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Association between maternal exposure to pollutant particulate matter 2.5 and congenital heart defects: a systematic review

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Abstract

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

Introduction: The environment is recognized as an important determinant of health for both the individual and population. Air pollution specifically is a major environmental risk factor impacting health with links to asthma, heart disease, obesity, and fetal developmental complications. Of the commonly monitored air pollutants, particulate matter 2.5 has associations with health, especially among vulnerable populations such as children and pregnant women. A congenital heart defect is a fetal complication that impacts 34.3 million infants globally, with more than 80% of the diagnoses having an unknown etiology. Although environmental risk factors such as air pollution are thought to be a risk factor in the diagnosis of a congenital heart defect, epidemiologic research evidence is limited.

Inclusion criteria: This review considered studies that evaluated maternal exposure to the air pollutant particulate matter 2.5 during the first trimester (weeks 1–12) of fetal development. The primary outcome was a diagnosis of a congenital heart defect in an infant within the first year of life.

Methods: A three-step search strategy was utilized in this review and included 11 databases and two websites. Studies published from January 2002 to September 2018 were eligible for inclusion. Only papers published in English were included. Eligible studies underwent critical appraisal by two independent reviewers using standardized critical appraisal instruments from JBI. Quantitative data were extracted from the included studies independently by two reviewers. Odds ratios (ORs) and 95% confidence intervals (CIs) were extracted for the individual outcome measures, specifically atrial septal defect, ventricular septal defect, and tetralogy of fallot, respectively. The defects were identified and pooled, where possible, in statistical meta-analysis. Where statistical pooling was not possible, findings were reported narratively.

Results: Five studies were identified that met the inclusion criteria, including three cohort and two case-control designs. Each individual study identified at least one statistically significant

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increase or inverse association between particulate matter 2.5 and a congenital heart defect. An increased risk was identified with more than seven isolated and two groupings of congenital heart defects. An inverse risk was identified with two isolated and one grouping of congenital heart defects. Meta-analysis results were: atrial septal defect, OR = 0.65 (95% CI, 0.37 to 1.15); ventricular septal defect, OR 1.02 (95% CI, 0.75 to 1.37); and tetralogy of fallot, OR = 1.16 (95% CI, 0.78 to 1.73), indicating no statistically significant findings.

Conclusion: There was no significant evidence to support an association between air pollutant particulate matter_{2.5} and a congenital heart defect in the first year of life. However, few studies met the rigorous inclusion criteria, and the studies that did had high heterogeneity, making it difficult to complete a meta-analysis with such a limited number of articles. Further research is needed to standardize the outcomes and pollutant monitoring methods, and provide comparable analysis results so that future synthesis of the literature can be conducted.

Keywords

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

Introduction

As early as Hippocrates and the Greeks, humans have tried to understand how the environment affects health.¹ As knowledge increased, science began to differentiate into more circumscribed areas of interest, such as biology and ecology, which focused on how the environment affects biological organisms, or medicine and the study of disease. However, as public health made strides in prevention and treatment of infectious disease, medical scientists again have increasingly considered how environment affects health and chronic illnesses and have turned to broader, socioecological models. Ecologic and socioecological models are being applied by World Health Organization (WHO); the Centers for Disease Control and Prevention; the National Academy of Sciences; and the ministries of health in Canada, Europe, Australia, and other developed and developing countries.

The environment is increasingly recognized as an important determinant of individual and population health. Air quality and exposures are important environmental contributors that affect both the morbidity and mortality of the population.^{2,3} Studies have focused on the effect of air quality on outcomes such as asthma,^{4,5} atherosclerosis,^{6,7} obesity,⁸ metabolic syndromes^{9,10} and other cardiopulmonary disorders. According to the WHO, 4.2 million premature deaths worldwide per year are attributed to air quality and pollution.¹¹ These factors impact vulnerable groups of the population such as children, expectant mothers and older persons.^{12–15} Air pollution has also been linked to fetal development complications including growth restrictions, pre-term births and stillbirths.^{16,17}

Many countries have adopted pollutant monitoring systems and standards for specific air pollutants based on recommendations set by the WHO.^{11,18} WHO guidelines established thresholds of specific air pollutants that are linked to health or environmental risks. Safe thresholds are created for both primary (risk to health) and secondary (detrimental to environment) concentrations by the WHO and the U.S. Environmental Protection Agency

(EPA).¹¹ For this review, analysis is focused on health risk and will explore primary threshold standards. In the United States, the EPA Clean Air Act (1970 and 1990) expanded and set air quality standards to include six major pollutants measured in ambient air.^{19,20} Considered most harmful to the environment and public health, the six criteria pollutants include particulate matter (PM)_{2.5} and PM₁₀, nitrogen dioxide (NO₂), sulfur dioxide (SO₂), ozone (O₃), lead and carbon monoxide (CO).²⁰ Some pollutants such as PM_{2.5} are more readily absorbed and are strongly associated with respiratory and cardiac health of the population.³

Particulate matter 2.5 is a mixture of small particles and liquid droplets that are emitted from sources such as car exhaust, construction sites or industrial plants, and measure less than 2.5 micro-meters (µm) in diameter.^{21,22} Because of the small size, molecules are easily absorbed through the lungs and circulated in the bloodstream.¹⁹ Safe 24-hour primary averages of PM_{2.5} set by WHO and the EPA are below 25 µg/m³ and 35 µg/m³, respectively, with annual levels not to exceed 10 µg/m³ (WHO) or 12 µg/m³ (EPA). Standards in other developed countries are similar to those set by the EPA and WHO guidelines.²³ 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”^{24(p.605)} and can affect mortality and morbidity for those exposed.

For example, studies have demonstrated a link between air pollution and birth defects. Among these defects are congenital heart defects (CHDs), which may be linked to exposure particularly during critical fetal development periods such as weeks 2 through 8 of embryological development when the fetal heart structures are formed.^{13,25,26} Often called the infant’s “critical exposure window”, exposure to toxins such as air pollutants during this period may affect development and result in a congenital defect.^{16,27}

Birth defects are common, affecting one out of every 33 infants born in the United States.²⁸ Congenital heart defects are the most common, affecting infants at a rate of three to nine per 1000 births per year in the United States and nine per 1000 births per year worldwide, resulting in 1.35 million newborns diagnosed with a CHD globally every year.^{27,29–31} The highest reported prevalences of CHDs at birth are in Asia and Europe, with the lowest in Africa.^{32,33} More than 34.3 million people globally and nearly 40,000 infants born in the United States have a CHD.^{30,32,33} However, more than 80% of CHD diagnoses have no known etiology.^{34–36} Most cases of CHD with a known etiology are attributed to genetic variations, maternal risk factors and environmental exposures.^{34,35} Although infant CHD mortality rates have decreased 39% worldwide in recent years, the impact on affected children and their family leads to life-altering morbidities and financial strain.^{37,38}

With both air quality and CHDs leading to infant mortality and morbidity, further review and synthesis of the evidence of association are necessary. All countries are affected by CHDs, representing a major global health burden that remains the leading cause of neonatal and infant mortality.^{31,37,39,40} However, environmental risk factors related to air pollution and specific pollutants associated with a CHD remain unclear.⁴¹

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 regarding the association between air pollution and CHDs. The identified systematic reviews focused on associations with various air pollutants not including the literature surrounding the specific pollutant PM_{2.5}.^{12,24} This systematic review focuses specifically on the pollutant PM_{2.5}. As research on air pollutant PM_{2.5} has increased rapidly in the past three years, a review to identify and evaluate this specific air pollutant's association with CHD was warranted. The objective of this review was to identify the association between maternal exposure to pollutant PM_{2.5} during the first trimester of pregnancy and congenital heart defects within the first year of life.

