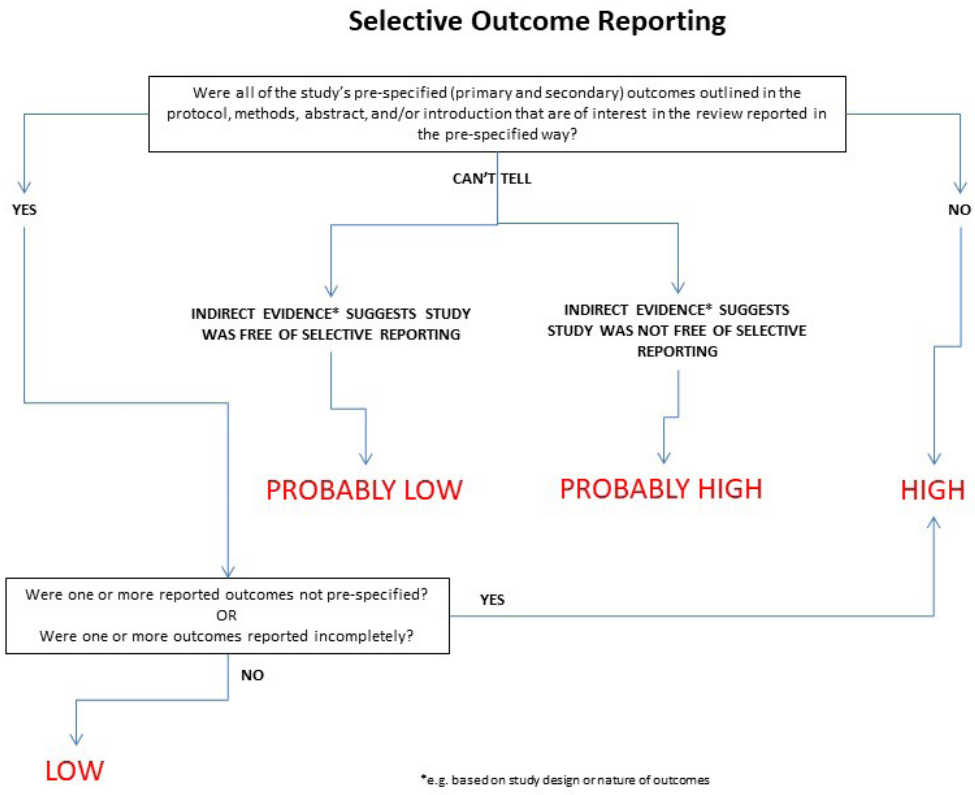

Exposure Assessment - Monitoring
Was source of exposure data specified?
NO
YES
Was the monitoring conducted using a personal exposure instrument?
NO
Has the monitoring methodology been validated for both the particular exposure and research scenario for which it was used e.g. government or other quality-controlled network using USEPA reference method (chemilunimesence)?
NO
YES
Has the monitoring methodology been validated for both the particular exposure and research scenario for which it was used?
NO
YES
Was the monitoring instrument worn for at least 4 hours each day?
YES
NO
Are the following factors alone or in combination likely to significantly reduce accuracy of exposure assessment?
• Input data suspected to systematically under- or over-estimate exposure
• High spatial variation (e.g. excessive distance from source) and/or low geographical/spatial accuracy (e.g. measurements at county-level vs. residential address)
• Monitoring site closest to residence
• High temporal variability and low temporal specificity (i.e. model does not pertain to the exposure period of interest e.g. years preceding outcome)
• Specified number of monitoring sites
• Low space-time coverage
• Incomplete address history (e.g., only home address at one point in time)
• Time varying probably have address history
• Based on limited data
• Methodology differs between cases and non-cases
• Analysis did not account for missing data (≥25%) or incorporate any imputations where necessary
• Surrogate metric (e.g. distance to freeway) that has not been validated for the research situation
• participants reported exposure status retrospectively, subject to recall bias
SOME EVIDENCE OF IMPACT ON EXPOSURE ASSESSMENT ACCURACY
PROBABLY HIGH
SUFFICIENT EVIDENCE AGAINST IMPACT ON EXPOSURE ASSESSMENT ACCURACY
LOW
SOME EVIDENCE AGAINST IMPACT ON EXPOSURE ASSESSMENT ACCURACY
PROBABLY LOW
SUFFICIENT EVIDENCE OF IMPACT ON EXPOSURE ASSESSMENT ACCURACY
HIGH


