Study Protocol

Relationship Between Air Pollution Exposure and Adult Asthma Incidence: A Systematic Review and Meta-Analysis

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1 BACKGROUND

Asthma is a chronic lung disease that is characterized by environmental sensitivity, airway hyper responsiveness, and inflammation. Exposure to ambient air pollution is associated with incident asthma in children and is plausibly related to incident asthma in adults. The development of adult-onset asthma in association with ambient air pollution exposures will be systematically reviewed herein. Adult asthma incidence in population studies, may be measured between a minimum of two follow-up (baseline and outcome), however cross-sectional measures of adult asthma prevalence (i.e., in cross-sectional studies reporting adult-onset asthma) will be accepted.

To understand the concentration-response relationship between air pollution (PM2.5, NO2, O3, and SO2 on adult asthma incidence. While multiple factors contribute to incident asthma, outdoor (ambient) air pollution is one of the most recognized, potentially modifiable exposures. We will be conducting a systematic review and meta-analysis to determine pooled effect estimates for the concentration-response dose-response relationship between air pollution (PM2, SO2, NO2, O3), and incident adult asthma.

2 Research Question

Is exposure to outdoor (ambient) air pollution associated with incident adult-asthma? Adult asthma is defined as development of asthma over the age of 18 years.

The following research question can be defined using the patient, exposure/intervention, comparison, and outcome (PECO) framework:

Patient population: Adults (age ≥18)
Exposure: Air Pollutants (including PM2.5, O3, NO2, SO2)
Comparison: Not applicable
Outcome: Incident asthma, asthma incidence, adult-onset asthma

3 Search Strategy

3.1 Searches

The first, preliminary search was performed on November 16, 2022. A search strategy was developed alongside Prubjot Gill with SL. The search strategy was developed in the following databases with the research question above:
- MEDLINE
- EMBASE (OVID)
- Cochrane Central Register of Controlled Trials (CENTRAL/CCTR)
- Web of Science

A grey literature search will be performed on a later date (est. June 10, 2023) with the same PECO criteria.

3.2 Search updates

Updates for searches will be performed following finalization of protocol and after the first search. Searches against databases are set up to run biweekly on Monday (first notification on May 15, 2023) and notified reviews via email to spenclee@student.ubc.ca. New articles are to be collected and screened through the review process.

4 Eligibility criteria

The eligibility criteria were used to identify eligible articles during each stage of the review (see notes for additional information):

	Inclusion Criteria	Exclusion Criteria
Title and Abstract Screening	o Contains 2 or more PECO elements o **Observational studies** including **cohort** (**prospective** and **retrospective**), **case-control**, and cross-sectional study designs will be included where incidence is reported. Conference abstracts and reports will be included. o **Studies where the study design is unclear and/or not mentioned in the abstract or titled with 2 PECO criteria met will be included for full-text review.** o English language	o Contains 1 or fewer PECO elements o **Experimental studies trials** including interventional trials and randomized control trials o **Reviews, letters, and presentations will be excluded.**
Full Text Review	o **Contains all 3 PECO criteria** o **Population:** Adults (age =>18). A lifetime exposure to air pollution (i.e. childhood exposure to air pollution) leading up to asthma diagnosis during adulthood was also accepted. o **Exposure:** Measurement/modelling of outdoor (ambient) air pollutants (specifically PM, O3, NO2, SO2) of biogenic or anthropogenic emission source where exposure level was established at given location over time. o **Outcome:** Asthma development during adulthood. Asthma development can be reported as incidence, incidence rate, diagnosis, and measure of prevalence with adult-onset asthma. (self-reported, physician diagnosed, using a case definition, or confirmed using objective measures of airway hyperresponsiveness)	o Missing full-text o **Population**: Childhood only studies (population is <18 yrs) where asthma outcome is reported only below 18 years of age. o **Exposure**: Studies which do not address ambient air pollutants in measurement including **indoor air pollution** measurements, and measures of air pollution which **do not include the individual components** (PM2.5, O3, SO2, NO2) o Study design (experimental trial, RCT, interventional trial, in-vitro study, in vivo study, and/or animal study)

Notes for full-text:
- Reasons for exclusion in Covidence during full-text review:

1. Article not available in English
2. Missing full-text
3. Wrong study design
4. Population (child populations, occupation)
5. Exposure assessment (do not address ambient air pollutants and/or do not include individual components)
6. Indoor air pollution
7. Wrong outcome (incidence not reported)

*Note this will also be the rank of exclusion reasons which will be used to clear disagreements on exclusion reason. Disagreements between inclusion vs. exclusion will still be resolved via a third reviewer.