The objectives, inclusion criteria and methods of analysis for this review were specified in advance and documented in an *a priori* protocol.⁴²

Review question

Is there an association between maternal exposure to pollutant PM_{2.5} during the first trimester of pregnancy and CHDs within the first year of life?

Inclusion criteria

Participants

This review considered studies that included infants up to one year of age, with no restriction on location.

Exposure of interest

Studies that evaluated maternal exposure to the air pollutant PM_{2.5} during the first trimester (weeks 1–12) of fetal development were included. The exposure of the air pollutant was 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.⁴³

Outcome

This review considered studies that included the outcome of a diagnosis of a CHD within the first year of life. A CHD was operationalized as a range of CHD diagnoses. Congenital heart defect diagnoses could include, but were not limited to, minor defects such as a patent ductus arteriosus or critical defects such as transposition of the great arteries and hypoplastic left heart syndrome.

Types of studies

This review considered analytical human epidemiological studies including prospective and retrospective cohort, case-control, ecological and cross-sectional analytical designs. This

review also considered correlational study designs including case series and individual case reports studies for inclusion. Studies published in English and with dates from 2002 to September 2018 were included. The earlier date was chosen because research publications related to general air pollution and the contribution to CHD began to be reported in the literature beginning in 2002.¹³ The full search strategy is provided in Appendix I.

Methods

The systematic review was conducted in accordance with the JBI methodology for systematic reviews of etiology and risk.⁴⁴ This review was conducted in accordance with an *a priori* published protocol.⁴² The protocol was registered in PROSPERO CRD42017079174.

Search strategy

The search strategy aimed to find both published and unpublished studies. A three-step search strategy was utilized. An initial limited search of PubMed and CINAHL was undertaken to identify studies 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 studies. A second search using all identified keywords and index terms was undertaken in September 2018 across all included databases: CINAHL, Embase, PubMed, Scopus, Cochrane Central Register of Controlled Trials, TOXNET: TOXLINE database, TOXNET: Developmental and Reproductive Toxicology (DART) database, Environment Complete and Europe PubMed Central. The search for unpublished studies included ProQuest Nursing and Allied Health Database (Dissertations and Theses), MedNar and government websites (e.g. CDC, WHO). Finally, the reference list of all studies selected for critical appraisal were screened for additional studies.

Study selection

Following the searches detailed in the review protocol, all identified citations were uploaded into End-Note X7.4 (Clarivate Analytics, PA, USA) and duplicates removed. Titles and abstracts were screened by two independent reviewers for assessment against the inclusion criteria for the review. The full texts of potentially eligible studies were retrieved and assessed in detail against the inclusion criteria by two independent reviewers. Details of studies that met inclusion criteria set forth in the protocol were imported into JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; Joanna Briggs Institute, Adelaide, Australia).^{42,44} Full-text studies that did not meet the inclusion criteria were excluded, and reasons for their exclusion are provided in Appendix II. Any disagreements that arose between the reviewers were resolved through discussion.

Assessment of methodological quality

Eligible studies were critically appraised independently by the two reviewers at the study level for methodological quality using standardized critical appraisal instruments from JBI, specifically the critical appraisal checklist for case-control studies tool and the critical appraisal checklist for cohort studies tool.⁴⁴ Any disagreements that arose between the reviewers were resolved through discussion.

To be inclusive of a limited number of studies in the literature surrounding this presumed association, no predetermined criteria or weighing of criteria were used for the critical appraisal. The information from the studies was evaluated for each appraisal question, and information was rated as present, missing, unclear or not applicable. However, all studies, regardless of methodological quality, were utilized in the review.

Data extraction

Data were extracted from studies using the standardized data extraction tool available in JBI SUMARI by the two reviewers.⁴⁴ The data extracted included specific details about the populations, study methods and outcomes of significance to the review question and specific objective. Any disagreements that arose between the reviewers were resolved through discussion.

Results from adjusted models including odds ratios (ORs) and 95% confidence intervals (CIs) were used when reported for specific outcome measures. When extracting data from the individual studies, several decisions were made as articles reported data by months of gestation and levels of pollutant exposure. In studies that presented data as reported by monthly values during pregnancy, data were extracted from the third month of gestation.⁴⁵ Resulted data that were presented by level of pollutant exposure, the 50th to >90th centile⁴⁶ or the third quartile⁴⁷ of exposure was utilized.

Decisions also were made related to extraction of data from different classifications of CHD found among the identified studies. A diagnosis of a ventricular septal defect (VSD) was reported in four of the five studies but was found to have various classifications. For example, in one study, VSDs were classified into three subgroupings⁴⁶ whereas others only utilized one group.^{45,47,48} When more than one subgrouping was identified, a decision was made to use the perimembranous VSD subgrouping because it is the most common diagnosis of VSD.⁴⁹

Data synthesis

Quantitative data were, where possible, pooled in statistical meta-analysis using Comprehensive Meta-Analysis Software Version 3 (Biostat, NJ, USA). The DerSimonian and Laird method was used for the meta-analysis. Based on guidance from Tufanaru *et al.*,⁵⁰ the random effects model was used for statistical calculations.⁵⁰ Heterogeneity was assessed statistically using the standard chi-squared and I^2 test. Separate meta-analyses were conducted for different types of CHDs: VSD, atrial septal defect (ASD) and tetralogy of fallot (TOF). Raw data were not available from several studies, which limited the ability for subgroup analyses. Where statistical pooling was not possible, the findings were presented in narrative form including tables and figures to aid in data presentation and interpretation where appropriate.

Results

Study inclusion

A systematic search of the literature initially yielded 11,370 studies for review. After duplicates were removed, 10,838 studies remained. Following a review of the titles and abstracts, 10,825 studies were excluded, leaving 13 studies for full-text review to determine if inclusion criteria were met. After full-text review, eight studies were excluded for reasons listed in Appendix II. The five remaining studies were either cohort or case-control epidemiologic designs. Figure 1 shows the PRISMA flowchart of the study inclusion and exclusion process.⁵¹

Methodological quality

Five studies that met inclusion criteria were critically appraised for methodological quality by two independent reviewers using the critical appraisal checklists for case-control studies and cohort studies. Following independent appraisals, the reviewers met for discussion to resolve any disagreements. Two case-control studies^{46,47} and three cohort studies^{14,45,48} were identified for appraisal. The reviewers were in agreement on all 10 critical appraisal criteria for the case-control studies. As only two studies were identified, the table was not presented.^{46,47}

The cohort studies, as presented in Table 1, resulted in “yes” on eight of the 11 questions in the critical appraisal checklist.^{14,45,48} The following information summarizes the deviations from “yes” on the critical appraisal checklist. Of the three cohort studies, one presented results on pollutant data from two monitoring stations and reported valid methods for data collection. However, the reliability of the results was questionable due to measurement across a large spatial area.⁴⁵ In three studies, whether the participants were free of the outcome at the moment of exposure to the pollutant was uncertain.^{14,45,48} It was also unclear whether the outcomes were measured using reliable methods in two of the studies.^{14,48} None of the studies had strategies for incomplete follow-up, and questions related to this were answered as “not applicable” on the critical appraisal tool.

