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The association between maternal exposure to pollutant particulate matter 2.5 and neonatal congenital heart defects: a systematic review protocol

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Review question

The objective of this review is to identify if there is an association between maternal exposure to pollutant particulate matter 2.5 during the first trimester of pregnancy and neonatal congenital heart defects within the first year of life.

Keywords

Air pollution; cardiovascular abnormalities; congenital abnormalities; heart defects; particulate matter

Background

Air pollution

Air pollution affects people worldwide leading to more than 3.7 million premature deaths.¹ It is associated with mortality and morbidity, particularly affecting vulnerable populations such as children, pregnant women and the elderly.^{2–5} Air pollution has also been linked to fetal development complications, including growth restrictions, pre-term births and stillbirths.^{6,7}

To protect the public health and establish safe levels of contaminants, many countries have developed pollutant monitoring systems and standards for specific air pollutants based on recommendations set by the World Health Organization (WHO).^{8,9} Globally, the WHO has guidelines for target thresholds of specific air pollutants that may pose health risks including particulate matter (PM), ozone (O₃), nitrogen dioxide (NO₂) and sulfur dioxide (SO₂).⁸ Specific to the United States (US), the Environmental Protection Agency (EPA) established the Clean Air Act of 1970 and revised it in 1990 which expanded the list and set air quality standards for six major pollutants.^{10,11} Considered most harmful to the environment and public health, the six criteria pollutants include PM_{2.5} and PM₁₀, NO₂, SO₂, O₃, lead and

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carbon monoxide.¹⁰ Globally and within the US the air pollutants are monitored using measured concentrations found in ambient air. Of the air pollutants identified, PM_{2.5} and O₃ have been most strongly associated with the health of the population, affecting the respiratory and cardiac systems of vulnerable populations such as small children, expectant mothers and their developing fetuses or the elderly.^{12,13} Studies have demonstrated a link between air pollution and birth defects such as congenital heart defects (CHDs), among the first of which was research conducted in the US.³ Research continued outside the US in countries such as the UK.¹⁴ Interest in the role of specific pollutants such as PM_{2.5} has expanded due to the potential association between air pollution and health.

Particulate matter is a mixture of small particles and liquid droplets that measure less than 2.5 µm in diameter. Due to the size, it is easily absorbed through the lungs and the bloodstream.¹² Particulate matter <2.5 can be emitted from sources such as car exhaust, construction sites or industrial plants.^{15,16} Primary standards for safe levels of PM_{2.5}, set by the WHO and by individual country organizations such as the US EPA, are concerned with the effects on the health of the population. Another important standard, the secondary standard, is set for the protection of the environment. The safe 24-hour averages of PM_{2.5} set by WHO and the US EPA should not exceed 25 and 35 µg/m³, respectively. Annual safe levels are set not to exceed 10 µg/m³ based on the WHO and 12 µg/m³ based on the US EPA for the primary standard, with both agencies setting the secondary standard limit as 15 µg/m³.^{11,16} Standards in other developed countries are similar to those set in the US EPA, which are based on established WHO guidelines.¹⁷ Despite safe level limits, air pollution continues to be a critical issue because “small increases in risk may therefore carry a large public health implication”,¹⁸(p.605) and can increase the burden of mortality and morbidity in those affected.

Fetal development and congenital heart defects

Fetal development is the phase starting at fertilization of the embryo through the birth of the neonate. During this time, vital organs of the fetus, needed to sustain life once the baby is born, are forming. A birth defect occurs when the structure of one or more parts of the body forms abnormally during fetal development. Birth defects are common, affecting one out of every 33 infants born in the US.¹⁹ Congenital heart defects are the most common defect, affecting US infants at a rate of three to nine per 1000 births yearly and nine per 1000 births yearly worldwide, resulting in 1.35 million newborns diagnosed with a CHD every year.^{20,21–23} The highest reported CHD birth prevalence is in Asia and Europe with the lowest in Africa. All countries are affected by CHD, representing a major global health burden as it remains the leading cause of neonatal and infant mortality.^{23–26} Although worldwide infant CHD mortality rates have decreased by 39% in recent years, the impact on the affected child and their family leads to life altering morbidities and financial impacts.^{26,27}

Prevalence of CHDs is estimated at 34.3 million people globally and affects nearly 40,000 infant births in the US alone.^{22,28,29} However, it is estimated that over 80% of CHD diagnoses have no known etiology.^{30–32} Of the 15–20% of CHDs with a known etiology, most cases are thought to be due to genetic variations, maternal risk factors and

environmental exposures.^{30,31} Genetic variations and maternal risk factors are well established in the literature.^{33,34} However, environmental risk factors, specifically air pollution and the specific pollutants associated with a CHD, remain less understood.³⁵

“There is growing evidence suggesting that ambient air pollution during pregnancy is associated with birth defects”,²⁴(p.1) especially at critical fetal development times. One such time is between weeks two to eight of embryological development when the fetal heart structures are formed.³⁶ During this time frame, known as the infant’s *critical exposure window*, exposure to toxins such as air pollutants may affect fetal development and result in a CHD.^{6,20} Therefore, it is important to monitor air quality during the prenatal period, especially during the identified critical exposure window when the heart is forming.