- If multiple exclusion reasons are met (i.e. missing full-text and population). Then the higher rank of the exclusion reason, listed above, will be selected for exclusion.
- In case of a disagreement between two reviewers on exclusion, the higher ranked exclusion reason will be selected as the exclusion reason.

Notes for inclusion and exclusion:

*Population:

Inclusion: Adults (age =>18). A lifetime exposure to air pollution (i.e., childhood exposure to air pollution) leading up to asthma diagnosis during adulthood was also accepted.

Exclusion: Childhood only studies (population is <18 yrs) where asthma outcome is reported only below 18 years of age.

Notes:
- We're looking at an adult population that is representative of the general population.
    o This would exclude specific populations such as occupations (i.e., mining workers, mill workers, firefighters, etc….).
        ▪ Occupational exposures should be excluded from full text.
    o However, a population which lives near an industrial site which emits pollution can be included in title/abstract screening.
- Child populations are excluded (if population is <18 yrs). However, if a diagnosis of asthma, or incident asthma was made during adulthood, with childhood exposure, then that would be included.
    o Exposure (during childhood) -> diagnosis during adulthood

Full-text notes:
- Studies may include childhood and adult populations.
    o A study could also follow individuals through childhood, and see their childhood exposure and how that leads to the development of adult-asthma.

*Exposure: Note with exposure, we are looking at ambient outdoor pollution.

Inclusion: Measurement/modelling of outdoor (ambient) air pollutants (specifically PM2.5, O3, NO2, SO2) of biogenic or anthropogenic emission source where exposure level was established at given location over time.

Exclusion: Studies which do not address ambient air pollutants in measurement including indoor air pollution measurements, and measures of air pollution which do not include the individual components listed above.

Notes:
- Exposures we are looking for are outdoor, ambient air pollution sources. These are generally defined in literature as outdoor air pollution and/or ambient pollution.
- Outdoor air pollution can have very different sources, from an urban area with lots of traffic, areas with industrial sources (i.e. coal power plants), wildfires, etc…
- We will be including both biogenic (naturally caused) or anthropogenic (human-caused) emission sources of ambient pollution.
- However, exposures such as indoor air pollution or occupational exposures to air pollution (i.e., coal mining), would not be considered as source of outdoor air pollution.
- Exposure assessment should include interval of exposure (follow-up period over time), level of exposure during that time-period (i.e. average annual exposure, average daily exposure, etc…), and location of exposure (i.e. postal code, census division, etc…).

Examples of inclusion:
- Cohort study which looks at ambient pollution levels nationally to determine incidence rate of adult asthma
- Study which looks at proximity to roadways, measured explicitly as NO2, PM2.5 to determine incident rates of adult asthma.
- Development of asthma in close proximity to ambient pollution emission sources.

Examples of exclusion:
- Effects of indoor air pollution on the development of adult asthma
- Second-hand smoking studies (indoor or outdoor)
- Seasonal pollen and allergens on the development of asthma
- Smoking
- Maternal factors on new cases of asthma.
- Occupational exposures (i.e. coal mining, dust exposure, wood dust, paper dust, asbestos, etc…)

*Outcomes:

We will include studies investigating adult incident asthma, as defined by: asthma development during adulthood, asthma diagnosis in adulthood, and/or prevalence of asthma with reported adult-onset as outcome measure. Asthma can be self-reported, physician diagnosed, using a case definition, or confirmed using objective measures of airway hyperresponsiveness.

- The main outcome we are looking for is **asthma incidence** (measured as new cases of asthma [overtime] or rate of new cases of asthma).
  - o Incidence has to be reported given an exposure to air pollution over time, this is important in full text! (what is the incidence attributable to air pollution over time).
  - o Given air pollution exposures to PM2.5, O3, NO2, and SO2.
- Though incidence can be applied in other outcomes such as hospitalizations, exacerbations, symptoms, etc... these are not the outcomes we will be using in this review.

Examples of inclusion:
- Incidence rate
- Rate of new cases
- Incident cases of asthma
- Onset of asthma

Examples of exclusion (incidence might be reported alongside this! So, make sure to double check):
- Hospitalizations
- Emergency room visits
- Prevalence (with no incidence outcome measure)
- Asthma symptoms or incidence of asthma symptoms (be especially careful with this one!)
- Asthma exacerbations or incidence of asthma exacerbations (also be careful with this one!)
- Health care spending
- Incidence of some other outcome not associated with the development of asthma.

Types of studies:

Inclusion:
- Human studies will be included
- Observational studies including cohort (prospective and retrospective), case-control, and cross-sectional study designs will be included where incidence is represented.
- Conference abstracts and reports will be included.