Characteristics of included studies

Five studies were included in the systematic review with their participants, air pollutants and outcomes of interest summarized in Appendix III. Two studies were case-control studies^{46,47} and three were cohort studies.^{14,45,48} Of the five studies, the first two identified by database searches were studies published in 2013^{46,48} on the association of PM_{2.5} and CHD, followed by one study in each of the following three years: 2014,⁴⁷ 2015¹⁴ and 2016.⁴⁵ Settings for these studies included the United States (n = 3)^{14,46,47} and other countries (n = 2)^{45,48} including the Tel Aviv, Israel⁴⁸ and Wuhan, China,⁴⁵ which demonstrate a global concern for air pollution and congenital defects, primarily heart defects.

The participants in the five studies were similar as they all were identified through data registries that were based on birth records. The number of cases in the studies ranged from 188 infants⁴⁵ to 3494 infants¹⁴ with identified CHD. A majority of cases for each of the studies were determined by clinical, surgical or autopsy reports. When determining inclusion

characteristics for the cases, four studies included live births, stillbirths and fetal deaths after 20 weeks' gestation as participants in their study.^{45–48} The remaining study only collected data on infants who were live births.¹⁴ Exclusion factors for cases varied among studies. Three studies excluded infants with chromosomal anomalies or identifiable syndromes.^{45,46,48} Two studies excluded infants if they had additional organ systems with a malformation.^{45,48} Two studies excluded infants born to mothers with pregestational diabetes⁴⁷ or diabetes prior to gestation.⁴⁶ Three studies excluded mothers based on distance between residential address and air monitoring stations with two studies using a cutoff distance of 50 km^{14,47} and one study using a cutoff distance of 10 km.⁴⁸ Single studies also identified exclusion factors such as incomplete demographic data,⁴⁵ infants with more than a simple, isolated CHD,⁴⁷ and infants born with multiple births.¹⁴

Controls were non-diagnosed infants randomly selected from data registries.^{14,46,47} Three studies utilized national or state birth defect registries specific to the study setting.^{14,46,47} One study pulled data from hospital data registry in the specific study setting.⁴⁵ The remaining study identified participants from a National Birth Defects Prevention Study, which collected data from nine states in the United States.⁴⁷

The exposure of interest was present in each of the five studies as measured solely by air-quality monitoring stations.^{14,45–48} However, the number of air monitoring stations used to obtain the air pollution data varied. As few as two¹⁴ and as many as 91 air monitoring stations⁴⁵ were utilized to obtain the data. The time frames of obtaining the air pollutant data were within the first trimester of gestation but varied on the intervals: two studies measured data weeks 3 through 8 of gestation,^{14,48} one study measured data weeks 2 through 8 of gestation,⁴⁷ one study measured data the first two months of gestation⁴⁶ and another measured the first three months of gestation.⁴⁵

The outcomes identified in the studies varied, with one having as few as three groupings of CHDs⁴⁵ and another having as many as 19 groupings of CHDs.⁴⁶ Three isolated CHDs, (VSD, ASD and TOF) were identified in more than one study. Meta-analysis was conducted for isolated CHDs when more than one study presented isolated results on the same outcome.

Review findings

The diagnosis of various CHDs were analyzed in all five of the identified studies in relation to the exposure to PM_{2.5} during the earlier stages of pregnancy.^{14,45–48} Each of the five included studies identified at least one statistically significant association, reporting either an increased or inverse risk that PM_{2.5} had on the development of a CHD. There were increased odds ranging from 1.10 (all CHD⁴⁵) to 8.80 (truncus arteriosus¹⁴) among the studies for different specific defects. An increased risk was noted for many different CHDs, including truncus arteriosus, total anomalous pulmonary venous return, coarctation of the aorta (COA), interrupted aortic arch, and any critical CHD;¹⁴ dextro-transposition of the great arteries;⁴⁶ hypoplastic left heart syndrome;⁴⁷ and VSD and all CHDs.⁴⁵ However, for other defects, PM_{2.5} was associated with decreased odds that ranged from 0.50 (ASD⁴⁷) to 0.77 (patent ductus arteriosus⁴⁸). An inverse risk was identified for CHDs including septal defects

and ASD,⁴⁷ and patent ductus arteriosus.⁴⁸ Specific ORs and 95% CIs can be found in Table 2.

Meta-analyses were conducted when two or more identified studies had similar outcomes and similar study designs that could be compared. While not always reporting statistically significant outcomes, there were three isolated CHD diagnoses associated with the air pollutant PM_{2.5} that were found in more than one study and were extracted to conduct the meta-analysis. Of the five studies identified,^{14,45–48} two case-control studies included ASD data,^{46,47} two case-control studies included VSD data,^{46,47} and two case control studies included TOF data.^{46,47} Cohort studies that included data on VSD contained high degrees of heterogeneity in the results and were not included in the meta-analysis.^{45,48} For all identified outcomes related to PM_{2.5} exposure, the combined effects were close to 1 and were not found to be significant. Further discussion regarding the performed meta-analyses can be found below.

Atrial septal defect

Of the five articles, only two included data for ASD.^{46,47} Dichotomous data from the two case-control studies investigating ASD were pooled in statistical meta-analysis^{46,47} (Figure 2).

Did maternal exposure to PM_{2.5} increase ASD in infants?

The mean OR was 0.651, indicating that exposure to PM_{2.5} decreased the odds of CHD by 35%. However, the 95% CI for the OR was 0.367 to 1.154 and crossed 1.0, indicating that the mean OR could fall anywhere in this range and was non-significant. The test of the null (that the true OR is 1) yielded a z-value of 1.470 and a corresponding P-value of 0.141. We could not reject the null that the true mean effect size was 1.0 with no difference in exposure to PM_{2.5} and CHD.

Did the effect size vary across studies?

The observed effect size varied somewhat from study to study, but a certain amount of variation was expected due to sampling error. Thus, further statistical analysis was performed to determine whether the observed variation fell within the range that could be attributed to sampling error (in which case there is no evidence of variation in true effects), or whether it exceeded that range.⁵²

The chi-squared or Q-statistic provided a test of the null hypothesis that all studies in the analysis shared a common effect size. If all studies shared the same effect size, the expected value of Q would be equal to the degrees of freedom (the number of studies minus 1).⁵² I^2 is another analysis used to determine what proportion of the observed variance reflected differences in true effects rather than sampling error.⁵² In this analysis, the Q-value was 4.71 with 1 degree of freedom and $P = 0.03$. The I^2 was 78.76%. Because Q was greater than the degrees of freedom and the I^2 value was greater than 75%, there was evidence of variance in true effects with a high level of heterogeneity.⁵³

In summary, the results were non-significant in establishing that the maternal exposure to PM_{2.5} was associated with decreased odds of developing an ASD, and the estimated results between studies showed moderate variability. Careful interpretation of this pooled effect is warranted.

Ventricular septal defect (case-control design)

Data on VSD was included in two^{46,47} of the five studies. Dichotomous data from the two case-control studies investigating VSD were pooled in statistical meta-analysis.^{46,47} (Figure 3).

Did maternal exposure to PM_{2.5} increase VSD in infants?