Confounding
To what extent did the study measure important potential confounders consistently across study groups using valid and reliable methods and account for them in design or analysis (i.e. matched, stratified, or statistically controlled for):
Age
Sex
Smoking
Alcohol consumption
Race
Diet
Medication
Comorbidity
Obesity (BMI)
Education
Occupation
Income
Individual or Neighborhood SES
Spatial autocorrelation
Greenness, noise
OR did the study report that potential confounders were evaluated and omitted because inclusion did not substantially affect the results?
ALL IMPORTANT CONFOUNDERS e.g. includes all of age, sex, smoking, SES + others
MOST IMPORTANT CONFOUNDERS AND THIS IS NOT EXPECTED TO INTRODUCE SUBSTANTIAL BIAS e.g. includes all of age, sex, smoking, SES
SOME BUT NOT ALL IMPORTANT CONFOUNDERS AND THIS IS EXPECTED TO INTRODUCE SUBSTANTIAL BIAS e.g. missing any 1 of age, sex, smoking, SES
DID NOT ACCOUNT FOR OR EVALUATE MULTIPLE IMPORTANT CONFOUNDERS e.g. missing 2 or more of age, sex, smoking, SES
LOW
PROBABLY LOW
PROBABLY HIGH
HIGH

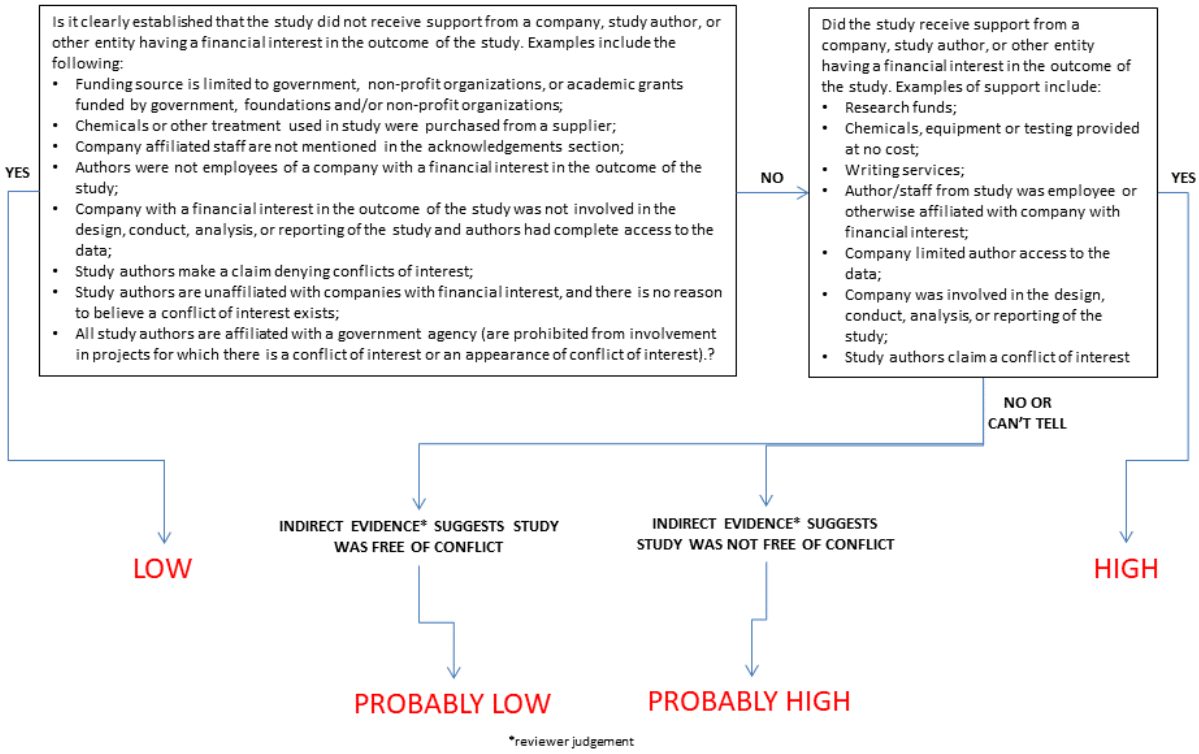

Outcome Assessment
What was the source of outcome data?
Vital statistics or hospital data coded according to international classification of diseases or based on validated clinical/ laboratory criteria
Vital statistics or hospital data not coded according to international classification of diseases nor based on validated clinical/ laboratory criteria
Self-report (e.g. next of kin)
Source poorly documented or assessment differed between exposure groups
Was there a validation sub-study or sensitivity analyses sufficient to suggest that risk of bias was minimized?
Was there a validation sub-study or sensitivity analyses sufficient to suggest that risk of bias was minimized?
YES
NO
YES
NO
LOW
PROBABLY HIGH
HIGH
PROBABLY LOW