Exclusion:
- Experimental trials including interventional trials and randomized control trials.
- Reviews, letters, presentations, and individual case-reports will be excluded.
- should be excluded

Notes:

- Some titles/abstracts may not explicitly state the study design. You will need to use your judgement at times. If unsure, flag as <u>Unsure</u> for now, and we can revisit later.
- If an article is a meta-analysis and follows 2/3 PECO criteria, include for full text.
- Studies for exclusion: murine (mouse), primate (monkeys), in-vitro, in-vivo, trial, etc…

5 Review Strategy

SL will screen all articles during abstract/title selection, full-text review, and data-extraction stages. Review by a second reviewer will be performed on 20% of the articles during abstract/title screening, and 100% of articles during full-text review. Data extraction will be performed by SL and in duplicate by a second reviewing on all eligible studies identified from full-text review and meeting the inclusion and exclusion criteria. Disagreements between reviewers will be resolved by a third reviewer during screening, full-text review, and data extraction steps.

Deduplication will be performed automatically within Covidence prior to the title and abstract screening step. Manual deduplication will be performed in instances where automatic deduplication was not performed.

Data will be extracted from each included study will include general study characteristics, including: study title, authors' name, year of publication, study location, study design , recruitment methodology, sample size, demographics (age groups, gender, sex, ethnicity), study case definition of asthma, categorization of asthma, co- morbidities, follow-up period, pollutants included (PM2.5, O3, NO2, SO2), exposure assessment and model methodology, exposure time window, confounders, statistical methods, key findings, and effect estimates.

Forward citation searching will be manually screened on included articles to identify additional studies. Reference lists of included articles will also be manually screened for inclusion of studies. All articles found in citation searching will have a full-text review and screened against the full-text inclusion criteria.

Records for database searches will be tracked in Covidence. Grey literature searches will be tracked by the individual reviewer and recorded in Table 3 below. Citations will be uploaded to Covidence, deduplicated, and tracked using this system. Inclusion and exclusion criteria will be applied in the Covidence system, as well as evaluation of bias.

5.1 Grey literature search

Spencer Lee (SL) and team members will be performing the grey literature search. A total of (x hours) will be allocated to SL and team members to perform the grey literature databases, search engines, governmental organizations, and non-governmental organizations listed below in Table 3 located in section 4.6.1. The grey literature search will be performed on date. Results in each database or search engine will be reviewed for a maximum of 20 minutes or

until 20 articles that meet the PICO criteria will be kept, whichever limit is reached first. Reviewers may decide to extend the length of a search in a particular database, and such exceptions will be recorded in Table 3. We will perform the grey literature search according to the list of search engines and databases below.

Sources for Grey Literature Search
- IGO/NGL search engine (information here https://www.library.northwestern.edu/libraries-collections/government-collection/index.html): https://cse.google.com/cse?cx=00674806816657287449:55ez0c3j3ey
- IGO/NGO search (https://www.ala.org/rt/godort/taskforces/internationaldocuments/idtf/igo-search): https://cse.google.com/cse?cx=012681683249965267634:q4g16p05-ao
- Google CSE (Carleton University made, searches fed, provincial, municipal sources https://library.carleton.ca/find/government-information/canada: https://cse.google.com/cse?cx=007843865286850066037%3A3ajwn2jlweq#gsc.tab=0&gsc.sort
- Des Libris: https://resources.library.ubc.ca/page.php?details=des-libris&id=2265
- CADTH Grey Matters: https://greymatters.cadth.ca/
- Trip Medical Database: https://www.tripdatabase.com/
- Google Scholar: https://scholar.google.ca/
- Canada Commons: https://canadacommons.ca/
- NIH Clinical Trials Database: https://www.clinicaltrials.gov/
- Google search (advanced parameters): https://google.com
- Government of Canada Publications: https://publications.gc.ca/site/eng/home.html

7 Data Extraction

7.1 Data collection process

Extraction of data will be placed into an excel file shared between authors, with duplicate extraction by two authors. Where there is discrepancy, a third author will adjudicate. No automation will be used for during data collection and abstraction.

The following data items were adapted from Khreis et al. (2017) in a similar study for traffic related air pollution and childhood asthma burden.

"Exposure to Traffic-Related Air Pollution and Risk of Development of Childhood Asthma: A Systematic Review and Meta-Analysis | Elsevier Enhanced Reader." Accessed December 15, 2022. https://doi.org/10.1016/j.envint.2016.11.012.

Notes:
- In cases of a same study two similar but separately published articles, the most comprehensive publication will be used for data extraction (only one of the publications will be extracted).
  - Example: conference abstract with later journal publication of the same study.