The mean OR was 1.016, indicating that maternal exposure to PM_{2.5} increased the odds of CHD by 1.6%. The 95% CI for the OR was 0.754 to 1.368 and crossed 1.0, indicating that the mean OR could fall anywhere in this range and was non-significant. The test of the null (that the true odds ratio is 1) yielded a z-value of 0.10 and a corresponding P-value of 0.92. We failed to reject the null that the true mean effect size was 1.0 with no difference in exposure to PM_{2.5} and CHD.

Did the effect size vary across studies?

The Q-value was 0.22 with 1 degree of freedom and P = 0.636. Because Q was less than the degrees of freedom, there was no evidence of variance in true effects.⁵² I^2 statistic indicated what proportion of the observed variance reflected differences in true effects rather than sampling error.⁵² Because the variance in true effects was zero, I^2 must be zero. Thus, there was homogeneity in the studies and no evidence that the true effect size varied from study to study.

In summary, the association between PM_{2.5} and VSD was only slightly increased but statistically non-significant with no degree of variability found among the study effect size.

Ventricular septal defect (cohort design)

VSD was also included in two identified cohort studies.^{45,48} The Q-value was 13.58 with 1 degree of freedom and P < 0.001. The I^2 value was 92.64%. Because Q was greater than the degrees of freedom and the I^2 was greater than 75%, there was evidence of variance in true effects and a high level of heterogeneity.⁵³ Because of considerable variation in effect results, especially the I^2 of 92.64%, the authors chose not to perform a meta-analysis using the cohort design studies.⁵⁴

Tetralogy of fallot

Of the five studies, only two included data for TOF.^{46,47} Dichotomous data from two case-control studies investigating TOF were pooled in statistical meta-analysis.^{46,47} (Figure 4).

Did maternal exposure to PM_{2.5} increase TOF in infants?

The mean OR was 1.162, indicating that maternal exposure to PM_{2.5} increased the odds of CHD by 16%. The 95% CI for the OR was 0.779 to 1.734, and included an odds ratio of 1.0,

indicating non-significant results. The test of the null (that the true odds ratio was 1) yielded a z-value of 0.74 and a corresponding P-value of 0.46. Therefore, we could not reject the null that the true mean effect size was 1.0 with no difference in exposure to PM_{2.5} and TOF.

Did the effect size vary across studies?

The Q-value was 1.23 with 1 degree of freedom and P = 0.27. The I^2 was 18.60%. Because Q was greater than the degrees of freedom and the I^2 was less than 25%, there was evidence of variance in true effects with a low heterogeneity.⁵³

In summary, exposure to PM_{2.5} was associated with an increased odds of developing TOF, but the results were not statistically significant with a low level of variation among the studies involved in the analysis.

Discussion

In this systematic review, we assessed the potential association between the maternal exposure to the air pollutant PM_{2.5} and the neonatal diagnosis of a CHD, specifically ASD, VSD and TOF, within the first year of life. We found no statistically significant evidence to support any of the associations. There were only five research studies that met inclusion criteria for the review, with variance noted in the methodology utilized, CHD classifications and reporting of the outcome data. Due to this heterogeneity, only two of the studies that met inclusion criteria were utilized for the meta-analysis.^{46,47} The remaining three studies that met inclusion criteria were presented in narrative form.^{14,45,48}

Previous literature did include other meta-analyses; however, none included the air pollutant PM_{2.5}. The meta-analysis conducted by Chen *et al.*¹² analyzed data on general air pollution and congenital anomalies. The only significant association found was between the air pollutant NO₂ and COA.¹² In the meta-analysis conducted by Vrijheid *et al.*,²⁴ the authors found increased risk of COA and TOF with air pollutants NO₂ and SO₂. PM₁₀ exposure was related to increased risk of ASD.²⁴ Our study expanded what is known about the association between CHD and air pollution by including PM_{2.5}. Of the five studies included in our analyses, all found either positive or inverse associations with PM and specific CHDs.^{14,45-48} There was additional literature suggesting that PM_{2.5} may be important in CHDs, but it did not meet inclusion criteria for this systematic review.⁵⁵⁻⁵⁷ Most of the literature not included, but noted to have identified associations, used advanced modeling techniques and spatial maps. Our *a priori* protocol stated that the review would include studies that directly measured air pollution, thus several studies were excluded that may still be relevant to the topic. The excluded studies identified an association between PM_{2.5} and an inverse risk of VSD,⁵⁵ septal defects⁵⁶ and obstructive defects,⁵⁶ as well as a small increased risk of pulmonary valve stenosis and TOF.⁵⁷

In looking at the results of each individual study, the results generated in the meta-analyses were not surprising. One of the two studies included for analysis was statistically significant with an inverse OR related to ASDs.⁴⁷ However, when combined with Padula *et al.*,⁴⁶ which also had a decreased OR but a non-significant wide CI in the meta-analysis, no significant risk was identified. For the analysis focused on VSD, neither of the individual studies found

a significant association, although one OR was slightly decreased⁴⁶ and the other showed a slightly increased risk.⁴⁷ In reviewing the studies for analysis for TOF, neither was significant because both had an increased risk but wide CIs. As more air pollution studies include PM_{2.5} as a component, the results of a future meta-analysis may be different.

The decreased risk of CHD with exposure to PM_{2.5} identified in some studies is initially counterintuitive and surprising. The epidemiologic studies that were included depended on obtaining sample data from large existing databases of birth records. Babies who had succumbed early in a pregnancy through spontaneous abortion were often not included in these databases. There was a reasonable hypothesis that exposure to PM_{2.5} could result in severe CHDs that are incompatible with life and lead to a spontaneous abortion early in pregnancy; therefore, exclusion of these data may present an incomplete assessment of the risk of exposure. Both Padula *et al.*⁴⁶ and Ritz⁵⁸ suggested that this may have impacted their findings.

Strengths of our meta-analysis included two reviewers, which reduced the inclusion bias; inclusion criteria that incorporated both case-control and cohort studies; rigorous, well-designed studies based on the critical appraisal; and studies that took into account potential confounding variables. Once studies were identified, the ability to conduct subgroup analysis on specific CHDs was a strength and added important information in the ability to understand a particular component in ambient air that might pose a risk to developing fetuses.

Several limitations with the review can be identified. An important limitation is the small number of studies in the systematic review and meta-analysis. After the critical appraisal, the plan was to include five studies in the meta-analysis. However, during the statistical analysis and data extraction, one study reported prevalence ratios and was not comparable to the remaining studies. Two others, both cohort studies, had high heterogeneity and were analyzed narratively. Only two studies were included in the analysis. While the included studies were rigorous, having only two that met the inclusion criteria indicated that this was an emerging area of investigation. Although the gray literature was searched based on the a priori inclusion criteria, no additional studies were identified.

Another limitation might be that the inclusion and exclusion criteria were too stringent. A priori we determined that we would only include studies that measured exposure based on stationary monitors. Studies excluded from our review included modeling of air pollution with meteorological, traffic, and/or satellite data, which might have provided additional information that could be useful in the meta-analysis. In addition, we included only studies that were published in English.

Despite the limitations and challenges in conducting a meta-analysis of the epidemiologic evidence on the association between PM_{2.5} and specific CHDs, this analysis did provide evidence that the number of studies, while still sparse, are growing. Epidemiologic studies of this type are difficult to design, expensive to complete and require large sample sizes. However, the research investigating possible links between specific pollutants and CHDs is

slowly increasing and is needed. It also highlights the need for future meta-analysis to be conducted as research in this area grows.

