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Ambient air pollution and depression – A protocol for a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 August 2024 and was last updated on 05 August 2024.

INTRODUCTION

Review question / Objective We will assess the evidence on the relationship between short- and long-term exposure to selected air pollutants (NO₂, PM_{2.5}, PM₁₀, O₃, and BC) and depression outcomes. We will do this by addressing the following research question that was formulated according to PECO framework (Participant, Exposure, Comparator and Outcome, see below): “Is the exposure to ambient air pollution associated with the risk of depression?” This protocol outlines a systematic review and meta-analysis aimed at updating existing evidence on the relationship between short- and long-term exposure to selected air pollutants (NO₂, PM_{2.5}, PM₁₀, O₃, and BC) and depression outcomes. Additionally, it seeks to investigate potential regional variations in this association.

Rationale The rapid urbanization and industrialization of the modern world has led to a

significant increase in ambient air pollution (AAP) levels especially in Asia and while there have been decreasing trends of some air pollutants it is still a significant health burden. AAP has been widely recognized to be a risk factor for non-communicable diseases such as cardiovascular diseases, cancers, and respiratory illnesses. Thus, air pollution stands as a significant global threat to public health, contributing to approximately 7 million premature deaths each year, with 4 million attributed to AAP (WHO, 2021). Moreover, air pollution emerges as a primary driver of climate change, posing a direct threat to our ecosystems (WHO, 2021). Clean air is rightfully acknowledged as a human right essential to health, leading the World Health Organization (WHO) to develop guidelines for air quality aimed at tackling this pervasive issue. AAP is a multifaceted mix of various pollutants, encompassing particulate matter (PM), gaseous pollutants, as well as metallic and organic compounds (Nathanson, 2023).

Particulate matter (PM) is commonly categorized into PM_{2.5} (particles with an aerodynamic diameter smaller than, or equal to, 2.5 µm) and PM₁₀ (particles with an aerodynamic diameter smaller than, or equal to, 10 µm). Sources of ambient air pollution are diverse and can originate from both natural and anthropogenic activities. While the impact of AAP on physical health is well-documented, its association with mental health, particularly depression, has gained attention in recent years. However, existing evidence remains inconclusive and often lacks consideration for regional differences in air pollution composition and climate.

Condition being studied Public health or policy reports rarely include mental health consequences of air pollution, partly due to insufficient evidence, but also due to the complexity of establishing an association between mental health and air pollution. There is emerging evidence to suggest that AAP adversely affects mental health. Recently, research within this topic has been expanding, especially for depression. Depression is a major global health issue, significantly impacting individuals and societies worldwide. It affects over 264 million people of all ages, making it a leading cause of disability globally.

METHODS

Search strategy

Pubmed:
 (((((((("Environmental Pollutants"[Mesh]) OR ("Environmental Pollution"[Mesh]) OR ("Nitrogen Oxides"[Mesh]) OR ("Particulate Matter"[Mesh]) OR ("Ozone"[Mesh]) OR ("Soot"[Mesh]) OR (((((((((((("air pollution"[Title/Abstract]) OR ("air pollutant*"[Title/Abstract]) OR ("environmental pollutant*"[Title/Abstract]) OR ("environmental pollution"[Title/Abstract]) OR ("environmental exposure*"[Title/Abstract]) OR ("nitrogen dioxide"[Title/Abstract]) OR ("nox"[Title/Abstract]) OR ("no2"[Title/Abstract]) OR ("nitrogen oxide*"[Title/Abstract]) OR ("ozone"[Title/Abstract]) OR ("o3"[Title/Abstract]) OR ("particulate matter"[Title/Abstract]) OR ("pm2.5"[Title/Abstract]) OR ("pm2,5"[Title/Abstract]) OR ("pm 2,5"[Title/Abstract]) OR ("pm10"[Title/Abstract]) OR ("pm 10"[Title/Abstract]) OR ("black carbon"[Title/Abstract])))) AND (((((((("Mood Disorders"[Mesh]) OR ("Depression"[Mesh]) OR (depression[Title/Abstract]) OR (depressed[Title/Abstract]) OR (depressive[Title/Abstract]) OR ("mood disorder*"[Title/Abstract]) OR ("affective disorder*"[Title/Abstract]))

Embase

((('air pollution'/exp OR 'ozone'/exp OR 'particulate matter'/exp OR 'soot'/exp OR 'nitrogen dioxide'/exp OR 'nitrogen oxide'/exp) OR ('air pollution':ab,ti OR 'environmental pollution':ab,ti OR 'nitrogen dioxide':ab,ti OR 'ozone':ab,ti OR 'o3':ab,ti OR 'particulate matter':ab,ti OR 'pm2.5':ab,ti OR 'pm2,5':ab,ti OR 'pm 2,5':ab,ti OR 'pm 2,5':ab,ti OR 'pm10':ab,ti OR 'pm 10':ab,ti OR 'soot':ab,ti OR 'black carbon':ab,ti OR 'nox':ab,ti OR 'no2':ab,ti OR 'air pollutant*':ab,ti OR 'environmental pollutant*':ab,ti OR 'environmental exposure*':ab,ti OR 'nitrogen oxide*':ab,ti)) AND ('depression'/exp OR 'mood disorder'/exp OR depression:ab,ti OR depressive:ab,ti OR depressed:ab,ti OR 'mood disorder*':ab,ti OR 'affective disorder*':ab,ti)