- Extraction will be performed on different Excel sheets and compared between duplicate reviewers who are performing the extraction.
  - Disagreements between extracted results will be resolved by a third reviewer.
  - Missing data by one reviewer found during the combining step will revise their data extraction and compared with by both reviewers again.

8 Data Synthesis and Meta-analysis

A meta-analysis will be performed by pollutant when adequate data exists across included studies and sufficient homogeneity between studies can be established. Data synthesis and meta-analysis will be performed using R statistical software (with appropriate meta-analysis package, such as R: meta), OpenMeta or RevMan.

To facilitate meta-analysis, pollutant concentrations will be converted to a common metric ($\mu g/m^3$). Concentration increments for summary effect estimates will be selected to represent 10% increments of the WHO Air Quality Guideline values. If a single study provides multiple effect estimates for a single pollutant, we will apply accepted methodology (i.e., from Khreis et al. (2017) to incorporate the highest level of precision, including selection of estimates with:
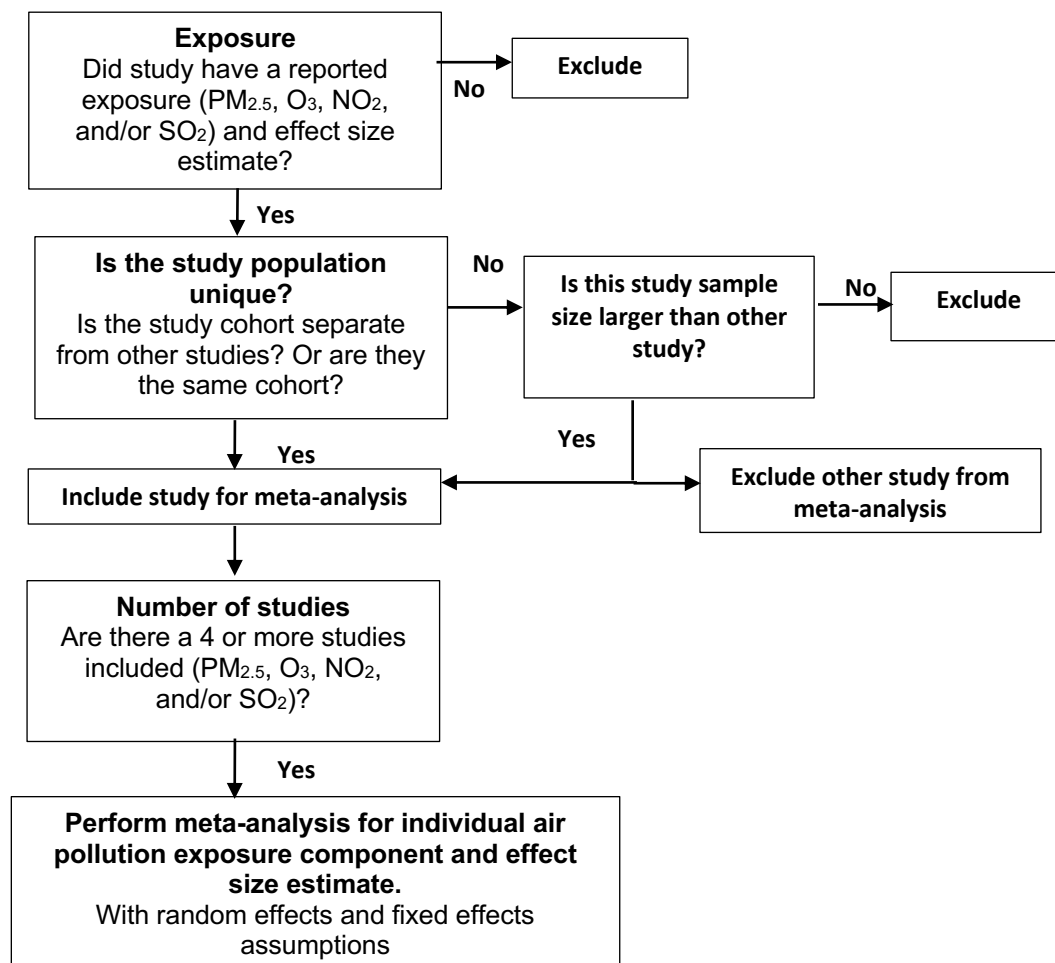a) The most restrictive asthma definition.
b) The longest time interval to capture asthma incidence.
c) Higher spatial resolution and more inclusive/longer time interval for exposure. Based on a literature scan we anticipate that studies reporting the relationship between pollutant exposure and asthma incidence will use annual exposure metrics.