Conclusions

The idea that the environment can impact the development of a fetus in utero, potentially resulting in a congenital defect, is not fully understood, but research is slowly increasing. Some studies have reported statistically significant findings regarding such associations. However, our analysis did not find statistically significant evidence to support any associations between air pollutant PM_{2.5} and the diagnosis of a CHD. The heterogeneity of the included studies, as well as the excluded studies, made it difficult to complete a meta-analysis on such a limited number of studies.

Recommendations for practice

Based on the results of this meta-analysis, a CHD diagnosis did not appear to be associated with maternal exposure to air pollution. The quality of evidence was too limited and heterogeneity too high to provide any recommendations related to these findings (Grade B “Weak”).⁵⁹ However, millions of infants are diagnosed with a CHD each year globally.^{29,31,32} While more than 80% of those diagnosed have an unidentified etiology, the literature shows that environmental factors, such as air pollution, may play a role in the development of a CHD. Although the overall meta-analysis did not find any statistically significant support of this association, the individual studies did find statistically significant findings. This shows that a risk of such association may be present. Therefore, it is important to communicate the risk, no matter how small and non-significant, to expected mothers with the hope of decreasing the number of infants born with a CHD (Grade B “Weak”).⁵⁹

Recommendations for research

Although research surrounding the association between PM_{2.5} and the diagnosis of a CHD is increasing, further research is needed with a focus on standardization. Identifying standardized definitions of CHD, more consistent spatial monitoring and comparable analysis methods would help combine future results and allow generalization of the results to mother and infant dyads globally.

Acknowledgments

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Appendix I:: Search strategy

Published literature:

PubMed – 172 records retrieved

1. “Air Pollutant” OR “Air Pollution”[MeSH] OR “Air Pollution” OR “Particulate Matter”[MeSH] OR “Particulate Matter” OR “Dust” OR “Coal Ash” OR “Smog” OR “Smoke” OR “PM” OR “PM25” OR “PM2.5”
2. “Congenital Abnormalities”[MeSH] OR “Congenital Abnormalities” OR “Congenital Abnormality” OR “Congenital Anomalies” OR “Congenital Anomaly” OR “Congenital Defect” OR “Heart Defects, Congenital”[MeSH] OR “Congenital Heart Defect” OR “Congenital Heart Disease” OR “Heart, Malformation of” OR “Cardiovascular abnormalities”[MeSH] OR “Cardiovascular Abnormalities” OR “Cardiovascular Abnormality” OR “Aortic Coarctation” OR “Arrhythmogenic Right Ventricular Dysplasia” OR “Cor Triatriatum” OR “Coronary Vessel Anomalies” OR “Myocardial Bridging” OR “Crisscross Heart” OR “Dextrocardia” OR “Ductus Arteriosus, Patent” OR “Ebstein Anomaly” OR “Ectopia Cordis” OR “Heart Septal Defects” OR “Aortopulmonary Septal Defect” OR “Endocardial Cushion Defects” OR “Heart Septal Defects, Atrial” OR “Heart Septal Defects, Ventricular” OR “Heterotaxy Syndrome” OR “Hypoplastic Left Heart Syndrome” OR “Isolated Noncompaction of the Ventricular Myocardium” OR “Levocardia” OR “Tetralogy of Fallot” OR “Transposition of Great Vessels” OR “Double Outlet Right Ventricle” OR “Tricuspid Atresia”
3. “Cardiac” OR “Heart”
4. #1 AND #2 AND #3
5. (Limits: English; Publications from January 2002)

CINAHL – 39 records retrieved

1. “Air Pollutant” OR (MH “Air Pollutants, Environmental”) OR “Air Pollution” OR (MH “Air Pollution+”) OR “Air pollution, Indoor” OR “Motor Vehicle Emissions” OR “Particulate Matter” OR (MH “Particulate Matter+”) OR “Dust” OR “Coal Ash” OR “Smoke” OR “Smog” OR “PM” OR “PM25” OR “PM2.5”
2. (MH “Heart Defects, Congenital+”) OR “Heart Defects, Congenital” OR “Cardiovascular Abnormalities” OR “Cardiovascular Abnormality” OR “Congenital Abnormality” OR “Congenital Abnormalities” OR “Congenital Anomaly” OR “Congenital Anomalies” OR “Congenital Defect” OR “Congenital Heart Defect” OR “Congenital Heart Disease” OR “Heart, Malformation of” OR “Aortic Coarctation” OR “Arrhythmogenic Right Ventricular Dysplasia” OR “Cor Triatriatum” OR “Coronary Vessel Anomalies” OR “Myocardial Bridging” OR “Crisscross Heart” OR “Dextrocardia” OR “Ductus Arteriosus, Patent” OR “Ebstein Anomaly” OR “Ectopia Cordis” OR “Heart Septal Defects” OR “Aortopulmonary Septal Defect” OR “Endocardial

Cushion Defects” OR “Heart Septal Defects, Atrial” OR “Heart Septal Defects, Ventricular” OR “Heterotaxy Syndrome” OR “Hypoplastic Left Heart Syndrome” OR “Isolated Noncompaction of the Ventricular Myocardium” OR “Levocardia” OR “Tetralogy of Fallot” OR “Transposition of Great Vessels” OR “Double Outlet Right Ventricle” OR “Tricuspid Atresia”

3. “Cardiac” OR “Heart”
4. #1 AND #2 AND #3
5. (Limits: English; Publications from January 2002)

Embase – 475 records retrieved

1. “Air Pollutant”/exp OR “Air Pollutant “ OR “Air Pollution”/exp OR “Air Pollution” OR “Particulate Matter”/exp OR “Particulate Matter” OR “Dust” OR “Coal Ash” OR “Smog” OR “Smoke” OR “PM” OR “PM25” OR “PM2.5”
2. “Congenital Heart Malformation”/exp OR “Congenital Heart Malformation” OR “Congenital Heart Defect” OR “Congenital Heart Disease”/exp OR “Congenital Heart Disease” OR “Cardiovascular Malformation” OR “Congenital Abnormalities” OR “Congenital Abnormality” OR “Congenital Anomalies” OR “Congenital Anomaly” OR “Congenital Defect” OR “Heart, Malformation of” OR “Cardiovascular Abnormality” OR “Aortic Coarctation” OR “Arrhythmogenic Right Ventricular Dysplasia” OR “Cor Triatriatum” OR “Coronary Vessel Anomalies” OR “Myocardial Bridging” OR “Crisscross Heart” OR “Dextrocardia” OR “Ductus Arteriosus, Patent” OR “Ebstein Anomaly” OR “Ectopia Cordis” OR “Heart Septal Defects” OR “Aortopulmonary Septal Defect” OR “Endocardial Cushion Defects” OR “Heart Septal Defects, Atrial” OR “Heart Septal Defects, Ventricular” OR “Heterotaxy Syndrome” OR “Hypoplastic Left Heart Syndrome” OR “Isolated Noncompaction of the Ventricular Myocardium” OR “Levocardia” OR “Tetralogy of Fallot” OR “Transposition of Great Vessels” OR “Double Outlet Right Ventricle” OR “Tricuspid Atresia”
3. “Cardiac” OR “Heart”
4. #1 AND #2 AND #3
5. (Limits: English; Publications from January 2002)