Web of science:

AB=("environmental pollutant*") OR AB=("air pollutant*") OR AB=("air pollution") OR AB=("environmental pollution") OR AB=("nitrogen oxide*") OR AB=("nitrogen dioxide") OR AB=(NO₂) OR AB=(NO_x) OR AB=(Ozone) OR AB=(O₃) OR AB=("particulate matter") OR AB=("pm_{2.5}") OR AB=("pm_{2,5}") OR AB=("pm 2,5") OR AB=("pm 2.5") OR AB=("pm₁₀") OR AB=("pm 10") OR AB=("black carbon") AND AB=("mood disorder*") OR AB=("affective disorder*") OR AB=(depression) OR AB=(depressive) OR AB=(depressed)

Scopus:

(((ABS ("black carbon")) OR (ABS ("pm 10")) OR (ABS ("pm10")) OR (ABS ("pm 2,5")) OR (ABS ("pm 2.5")) OR (ABS ("pm2,5")) OR (ABS ("pm2.5")) OR (ABS ("particulate matter")) OR (ABS ("o3")) OR (ABS ("ozone")) OR (ABS ("nox")) OR (ABS ("nitrogen oxide*")) OR (ABS ("no2")) OR (ABS ("nitrogen dioxide")) OR (ABS ("environmental exposure*")) OR (ABS ("environmental pollution")) OR (ABS ("environmental pollutant*")) OR (ABS ("air pollutant*")) OR (ABS ("air pollution"))) AND ((ABS (depression)) OR (ABS (depressed)) OR (ABS ("mood disorder*")) OR (ABS (depressive)) OR (ABS ("affective disorder*"))) .

Participant or population Any human population.

Intervention Exposure: Ambient (environmental) air pollution, both short-term and long-term of the following pollutants, both measured and modelled: Nitrogen dioxide (NO₂), particulate matter (PM_{2.5}, PM₁₀), ozone (O₃) and black carbon (BC) .

Comparator Humans exposed to higher levels of ambient air pollution compared with those exposed to less. The association needs to be reported quantitatively, using risk estimates such

as odds ratio (OR), hazard ratio (HR) or relative risk (RR) for exposure categories with their concentration ranges reported, or per (x-fold) unit increase in exposure.

Study designs to be included Epidemiological (e.g., follow-up, case-control and cross-sectional studies, but not ecological design studies) including exposure assessment providing for an exposure effect analysis. Only peer-reviewed published studies will be considered for the data synthesis.

Eligibility criteria Studies which are not primary research studies, studies where the outcome depression is only included in a larger outcome group such as “mental health disorders”, studies where the outcome is collected through self-diagnostic tools with no clinical input on the diagnosis. Studies where the exposure is exclusively indoor air pollution or occupational exposure thus making it challenging to distinguish the effects of air pollution from the other influencing factor. Studies including persons with depression at baseline, except for the outcome “depression exacerbation”.

Information sources Based on the PECO statement, the search strategy was developed in collaboration with a research librarian. Information sources include bibliographic databases Pubmed, Cinahl, Scopus and Web of Science. Additionally, relevant publications will be identified by searching references from related studies and reports. Reference managing, screening and data extraction will be done using the software Covidence (<https://www.covidence.org/>). The search strategy is based on the combination of terms for ambient air pollution with different terms for depression, using controlled vocabulary, such as MeSH terms. Furthermore, given the potential variation in the thesaurus terms, the search strategy was adapted to each database. No language filter will be applied to ensure a greater probability of including all the studies addressing the research question of interest in this systemic review and to minimize selection bias (Higgins et al., 2019). Finally, when all studies have been transferred to Covidence, before the manual screening process, duplicates will be removed through an automatic tool in Covidence.

Main outcome(s) Diagnosis of depression, or post-partum depression either from clinical or insurance registers, self-reported doctor’s diagnosis (“have you ever been told by a medical professional that you have depression?”) or by a clinical assessment, including application of

depression test questionnaires. Additionally, for studies with the exacerbation of depression as an outcome, could be reported using number of hospital visits, change in medication use or change in the severity of depression.