Recognizing that single-pollutant estimates may be adjusted variably for additional pollutants in the published literature, we will conduct sensitivity analyses to separately analyze the results of models that account for multiple pollutants when sufficient data are available.

We will use both qualitative and quantitative approaches to assessing heterogeneity of across studies. When analyzing the heterogeneity of exposures, settings, population, and definition of outcomes may also affect results, representing heterogeneity qualitatively will also be considered. To statistically assess for heterogeneity, the I^2 test will be applied and cut off above 50% to indicate substantial heterogeneity. I will use the p-value of the χ^2 test to assess for statistically significant heterogeneity. Publication bias will be assessed with funnel plots. For each pollutant, summary effect estimates, and 95% confidence intervals will be calculated, with choice of application of fixed effects or random effects model informed by quantitative and qualitative heterogeneity between included studies, to best address the question "what is the average effect?".

A meta-analysis algorithm was implemented for the following pollutant and effect size estimates. To determine whether an effect size measure was appropriate for meta-analysis, including random effect, fixed effect, and further meta-regression was appropriate, the following decision algorithm was applied for each included study to determine inclusion for meta-analysis:

Figure 1. Meta-analysis decision algorithm.

```
Exposure
Did study have a reported
exposure (PM2.5, O3, NO2,
and/or SO2) and effect size
estimate?                    ──No──▶  Exclude
        │
        Yes
        ▼
Is the study population        ──No──▶  Is this study sample    ──No──▶  Exclude
unique?                                  size larger than other
Is the study cohort separate             study?
from other studies? Or are they              │
the same cohort?                             Yes
        │                                     │
        Yes                                   ▼
        ▼                            Exclude other study from
Include study for meta-analysis ◀──  meta-analysis
        │
        ▼
Number of studies
Are there a 4 or more studies
included (PM2.5, O3, NO2,
and/or SO2)?
        │
        Yes
        ▼
Perform meta-analysis for individual air
pollution exposure component and effect
size estimate.
With random effects and fixed effects
assumptions
```

*Parts of this decision algorithm was informed by previous publications, including Khreis et al. (2017) and Anderson et al. (2013).

We will perform meta-analysis on the adjusted effect size estimates for the included studies for each individual air pollution component. Studies will be weighted using the inverse variance calculation, a measure inversely proportional to population size. The meta R package will be used to perform the analysis. Forest plots will be generated using the included studies (using the metgen() function. Summary statistics including the I^2 statistic will be used to demonstrate statistical heterogeneity.

Across studies included, we have determined that there will be significant heterogeneity between studies. Specifically, asthma outcomes are likely affected by baseline exposures between study groups, model adjustment for co-pollutants, region, sex/gender composition, and case definition of incident asthma.

Meta-regression of included studies for meta-analysis will be explored to explain heterogeneity between studies. Included co-variates for the meta-regression will briefly include study characteristics, case definition, exposure, and adjustment for co-pollutants (**Table 1**).

Co-variate	Type of variable	Measure	# of measures
Region (continent)	Categorical	E (Europe), A (Asia, Australia), N (Americas)	3
Sex/gender	Continuous	Proportion (%)	1
Case definition	Categorical	S (self-reported), A (administrative definition)	2
Baseline exposure	Continuous	Annual exposure ($\mu g/m^3$)	1
Adjustment for co-pollutant(s)	Categorical	Boolean (T/F)	2
		Minimum degrees of freedom required	9

8.1 Effect measures

Air pollution will comprise of concentration-response relationship between incidence of asthma and other available outcomes. Effect measures of the concentration-response relationship between exposure and asthma outcomes will include measures such as yearly exposure to $PM_{2.5}$, NO_2, SO_2, and O_3 (ug/m^3 per year, or ppb) and measure of asthma incidence.

Notes:
- We anticipate the most common time horizon for exposure measurement to be:
  - Annual or daily mean exposure (PM2.5, NO2, SO2)
  - Summer peak exposure for O3 (April – Oct, 8-hr rolling average)
- Pooling of effect size estimates will be reported on a [yearly?] basis.
- Studies with adjusted and unadjusted effect size estimates available will undergo meta-analysis with their adjusted and unadjusted results.
- Sensitivity analysis will be preformed

9 Publication and Dissemination

A paper will be submitted to a leading journal in the field of environmental exposures and health, or respiratory health related journal (i.e., Annals of the ATS, European Respiratory Journal, Journal of Environmental Research and Public Health, American Journal of Respiratory and Critical Care Medicine, etc….). Furthermore, the findings of this study may be presented as an abstract, presentation, and/or poster during a conference during research proceedings. The findings and corresponding manuscript will also be adapted for a thesis chapter for SL.