Scopus – 2260 records retrieved

1. “Air Pollutant” OR “Air Pollution” OR “Particulate Matter” OR “Dust” OR “Coal Ash” OR “Smoke” OR “Smog” OR “PM” OR “PM25” OR “PM2.5”
2. “Congenital Abnormalities” OR “Congenital Abnormality” OR “Congenital Anomalies” OR “Congenital Anomaly” OR “Congenital Defect” OR “Congenital Heart Defect” OR “Congenital Heart Disease” OR “Heart, Malformation of” OR “Cardiovascular Abnormalities” OR “Cardiovascular Abnormality” OR “Aortic Coarctation” OR “Arrhythmogenic Right Ventricular

Dysplasia" OR "Cor Triatriatum" OR "Coronary Vessel Anomalies" OR "Myocardial Bridging" OR "Crisscross Heart" OR "Dextrocardia" OR "Ductus Arteriosus, Patent" OR "Ebstein Anomaly" OR "Ectopia Cordis" OR "Heart Septal Defects" OR "Aortopulmonary Septal Defect" OR "Endocardial Cushion Defects" OR "Heart Septal Defects, Atrial" OR "Heart Septal Defects, Ventricular" OR "Heterotaxy Syndrome" OR "Hypoplastic Left Heart Syndrome" OR "Isolated Noncompaction of the Ventricular Myocardium" OR "Levocardia" OR "Tetralogy of Fallot" OR "Transposition of Great Vessels" OR "Double Outlet Right Ventricle" OR "Tricuspid Atresia"

3. "Cardiac" OR "Heart"
4. #1 AND #2 AND #3
5. (Limits: English; Publications from January 2002)

Cochrane Central Register of Controlled Trials – 10 records retrieved

1. "Air Pollutant" OR (MH "Air Pollution") OR "Air Pollution" OR (MH "Particulate Matter") OR "Particulate Matter" OR "PM" OR "PM25" OR "PM2.5" OR "Dust" OR "Coal Ash" OR "Smoke" OR "Smog"
2. "Congenital Abnormalities" OR "Congenital Abnormality" OR "Congenital Anomalies" OR "Congenital Anomaly" OR "Congenital Defects" OR (MH "Congenital Heart Disease") OR "Congenital Heart Disease" OR "Congenital Heart Defects" OR "Heart Defects, Congenital" OR "Heart, Malformation of" OR "Cardiovascular Abnormalities" OR "Cardiovascular Abnormality" OR "Aortic Coarctation" OR "Arrhythmogenic Right Ventricular Dysplasia" OR "Cor Triatriatum" OR "Coronary Vessel Anomalies" OR "Myocardial Bridging" OR "Crisscross Heart" OR "Dextrocardia" OR "Ductus Arteriosus, Patent" OR "Ebstein Anomaly" OR "Ectopia Cordis" OR "Heart Septal Defects" OR "Aortopulmonary Septal Defect" OR "Endocardial Cushion Defects" OR "Heart Septal Defects, Atrial" OR "Heart Septal Defects, Ventricular" OR "Heterotaxy Syndrome" OR "Hypoplastic Left Heart Syndrome" OR "Isolated Noncompaction of the Ventricular Myocardium" OR "Levocardia" OR "Tetralogy of Fallot" OR "Transposition of Great Vessels" OR "Double Outlet Right Ventricle" OR "Tricuspid Atresia"
3. "Cardiac" OR "Heart"
4. #1 AND #2 AND #3
5. (Limits: English; Publications from January 2002)

TOXNET: TOXLINE Database – 0 records retrieved

1. "Air Pollutant" OR "Air Pollution" OR "Particulate Matter" OR "PM" OR "PM25" OR "PM2.5" OR "Dust" OR "Coal Ash" OR "Smoke" OR "Smog"
2. "Congenital abnormalities" OR "Congenital Abnormality" OR "Congenital Anomalies" OR "Congenital Anomaly" OR "Congenital Defect" OR

“Congenital Heart Disease” OR “Congenital Heart Defect” OR “Heart Defects, Congenital” OR “Heart, Malformations of” OR “Cardiovascular Abnormalities” OR “Cardiovascular Abnormality” OR “Aortic Coarctation” OR “Arrhythmogenic Right Ventricular Dysplasia” OR “Cor Triatriatum” OR “Coronary Vessel Anomalies” OR “Myocardial Bridging” OR “Crisscross Heart” OR “Dextrocardia” OR “Ductus Arteriosus, Patent” OR “Ebstein Anomaly” OR “Ectopia Cordis” OR “Heart Septal Defects” OR “Aortopulmonary Septal Defect” OR “Endocardial Cushion Defects” OR “Heart Septal Defects, Atrial” OR “Heart Septal Defects, Ventricular” OR “Heterotaxy Syndrome” OR “Hypoplastic Left Heart Syndrome” OR “Isolated Noncompaction of the Ventricular Myocardium” OR “Levocardia” OR “Tetralogy of Fallot” OR “Transposition of Great Vessels” OR “Double Outlet Right Ventricle” OR “Tricuspid Atresia”

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 – 0 records retrieved

1. “Air Pollutant” OR “Air Pollution” OR “Particulate Matter” OR “PM” OR “PM25” OR “PM2.5” OR “Dust” OR “Coal Ash” OR “Smoke” OR “Smog”
2. “Congenital abnormalities” OR “Congenital Abnormality” OR “Congenital Anomalies” OR “Congenital Anomaly” OR “Congenital Defect” OR “Congenital Heart Disease” OR “Congenital Heart Defect” OR “Heart Defects, Congenital” OR “Heart, Malformations of” OR “Cardiovascular Abnormalities” OR “Cardiovascular Abnormality” OR “Aortic Coarctation” OR “Arrhythmogenic Right Ventricular Dysplasia” OR “Cor Triatriatum” OR “Coronary Vessel Anomalies” OR “Myocardial Bridging” OR “Crisscross Heart” OR “Dextrocardia” OR “Ductus Arteriosus, Patent” OR “Ebstein Anomaly” OR “Ectopia Cordis” OR “Heart Septal Defects” OR “Aortopulmonary Septal Defect” OR “Endocardial Cushion Defects” OR “Heart Septal Defects, Atrial” OR “Heart Septal Defects, Ventricular” OR “Heterotaxy Syndrome” OR “Hypoplastic Left Heart Syndrome” OR “Isolated Noncompaction of the Ventricular Myocardium” OR “Levocardia” OR “Tetralogy of Fallot” OR “Transposition of Great Vessels” OR “Double Outlet Right Ventricle” OR “Tricuspid Atresia”
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 – 21 records retrieved