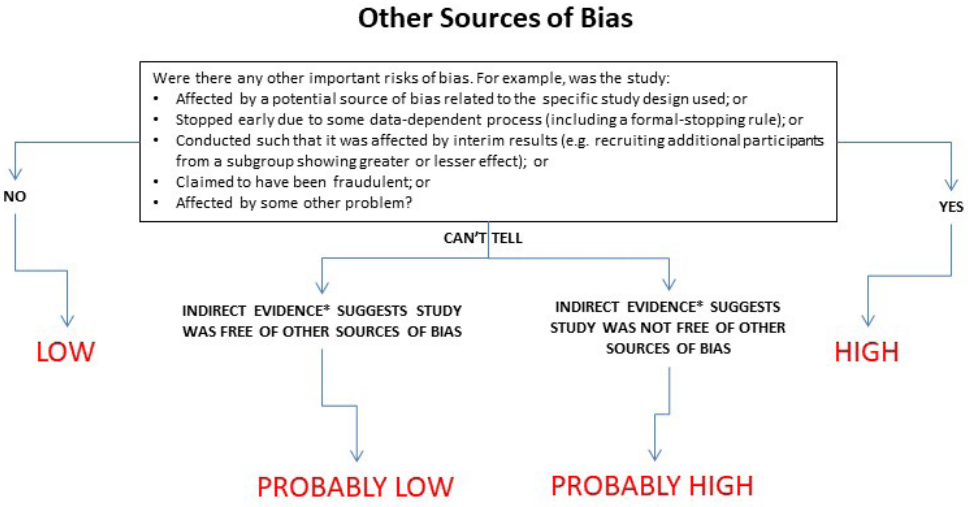


*e.g. based on study design


Selective Outcome Reporting
Were all of the study's pre-specified (primary and secondary) outcomes outlined in the protocol, methods, abstract, and/or introduction that are of interest in the review reported in the pre-specified way?
YES
CAN'T TELL
NO
INDIRECT EVIDENCE* SUGGESTS STUDY WAS FREE OF SELECTIVE REPORTING
INDIRECT EVIDENCE* SUGGESTS STUDY WAS NOT FREE OF SELECTIVE REPORTING
PROBABLY LOW
PROBABLY HIGH
HIGH
Were one or more reported outcomes not pre-specified?
OR
Were one or more outcomes reported incompletely?
YES
NO
LOW
*e.g. based on study design or nature of outcomes

Conflict of Interest





*reviewer judgement

ANNEXE C : EXCLUDED STUDIES (WITH RATIONALE)

TABLE C.1: Full-Text Articles Included in Systematic Review but Excluded from Meta-Analysis Due to Overlap and Risk of Bias (with Rationale)

Cohort	Excluded Study	Rationale	Included Study
CanCHEC 1991	Cakmak et al. 2018	Analysis limited to cohort members residing within a given proximity to a weather station	Crouse et al. 2015
CanCHEC 1991	Weichenthal et al. 2016	Analysis limited to cohort members residing within a given proximity to monitor	Crouse et al. 2015
CanCHEC 2001	Crouse et al. 2020	Lack of adjustment for potential confounding by smoking	Erickson et al. 2019
CanCHEC 2001	Pinault et al. 2017	Lack of adjustment for potential confounding by smoking	Erickson et al. 2019
ONPHEC	Weichenthal et al. 2017	Used a sub-population of the cohort fully represented in Bai et al. (2019)	Bai et al. 2019
CNBSS	Tomczak et al. 2016	Study authors indicated that lung cancer incidence results in their study were under re-evaluation (P. Villeneuve, personal communication, Feb 19, 2020).	To et al. 2015

Abbreviations: **CanCHEC–**Canadian Census Health and Environment Cohorts; **CNBSS**–Canadian National Breast Screening Study; **ONPHEC–**ONtario Population Health and Environment Cohort.