Data management For this review a comprehensive and systematic approach will be utilized to identify relevant studies that meet the eligibility criteria above and will be done by two reviewers in Covidence. The title and abstract of each record will be screened. In cases where there is a discrepancy among the reviewers, the study will move to the second stage (full-text screening). During the second stage, studies that pass the initial title and abstract screening will undergo a full-text review. In the appearance of a conflicting assessment among the reviewers during this process, and if the two reviewers cannot reach consensus, a third reviewer will be consulted to make the final determination. A record will be excluded when it does not adhere with the inclusion criteria or if it contains an exclusion criterion. The exclusion reported based on failing to meet the criteria for “Population”, “Study design”, “Exposure”, “Outcome”, “Comparator”, and “other”, with a further description of the exclusion reason. The compilation of studies excluded during the title and abstract screening or the full-text screening stage, along with the rationale for their exclusion, will be provided in the supplementary material and in a PRISMA Flow Diagram.

Quality assessment / Risk of bias analysis The risk of bias (ROB) assessment will be done independently by two reviewers. Again, if consensus is not reached, a third reviewer will be involved to adjudicate the final assessment. This review will use the Office of Health Assessment and Translation (OHAT), which is a well-recognized risk of bias tool for observational studies (OHAT, 2015). This tool includes 6 domains of selection, confounding, performance attrition/exclusion bias, detection, selective reporting and has a total of 11 questions. For each domain, studies will be rated as “low risk”, “probably low risk”, “probably high risk”, “high risk” or “not applicable” according to the instructions listed in Appendix B.

Following the OHAT handbook’s recommendations, we will implement a 3-Tier system to synthesize study findings, particularly when there is variation in the risk of bias (ROB) across studies or different analyses within the same study. This approach is based on three key criteria: confidence in randomization and concealment of subject allocation, confidence in characterizing exposure, and confidence in

assessing outcomes. The application of the tier approach within a single study may yield varying results, influenced by factors such as the nature of the outcome, type of exposure, and the method used for exposure assessment. To depict the distribution of risk of bias (ROB) across studies or analyses, heat maps can be generated for visualization purposes.

A Tier 1 study must exhibit "definitely low" or "probably low" ROB for the key criteria all other criteria. A Tier 3 study, on the other hand, scores "definitely high" or "probably high" ROB for the key criteria and all other criteria. A Tier 2 study does not meet the stringent criteria for Tier 1 or Tier 3, falling somewhere in between.

Strategy of data synthesis The included studies will most likely report their effect estimates using different measures which usually are either risk ratios (RR), hazard ratios (HR) or odds ratios (OR). We will collectively refer to these as relative risk measures. If studies report slopes, we will transform these to relative risks by exponentiation. Furthermore, for comparability, each adjusted effect estimate extracted from included studies, along with their 95% CI will be standardized to a fixed air pollution concentration increment of 10 $\mu\text{g}/\text{m}^3$.

Studies reporting results only for exposure categories, we will standardize the results to 10 $\mu\text{g}/\text{m}^3$ by using the median (if not available: mean) of the exposure categories. If the highest category is reported without a range, median or mean, the width of the previous exposure category is assumed.

Synthesis (meta-analyses)

For each exposure-outcome pair with two or more studies that meet the eligibility criteria, we will assess whether a quantitative synthesis in form of a meta-analysis is meaningful, given similarities in study populations, outcome definitions, and exposure assessments. If it is deemed that a meta-analysis is not appropriate, results will be synthesized qualitatively.

For the exposure (NO₂, PM_{2.5}, PM₁₀, O₃, and BC) and outcome pairs for "depression incidence" and "PPD", we will stratify meta-analyses by exposure period: short-term (equal to or less than 1 month) and long-term (more than 1 month). For the exposure (NO₂, PM_{2.5}, PM₁₀, O₃, and BC) and outcome pairs "depression exacerbation", we will only assess short-term exposure periods.

We will compute an overall association, as well as further stratify by region (Europe, North America, South America, Africa, Asia, others), when meaningful.

All the statistical analyses for this systematic review will be conducted using the latest version of R (R Foundation for Statistical Computing, Vienna, Austria. URL: <https://www.R-project.org>). We will compute overall association measures using random-effect models and report I² and Tau² statistics for heterogeneity (Kirkwood & Sterne, 2003). The evaluation of publication bias will be performed by visually assessing funnel plots (Sterne & Egger, 2001). Additionally, since visually assessment of a funnel plot on its own is not always reliable, the presence of publication bias will be assessed using Egger's linear regression test.

Subgroup analysis Subgroup analysis includes further stratification by region (Europe, North America, South America, Africa, Asia, others), when meaningful.

Sensitivity analysis As a sensitivity analysis and to inspect potential sources of heterogeneity, we will stratify the meta-analyses by gender. We will assess whether results are sensitive to study quality by stratifying by ROB status.

Language restriction No language restriction.

Country(ies) involved Denmark and Sweden.

Keywords Depression; air pollution; public health; environment.

Dissemination plans This study is part of a bigger EU project called MARCHES. The overall goal of marches is to assess the health costs associated with a range of environmental exposures – such as air pollution on both somatic and mental illnesses. This will lead to creating models to better understand pollution exposure across Europe. And ultimately, with the input from experts and stakeholders create guidelines that can be routinely used in the future by the EU and other national authorities.

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