1. "Air Pollutant" OR "Air Pollution" OR "Particulate Matter" OR "PM" OR "PM25" OR "PM2.5" OR "Dust" OR "Coal Ash" OR "Smoke" OR "Smog"
2. "Congenital Abnormalities" OR "Congenital Abnormality" OR "Congenital Anomalies" OR "Congenital Anomaly" OR "Congenital Defects" OR "Congenital Heart Disease" OR "Congenital Heart Defects" OR "Heart Defects, Congenital" OR "Congenital Disorders" OR "Cardiovascular Abnormalities" OR "Cardiovascular Abnormality" OR "Aortic Coarctation" OR "Arrhythmogenic Right Ventricular Dysplasia" OR "Cor Triatriatum" OR "Coronary Vessel Anomalies" OR "Myocardial Bridging" OR "Crisscross Heart" OR "Dextrocardia" OR "Ductus Arteriosus, Patent" OR "Ebstein Anomaly" OR "Ectopia Cordis" OR "Heart Septal Defects" OR "Aortopulmonary Septal Defect" OR "Endocardial Cushion Defects" OR "Heart Septal Defects, Atrial" OR "Heart Septal Defects, Ventricular" OR "Heterotaxy Syndrome" OR "Hypoplastic Left Heart Syndrome" OR "Isolated Noncompaction of the Ventricular Myocardium" OR "Levocardia" OR "Tetralogy of Fallot" OR "Transposition of Great Vessels" OR "Double Outlet Right Ventricle" OR "Tricuspid Atresia"
3. "Cardiac" OR "Heart"
4. #1 AND #2 AND #3
5. (Limits: English; Publications from January 2002)

Europe Pubmed Central – 3402 records retrieved

1. "Air Pollutant" OR "Air Pollution" OR "Particulate Matter" OR "PM" OR "PM25" OR "PM2.5" OR "Dust" OR "Coal Ash" OR "Smoke" OR "Smog"
2. "Congenital Abnormalities" OR "Congenital Abnormality" OR "Congenital Anomalies" OR "Congenital Anomaly" OR "Congenital Defect" OR "Heart Defects, Congenital" OR "Congenital Heart Defect" OR "Congenital Heart Disease" OR "Heart, Malformation of" OR "Cardiovascular abnormalities" OR "Cardiovascular Abnormality" OR "Aortic Coarctation" OR "Arrhythmogenic Right Ventricular Dysplasia" OR "Cor Triatriatum" OR "Coronary Vessel Anomalies" OR "Myocardial Bridging" OR "Crisscross Heart" OR "Dextrocardia" OR "Ductus Arteriosus, Patent" OR "Ebstein Anomaly" OR "Ectopia Cordis" OR "Heart Septal Defects" OR "Aortopulmonary Septal Defect" OR "Endocardial Cushion Defects" OR "Heart Septal Defects, Atrial" OR "Heart Septal Defects, Ventricular" OR "Heterotaxy Syndrome" OR "Hypoplastic Left Heart Syndrome" OR "Isolated Noncompaction of the Ventricular Myocardium" OR "Levocardia" OR "Tetralogy of Fallot" OR "Transposition of Great Vessels" OR "Double Outlet Right Ventricle" OR "Tricuspid Atresia"
3. "Cardiac" OR "Heart"
4. #1 AND #2 AND #3

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

Unpublished Literature:

ProQuest Dissertations & Theses Sciences & Engineering Collection – 4792 records retrieved

1. “Air Pollutant” OR “Air Pollution” OR “Particulate Matter” OR “PM” OR “PM25” OR “PM2.5” OR “Dust” OR “Smoke” OR “Smog”
2. “Congenital Abnormalities” OR “Congenital Abnormality” OR “Congenital Anomalies” OR “Congenital Anomaly” OR “Congenital Defect” OR “Heart Defects, Congenital” OR “Congenital Heart Defect” OR “Congenital Heart Disease” OR “Congenital Heart Malformation” OR “Heart, Malformation of” OR “Cardiovascular Abnormalities” OR “Cardiovascular Abnormality” OR “Cardiovascular Malformation” OR “Aortic Coarctation” OR “Arrhythmogenic Right Ventricular Dysplasia” OR “Cor Triatriatum” OR “Coronary Vessel Anomalies” OR “Myocardial Bridging” OR “Crisscross Heart” OR “Dextrocardia” OR “Ductus Arteriosus, Patent” OR “Ebstein Anomaly” OR “Ectopia Cordis” OR “Heart Septal Defects” OR “Aortopulmonary Septal Defect” OR “Endocardial Cushion Defects” OR “Heart Septal Defects, Atrial” OR “Heart Septal Defects, Ventricular” OR “Heterotaxy Syndrome” OR “Hypoplastic Left Heart Syndrome” OR “Isolated Noncompaction of the Ventricular Myocardium” OR “Levocardia” OR “Tetralogy of Fallot” OR “Transposition of Great Vessels” OR “Double Outlet Right Ventricle” OR “Tricuspid Atresia”
3. #1 AND #2
4. (Limits: English; Publications from January 2002)

MedNar – 199 records retrieved

1. “Air Pollutant” OR “Air Pollution” OR “Particulate Matter” OR “PM” OR “PM25” OR “PM2.5” OR “Dust” OR “Smoke” OR “Smog”
2. “Congenital Abnormalities” OR “Congenital Abnormality” OR “Congenital Anomalies” OR “Congenital Anomaly” OR “Congenital Defect” OR “Heart Defects, Congenital” OR “Congenital Heart Defect” OR “Congenital Heart Disease” OR “Heart, Malformation of” OR “Cardiovascular Abnormalities” OR “Cardiovascular Abnormality” OR “Aortic Coarctation” OR “Arrhythmogenic Right Ventricular Dysplasia” OR “Cor Triatriatum” OR “Coronary Vessel Anomalies” OR “Myocardial Bridging” OR “Crisscross Heart” OR “Dextrocardia” OR “Ductus Arteriosus, Patent” OR “Ebstein Anomaly” OR “Ectopia Cordis” OR “Heart Septal Defects” OR “Aortopulmonary Septal Defect” OR “Endocardial Cushion Defects” OR “Heart Septal Defects, Atrial” OR “Heart Septal Defects, Ventricular” OR “Heterotaxy Syndrome” OR “Hypoplastic Left Heart Syndrome” OR “Isolated Noncompaction of the Ventricular Myocardium” OR “Levocardia” OR “Tetralogy of Fallot” OR

“Transposition of Great Vessels” OR “Double Outlet Right Ventricle” OR
“Tricuspid Atresia”

3. #1 AND #2
4. (Limits: English; Publications from January 2002)

Government Websites:

Centers for Disease Control and Prevention – [cdc.gov](https://www.cdc.gov) – 0 records retrieved

1. “Air Pollution” OR “Air Pollutant” OR “Particulate Matter” OR “PM” OR
“PM25” OR “PM2.5”
2. “Congenital abnormalities” OR “Congenital Abnormality” OR “Congenital
Anomalies” OR “Congenital Anomaly” OR “Congenital Defect” OR
“Congenital Heart Disease” OR “Congenital Heart Defect” OR “Heart Defects,
Congenital” OR “Heart, Malformations of” OR “Cardiovascular Abnormalities”
OR “Cardiovascular Abnormality”
3. #1 AND #2

World Health Organization – [who.int](https://www.who.int) – 0 records retrieved

1. “Air Pollution” OR “Air Pollutant” OR “Particulate Matter” OR “PM” OR
“PM25” OR “PM2.5”
2. “Congenital abnormalities” OR “Congenital Abnormality” OR “Congenital
Anomalies” OR “Congenital Anomaly” OR “Congenital Defect” OR
“Congenital Heart Disease” OR “Congenital Heart Defect” OR “Heart Defects,
Congenital” OR “Heart, Malformations of” OR “Cardiovascular Abnormalities”
OR “Cardiovascular Abnormality”
3. #1 AND #2

Appendix II:: Studies ineligible following full text review

Girguis MS, Strickland MJ, Hu X, Liu Y, Bartell SM, Vieira VM. Maternal exposure to traffic-related air pollution and birth defects in Massachusetts. *Environ Res.* 2015; 146: 1–9.