ANNEXE D : QUALITATIVE SYNTHESIS

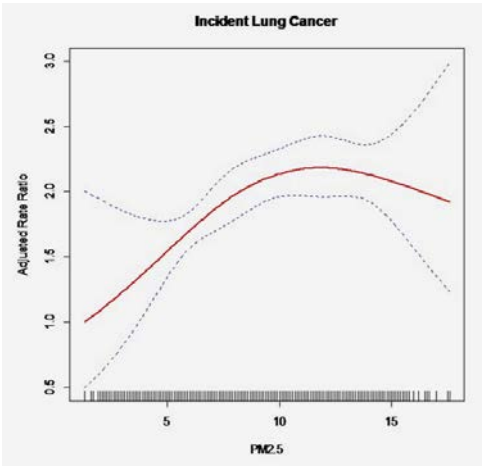
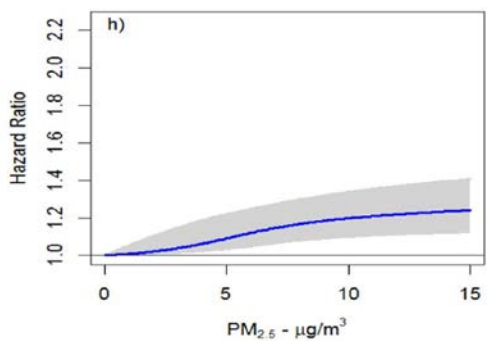
TABLE D.1: Study Characteristics of Canadian Cohort Studies with Multipollutant or Oxidative Potential of $PM_{2.5}$ Models

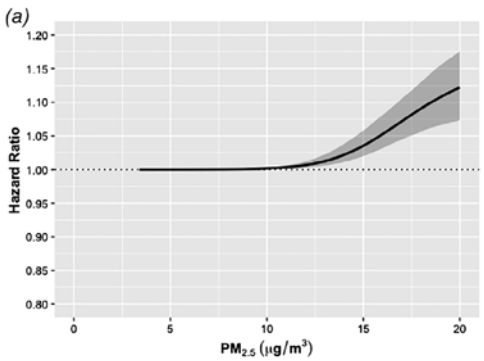
Author	Cohort	Outcome	Descriptive Statistics	Effect estimate (95% CI)	Other Covariates in Model
Crouse et al. 2015	CanCHEC 1991; Canada	Mortality	$PM_{2.5}$ (µg/m^3): Mean = 8.9 Mean–5th percentile = 5.0 O_3 (ppb): Mean = 39.6 Mean–5th percentile = 9.5 NO_2 (ppb): Mean = 11.6 Mean–5th percentile = 8.1	$PM_{2.5}$ only: HR per 5 µg/m^3 = 1.064 (1.040, 1.088) HR per 10 µg/m^3 = 1.132 (1.082, 1.184) $PM_{2.5}$ adjusted for O_3 and NO_2: HR per 5 µg/m^3 = 1.059 (1.020, 1.100) HR per 10 µg/m^3 = 1.121 (1.040, 1.209)	Stratified by age and sex, adjusted for personal and contextual covariates, and **indirectly adjusted for smoking** and obesity
Weichenthal et al. 2016	CanCHEC 1991; Ontario	Mortality	$PM_{2.5}$ (µg/m^3): Mean (SD) = 9.81 (1.59) IQR = 2.17 $PM_{2.5}$×OP^{GSH}: Mean (SD) = 1.46(0.72) IQR = 1.28 $PM_{2.5}$×OP^{AA}: Mean (SD) = 2.54 (0.91) IQR = 1.02	$PM_{2.5}$ only: HR per 2.17 µg/m^3 = 1.037 (0.986, 1.090) HR per 10 µg/m^3 = 1.182 (0.938, 1.490) $PM_{2.5}$×OP^{GSH}: HR per 1.28 µg/m^3 = 1.073 (1.005, 1.146) HR per 10 µg/m^3 = 1.734 (1.038, 2.896) $PM_{2.5}$×OP^{AA}: HR per 1.02 µg/m^3 = 0.970 (0.933, 1.009) HR per 10 µg/m^3 = 0.742 (0.505, 1.089)	Adjusted for age, sex, Aboriginal ancestry, visible minority status, immigrant status, marital status, highest level of education, employment status, occupational classification, and household income with **indirect adjustment for smoking** and obesity for models for $PM_{2.5}$ and $PM_{2.5}$×OP^{GSH} (but not for $PM_{2.5}$×OP^{AA})
Weichenthal et al. 2017	ONPHEC; Toronto	Incidence	$PM_{2.5}$ (µg/m^3): Mean (SD) = 10.9 (2.1) IQR = 3.2 NO_2 (ppb): Mean (SD) = 21.4 (3.5) IQR = 4.1 UFP (count/cm^3): Mean (SD) = 28,473 (9,226) IQR = 10,097	$PM_{2.5}$ only: HR per 3.2 µg/m^3 = 1.05 (1.03, 1.08) HR per 10 µg/m^3 = 1.16 (1.08, 1.25) $PM_{2.5}$ adjusted for NO_2: HR per 3.2 µg/m^3 = 1.04 (1.02, 1.07) HR per 10 µg/m^3 = 1.13 (1.05, 1.22)	Stratified by one-year age and sex, adjusted for neighbourhood-level covariates and comorbid diseases (but not adjusted for smoking in these models)
Cakmak et al. 2018	CanCHEC 1991; Canada	Mortality	$PM_{2.5}$ (µg/m^3): Mean (SD) in Zone 1 = 3.8 (1.2) Mean (SD) in Zone 3 = 7.4 (2.2) O_3 (ppb): Mean (SD) in Zone 1 = 15.0 (6.4) Mean (SD) in Zone 3 = 43.0 (5.6)	$PM_{2.5}$ only: HR per 10 µg/m^3 = 1.26 (1.04, 1.53) $PM_{2.5}$ adjusted for O_3: HR per 10 µg/m^3 = 1.49 (1.23, 1.88)	Stratified by age (5-year increments) and sex; adjusted for personal covariates, and **indirectly adjusted for smoking** and obesity