Finding an association

With both air quality and CHDs leading to infant mortality and morbidity, further review and synthesis of the evidence on an association is necessary. An initial preliminary search conducted in September 2016 of PubMed, Cochrane Database of Systematic Reviews, *JBIR Database of Systematic Reviews and Implementation Reports*, Scopus, Prospero, Campbell and CINAHL identified two systematic reviews looking at the association between air pollution and CHD. The identified systematic reviews focused on associations of air pollution in general without limiting the literature to a link with a specific component such as PM_{2.5}.^{2,18} This systematic review will focus specifically on the criteria pollutant PM_{2.5}. As research on the air pollutant PM_{2.5} has increased rapidly in the last three years, a review to identify and evaluate this specific air pollutant’s association with CHD is warranted.

Inclusion criteria

Types of participants

The current review will consider studies that include neonates (a child under 28 days of age) and infants up to one year of age.

Exposure of interest

Studies that evaluate maternal exposure to the air pollutant PM_{2.5} during the first trimester (weeks one to 12) of fetal development will be included. The exposure of the air pollutant will be operationalized as measured concentrations of air pollutants during the fetal development period obtained from air quality sampling stations. Air quality sampling stations are operated by state or local governments and are placed in locations based on the purpose of the monitoring, such as to support health standards or to establish background pollution levels.³⁷

Outcomes

The current review will consider studies that include the outcome of a diagnosis of a CHD within the first year of life. A CHD is operationalized as a range of CHD diagnoses. Congenital heart defect diagnoses may include but are not limited to: minor defects such as a patent ductus arteriosus or critical defect such as transposition of the great arteries and hypoplastic left heart syndrome.

Types of studies

The current review will consider analytical human epidemiological studies, including prospective and retrospective cohort, case-control, ecological and cross-sectional analytical designs. This review will also consider correlational study designs, including case series and individual case reports studies for inclusion.

Search strategy

The search strategy will aim to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of PubMed and CINAHL has been undertaken to identify articles on this topic, followed by analysis of the text words contained in the titles and abstracts, and of the index terms used to describe these articles. A second search using all identified keywords and index terms will be undertaken across all included databases. A proposed search strategy for each of the databases is detailed in Appendix I. Third, the reference list of all studies selected for critical appraisal will be screened for additional studies.

Studies published in English and between 2002 to the present will be included. This date was chosen as research publications related to general air pollution and the contribution to CHD started emerging in 2002.

Information sources

The databases to be searched include: CINAHL, Embase, PubMed, Scopus, Cochrane Central Register of Control Trials, TOXNET: TOXLINE Database, TOXNET: Developmental and Reproductive Toxicology (DART) Database, Environment Complete, Europe PubMed Central.

The search for unpublished studies will include: ProQuest Nursing and Allied Health Source (Dissertations and Theses), MedNar.

Government websites: Centers for Disease Control and Prevention, World Health Organization.

The search strategies will be tailored for each database searched. Different combinations of keywords will be combined in the search strategies using AND or OR. All studies identified during the database search will be assessed for relevance to the review based on the information provided in the title, abstract and key terms. Studies identified from reference list searches will be assessed for relevance based on the study title. Articles meeting inclusion criteria will be retrieved for further review. If either reviewer feels a study may be relevant, the full paper will be retrieved for further review.

Study selection

Following the search, all identified citations will be uploaded into EndNote (Clarivate Analytics, PA, USA) and duplicates removed. Titles and abstracts will then be screened independently for inclusion by the two reviewers. Full text studies that may meet inclusion criteria will be retrieved and imported into the Joanna Briggs Institute System for the

Unified Management, Assessment and Review of Information (JBI SUMARI). Assessment of inclusion and exclusion will be conducted by both reviewers independently. Full text studies that do not meet the inclusion criteria will be excluded and the rationale for exclusion will be provided in an appendix in the final systematic review report and presented in a PRISMA flow diagram. Discrepancies in whether a study meets the inclusion criteria or should be excluded will be discussed to reach consensus; if a consensus cannot be reached, a third reviewer will be included.