Author	Cohort	Outcome	Descriptive Statistics	Effect estimate (95% CI)	Other Covariates in Model
Crouse et al. 2020	CanCHEC 2001; Canada	Mortality	$PM_{2.5}$ (μg/m³) for 3-year, 1-km: Mean (SD) = 7.43 (2.65) O_x (ppb): Mean (SD) = 11.56 (6.58) O_3 (ppb): Mean (SD) = 38.98 (7.12) NO_2 (ppb): Mean (SD) = 29.65 (5.47)	**3-year, 1-km** $PM_{2.5}$ only: HR per 10 μg/m³ = 1.15 (1.07, 1.24) $PM_{2.5}$ adjusted for O_x: HR per 10 μg/m³ = 1.26 (1.16, 1.38) $PM_{2.5}$ adjusted for O_3: HR per 10 μg/m³ = 1.24 (1.15, 1.35) $PM_{2.5}$ adjusted for NO_2: HR per 10 μg/m³ = 1.09 (1.00, 1.19) **8-year, 1-km** $PM_{2.5}$ only: HR per 10 μg/m³ = 1.10 (1.02, 1.19) $PM_{2.5}$ adjusted for O_x: HR per 10 μg/m³ = 1.22 (1.12, 1.33) $PM_{2.5}$ adjusted for O_3: HR per 10 μg/m³ = 1.21 (1.11, 1.31) $PM_{2.5}$ adjusted for NO_2: HR per 10 μg/m³ = 1.03 (0.95, 1.13)	Stratified by sex and 5-year age groups, adjusted for Aboriginal identity, visible minority status, marital status, highest level of education, employment status, household income adequacy quintiles, community size, community-level marginalization, and airshed

Abbreviations: **CanCHEC**–Canadian Census Health and Environment Cohorts; **ONPHEC**–ONtario Population Health and Environment Cohort; **$PM_{2.5}$**–fine particulate matter; **O3**–ozone; **NO2**–nitrogen dioxide; **$PM_{2.5}$×OPGSH**–glutathione-related oxidative burden; **$PM_{2.5}$×OPAA**–ascorbate-related oxidative burden; **UFP**–ultrafine particulate matter; **Ox**–total oxidants; **IQR**–interquartile range; **SD**–standard deviation; **HR**–hazard ratio.

TABLE D.2: Study Characteristics of Canadian Cohort Studies Assessing Shape of the Concentration-Response Relationship between Lung Cancer and $PM_{2.5}$ Exposure

Author	Cohort	Outcome Measure	Method	Concentration-Response Curve	Results
Tomczak et al. 2016	CNBSS; Canada	Incidence	Natural cubic spline functions with three degrees of freedom within the fully adjusted Cox regression model (adjusted for age group at entry, occupation, marital status, attained education, BMI, smoking, and four contextual variables derived from census area measures)		"We observed a nonlinear pattern with incidence of lung cancer, where at lower concentration levels of $PM_{2.5}$ there was a steep positive slope that appeared to flatten after 12 µg/m^3."
Pinault et al. 2017	CanCHEC 2001; Canada	Mortality	SCHIF in the fully adjusted models (which did not include any adjustment for smoking and BMI)		"For lung cancer, there was some suggestion that the curves were sub-linear."

Author	Cohort	Outcome Measure	Method	Concentration-Response Curve	Results
Bai et al. 2019	ONPHEC; Ontario	Incidence	SCHIF		"We observed sublinear associations between incident lung cancer and $PM_{2.5}$ with some evidence of thresholds at 10 µg/m^3…"

Note: Crouse et al. (2015), Villeneuve et al. (2015), and Pinault et al. (2016) examined the shape of concentration-response relationship, but were not specific to lung cancer and therefore are not included in the evidence map.

Abbreviations: **$PM_{2.5}$**–fine particulate matter; **CanCHEC**–Canadian Census Health and Environment Cohorts; **CNBSS**–Canadian National Breast Screening Study; **ONPHEC**–ONtario Population Health and Environment Cohort; **SCHIF**–Shape Constrained Health Impact Function; **BMI**–body mass index. Definition: sublinear, i.e., a shallow slope at low concentrations and steeper slope at higher concentrations.

Figures were reproduced from Tomczak et al. (2016) and Bai et al. (2019) with permission from John Wiley and Sons, and from Pinault et al. (2017) with permission from Elsevier.

ANNEXE E : PUBLISHED SYSTEMATIC REVIEWS WITH META-ANALYSIS

TABLE E.1: Systematic Reviews with Meta-Analysis on the Association between $PM_{2.5}$ Exposure and Lung Cancer from North American and/or European Studies

Author	Region	Search Period	Inclusion Criteria	Outcome Measure	Model	No. of Studies	Pooled Effect Estimate (95% CI)	Heterogeneity
Ghazipura et al. 2019	North America and Europe	Jan 1985 to Jun 2017	• Incidence only (no mortality) • Case-control or cohort studies	Incidence	Random effects	6	pRR per 10 μg/m³ = 1.25 (1.12, 1.40)	I^2 = 15%, p = 0.31
Gogna et al. 2019a	Canada	Up to Aug 2018	• Same criteria as Hamra et al. 2014, limited to Canada	Combined	Fixed effects	6	pRR per 10 μg/m³ = 1.09 (1.06, 1.12)	I^2 = 42.1%, p = 0.12
Huang et al. 2017	North America		• Mortality and/or incidence • Case-control and cohort studies	Mortality	Random effects	5	pRR per 10 μg/m³ = 1.15 (1.07, 1.24)	I^2 = 0.0%, p = 0.406
				Incidence	Random effects	4	pRR per 10 μg/m³ = 1.06 (1.01, 1.11)	I^2 = 0.0%, p = 0.410
				Combined	Random effects	9	pRR per 10 μg/m³ = 1.11 (1.05, 1.18)	I^2 = 26.8%, p = 0.205
Cui et al. 2015	USA	Up to Oct 2013	• Mortality or incidence • Cohort studies only	Mortality	Fixed effects	6	pRR per 10 μg/m³ = 1.14 (1.07, 1.21)	I^2 = 0.0%, p = 0.687
Hamra et al. 2014	North America	Up to October 2013	• Mortality and/or incidence • Case-control or cohort studies • Adjusted for age and sex	Combined	Random effects	8	pRR per 10 μg/m³ = 1.11 (1.05, 1.16)	I^2 = 0.0%, p = 0.490
	Europe			Combined	Random effects	4	pRR per 10 μg/m³ = 1.03 (0.89, 1.20)	I^2 = 50.0%, p = 0.112
Chen et al. 2008	North America	Jan 1950 to Dec 2007	• Mortality only • Case-control or cohort studies	Mortality	Random effects	3	pRR per 10 μg/m³ = 1.15 (1.07, 1.25)	I^2 = 0.0%, p = 0. 627
	North America and Europe			Mortality	Random effects	5	pRR per 10 μg/m³ = 1.21 (1.10, 1.32)	I^2 = 24.5%, p = 0.26

Abbreviations: **$PM_{2.5}$**–fine particulate matter; **pRR**–pooled relative risk; **CI**–confidence interval.