Assessment of methodological quality

All selected studies will be critically appraised independently by the two reviewers at the study level for methodological quality in the review using standardized critical appraisal instruments from the JBI for cohort studies, case-control, cross-sectional, ecological, descriptive/case studies or descriptive/case-series and correlational designs.³⁸ Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer. The results of critical appraisal will be reported in narrative form and in a table.

Data extraction

Data will be extracted from papers included in the review using the standardized data extraction tool available in JBI SUMARI by the two reviewers independently and discussed prior to collation into one document.³⁸ The data extracted will include specific details about the populations, study methods and outcomes of significance to the review question and specific objectives. Again, at this stage, any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer. Authors of papers will be contacted to request missing or additional data where required.

Data synthesis

Findings of papers will be pooled in statistical meta-analysis using JBI Meta Analysis of Statistics Assessment and Review Instrument (JBI MASTARI) when possible. Effect sizes will be expressed as relative risk for cohort studies, odds ratios for case-control studies (for categorical data) and descriptive parametric and non-parametric statistics for cross-sectional analytical and ecological studies with 95% confidence intervals also calculated for analysis. Heterogeneity will be assessed statistically using the standard chi-squared test. Subgroup analyses will be conducted where there is sufficient data to investigate the different types of CHDs, infant age at diagnosis, level of PM_{2.5} exposure and geographical location of participants. Sensitivity analyses will be conducted to test decisions made regarding the exposure of PM_{2.5} and the diagnosis of a CHD. Where statistical pooling is not possible, the findings will be presented in narrative form, and in tables and figures to aid in data presentation and interpretation, where appropriate.

A funnel plot will be generated within JBI SUMARI to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger, Begg and Harbord tests) will be performed where appropriate.

Assessing confidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for assessing confidence in the quality of evidence will be used for this review, with the results presented in a summary of findings table created using GRADEPro.

Acknowledgments

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Appendix I: Search strategy for published and unpublished literature

Published literature

PubMed

1. "Air Pollutants" OR "Air Pollution"[MeSH] OR "Particulate Matter"[MeSH] OR "PM"
2. "Congenital Abnormalities"[MeSH] OR "Congenital Anomalies" OR "Congenital Defect" OR "Heart Defects, Congenital"[MeSH] OR "Congenital Heart Defect" OR "Congenital Heart Disease" OR "Heart, Malformation of" OR "Cardiovascular abnormalities"[MeSH])
3. "Cardiac" OR "Heart"
4. #1 AND #2 AND #3
5. (Limits: English; Publications from January 2002)

CINAHL

1. "Air Pollutants, Environmental" (TI, MH, AB) OR "Air Pollution" (TI, MH, AB) OR "Particulate Matter" (TI, MH, AB)
2. "Heart Defects, Congenital" (TI, MH, AB) OR "Cardiovascular Abnormalities" (TI, MH, AB)
3. #1 AND #2
4. (Limits: English; Publications from January 2002)

Embase

1. "Air Pollutant"/exp OR "Air Pollutant*":ti,ab OR "Air Pollution":ti,ab OR "Particulate Matter"/exp OR "Particulate Matter":ti,ab
2. "Congenital Heart Malformation"/exp OR "Congenital Heart Malformation":ti,ab OR "Congenital Heart Defect"/exp OR "Congenital Heart Defect":ti,ab OR "Congenital Heart Disease"/exp OR "Congenital Heart Disease":ti,ab OR "Cardiovascular Malformation"/exp OR "Cardiovascular Malformation":ti,ab
3. #1 AND #2

4. (Limits: English; Publications from January 2002)

Scopus

1. "Air Pollutants" OR "Air Pollution" OR "Particulate Matter" OR "PM" (TITLE-ABS-KEY)
2. "Congenital Abnormalities" OR "Congenital Anomalies" OR "Congenital Defect" OR "Congenital Heart Defect" OR "Congenital Heart Disease" OR "Heart, Malformation of" OR "Cardiovascular Abnormalities" (TITLE-ABS-KEY)
3. "Cardiac" OR "Heart" (TITLE-ABS-KEY)
4. #1 AND #2 AND #3
5. (Limits: English; Publications from January 2002)

Cochrane Central Register of Controlled Trials

1. "Air Pollutants" (TI, MH, AB) OR "Air Pollution" (TI, MH, AB) OR "Particulate Matter" (TI, MH, AB)
2. "Congenital Abnormalities" (TI, MH, AB) OR "Congenital Anomalies" (TI, MH, AB) OR "Congenital Defects" (TI, MH, AB) OR "Congenital Heart Disease" (TI, MH, AB) OR "Congenital Heart Defects" (TI, MH, AB) "Heart Defects, Congenital" (TI, MH, AB) OR "Heart, Malformations of" (TI, MH, AB) OR "Cardiovascular Abnormalities" (TI, MH, AB)
3. "Cardiac" (TI, MH, AB) OR "Heart" (TI, MH, AB)
4. #1 AND #2 AND #3
5. (Limits: English; Publications from January 2002)

TOXNET: TOXLINE Database

1. "Air Pollutants" OR "Air Pollution" OR "Particulate Matter"
2. "Congenital abnormalities" OR "Congenital Anomalies" OR "Congenital Defect" OR "Congenital Heart Disease" OR "Congenital Heart Defect" OR "Heart Defects Congenital" OR "Heart Malformations of" OR "Cardiovascular Abnormalities"
3. "Cardiac" OR "Heart"
4. #1 AND #2 AND #3
5. (Limits: NOT including PubMed Records; Search Term: Word Variants; Records with the phrase; English, Publications from January 2002)

TOXNET: Developmental and Reproductive Toxicology (DART) Database

1. "Air Pollutants" OR "Air Pollution" OR "Particulate Matter"

2. “Congenital abnormalities” OR “Congenital Anomalies” OR “Congenital Defect” OR “Congenital Heart Disease” OR “Congenital Heart Defect” OR “Heart Defects Congenital” OR “Heart Malformations of” OR “Cardiovascular Abnormalities”
3. “Cardiac” OR “Heart”
4. #1 AND #2 AND #3
5. (Limits: NOT including PubMed Records; Search Term: Word Variants; Records with the phrase; English, Publications from January 2002)

Environment Complete

1. “Air Pollutants” (TI, AB, GE) OR “Air Pollution” (TI, AB, GE) OR “Particulate Matter” (TI, AB, GE)
2. “Congenital Abnormalities” (TI, AB, GE) OR “Congenital Anomalies” (TI, AB, GE) OR “Congenital Defects” (TI, AB, GE) OR “Congenital Heart Disease” (TI, AB, GE) OR “Congenital Heart Defects” (TI, AB, GE) “Heart Defects, Congenital” (TI, AB, GE) OR “Congenital Disorders” (TI, AB, GE) OR “Cardiovascular Abnormalities” (TI, AB, GE)
3. “Cardiac” (TI, AB, GE) OR “Heart” (TI, AB, GE)
4. #1 AND #2 AND #3
5. (Limits: English; Publications from January 2002)

Europe PubMed Central

1. “Air Pollutants” OR “Air Pollution” OR “Particulate Matter” OR “PM”
2. “Congenital Abnormalities” OR “Congenital Anomalies” OR “Congenital Defect” OR “Heart Defects, Congenital” OR “Congenital Heart Defect” OR “Congenital Heart Disease” OR “Heart, Malformation of” OR “Cardiovascular abnormalities”
3. “Cardiac” OR “Heart”
4. #1 AND #2 AND #3
5. (Limits: English; Publications from January 2002)

Unpublished literature

ProQuest Dissertations and Theses – Sciences and Engineering Collection

1. “Air Pollutants” OR “Air Pollution” OR “Particulate Matter”
2. “Congenital Heart Defect” OR “Congenital Heart Disease” OR “Congenital Heart Malformation” OR “Cardiovascular Abnormalities” OR “Cardiovascular Malformation”
3. #1 AND #2

4. (Limits: English; Publications from January 2002)

MedNar

1. “Air Pollutants” OR “Air Pollution” OR “Particulate Matter”
2. “Congenital Heart Defect” OR “Cardiovascular Abnormalities”
3. #1 AND #2
4. (Limits: English; Publications from January 2002)

Government websites

Centers for Disease Control and Prevention – cdc.gov

1. “Congenital Heart Defect” OR “Congenital Heart Disease” OR “Congenital Heart Malformation” OR “Cardiovascular Abnormalities” OR “Cardiovascular Malformation”
2. “Air Pollution” OR “Air Pollutant” OR “Particulate Matter”
3. #1 AND #2

World Health Organization – who.int

1. “Air Pollution” OR “Air Pollutant” OR “Particulate Matter”
2. “Congenital Heart Defects” OR “Congenital Heart Disease” OR “Congenital Heart Malformation” OR “Cardiovascular Abnormalities” OR “Cardiovascular Malformation”
3. #1 AND #2