Reason for exclusion:

The article utilized satellite remote sensing, meteorological and land use data to obtain exposure of interest, which varied from the operational definition of the air pollutant set in the inclusion criteria.

Hansen CA, Barnett AG, Jalaludin BB, Morgan GG. Ambient air pollution and birth defects in Brisbane, Australia. *PLoS One.* 2009; 4(4): e5408.

Reason for exclusion: The exposure of interest did not include PM_{2.5}.

Hwang B, Lee YL, Jaakkola, JJK. Air pollution and the risk of cardiac defects. *Medicine*. 2015; 94(44): e1883.

Reason for exclusion:

The exposure of interest did not include PM_{2.5}.

Pedersen M, Garne E, Hansen-Nord N, Hjortebjerg D, Ketzel M, Raaschou-Nielsen O, et al. Exposure to air pollution and noise from road traffic and risk of congenital anomalies in the Danish national birth cohort. *Environ Res*. 2017; 159: 39–45.

Reason for exclusion:

The exposure of interest did not include PM_{2.5}.

Schembari A, Nieuwenhuijsen MJ, Salvador J, de Nazelle A, Cirach M, Dadvand P. Traffic-related air pollution and congenital anomalies in Barcelona. *Environ Health Perspect*. 2014; 122(3): 317–23.

Reason for exclusion:

The article utilized spatial land use regression modeling with spatiotemporal exposure estimates to obtain exposure of interest, which varied from the operational definition of the air pollutant set in the inclusion criteria.

Strickland MJ, Klein M, Correa A, Reller M, Mahle WT, Riehle-Colarusso TJ, et al. Ambient air pollution and cardiovascular malformations in Atlanta, Georgia, 1986–2003. *Am J Epidemiol*. 2009; 169(8): 1004–14.

Reason for exclusion:

The exposure of interest did not include PM_{2.5}.

Vinikoor-Imler LC, Stewart TG, Luben TJ, Davis JA, Langlois PH. An exploratory analysis of the relationship between ambient ozone and particulate matter concentrations during early pregnancy and selected birth defects in Texas. *Environ Pollut*. 2015; 202: 1–6.

Reason for exclusion:

The article utilized modeled air pollution estimates to obtain exposure of interest, which varied from the operational definition of the air pollutant set in the inclusion criteria.

Warren JL, Stingone JA, Herring AH, Luben TJ, Fuentes M, Aylsworth AS, et al. Bayesian multinomial probit modeling of daily windows of susceptibility for maternal PM_{2.5} exposure and congenital heart defects. *State Med*. 2016; 35(16): 2786–801.

Reason for exclusion:

The article utilized modelled air pollution estimates to obtain exposure of interest, which varied from the operational definition of the air pollutant set in the inclusion criteria.

Appendix III:: Characteristics of included studies

Reference	Data source	Design	Congenital categories	Exposure assessment	Air pollutants	Cardiac findings* aOR (95% CI)
Agay-Shay <i>et al.</i> ⁴⁸ (Israel)	National Birth and Birth Defect Registry operated by Israeli Ministry of Health Controls: n = 130,402 Cases: n = 1867	Cohort	4 cardiac malformation groups • 3 isolated defects (ASD, VSD, PDA) • 1 multiple defects	Weekly means for weeks 3–8 calculated for each of 19 stations; estimated using interpolation for each birth according to maternal residence	CO, NO ₂ , O ₃ , SO ₂ , PM ₁₀ , PM _{2.5}	PDA (inverse) cOR = 0.77 (0.66, 0.99)
Padula <i>et al.</i> ⁴⁶ (USA)	California Center of the National Birth Defects Prevention Study - specifically from California Birth Defects Monitoring Program Controls: n = 849 Cases: n = 822	Case-control	CHD cases in 27 subgroups: heterotaxia, dTGA, TOF, DORV-other, DORV-TGA, atrioventricular septal defect, TAPVR, HLHS, COA, aortic stenosis, PA, tricuspid atresia, pulmonary stenosis, pVSD, mVSD, VSD conotruncal, ASD secundum, ASD other, single ventricle, partial anomalous pulmonary venous return, IAA type A, IAA type B, truncus arteriosus, Ebstein anomaly, VSD other, LTGA, other heart defects	Daily averages of pollutants during first and second month of pregnancy by monitor near maternal residence (maximum radius 25 to 50 km depending on pollutant)	CO, NO, NO ₂ , PM ₁₀ , PM _{2.5} , O ₃	dTGA 2.6 (1.1, 6.5)
Stingone <i>et al.</i> ⁴⁷ (USA)	National Birth Defects Prevention Study Controls: n = 4407 Cases: n = 3311	Case-control	Identified by isolated CHD and defect groups due to small sample size (17 total): LVOT obstruction, aortic stenosis, COA, HLHS, conotruncal, dTGA, TOF, other conotruncal, APVR, TAPVR, atrioventricular septal defect, RVOT obstruction, pulmonary/tricuspid atresia, pulmonary valve stenosis, septal, ASD, VSD	Average daily maximum or 24-hour measurements for weeks 2–8 of pregnancy (measuring 1-week and 7-week averages) from maximum of 50 km and closest air monitor	CO, NO ₂ , SO ₂ , O ₃ , PM ₁₀ , PM _{2.5}	Based on 7-week average: HLHS • 2.04 (1.07, 3.89) >90 th centile exposure Septal (inverse) • 0.66 (0.53, 0.83) and 0.62 (0.45, 0.85) with increasing exposure ASD (inverse) • 0.50 (0.38, 0.65) and 0.54 (0.35, 0.81) with increasing exposure

Reference	Data source	Design	Congenital categories	Exposure assessment	Air pollutants	Cardiac findings* aOR [†] (95% CI)
Tanner <i>et al.</i> ¹⁴ (USA)	Florida Birth Defect Registry Controls: n = 212,3874 Cases: n = 3494	Cohort	16 malformation groups • 1 spina bifida • 3 orofacial clefts • 12 isolated cardiac defects (dTGA, DORV, HLHS, TOF, truncus arteriosus, TAPVR, pulmonary atresia with intact septum, tricuspid atresia, Ebstein anomaly, COA, interrupted aortic arch, single ventricle) and all CHD	Daily mean calculated for each census block group surrounding maternal residence for 3–8 weeks' gestation (maximum was 50 km); interpolation of air pollutants utilized	PM _{2.5} , benzene	Non-isolated truncus arteriosus • 8.80 (1.11, 69.50) Non-isolated total anomalous pulmonary venous return • 5.00 (1.10, 22.84) Non-isolated COA • 1.60 (1.07, 2.41) Non-isolated interrupted aortic arch • 5.50 (1.22, 24.82) Any critical CHD • 1.33 (1.07, 1.65) Isolated: any critical CHD • 1.13 (1.02, 1.25)
Zhang <i>et al.</i> ⁴⁵ (China)	Births from a perinatal health-care system for women and children of Wuhan Controls: n = 105,988 Cases: n = 188	Cohort	3 malformation groups • all CHDs combined • VSD • TOF	1-month and 1-week averages for first 3 months of pregnancy based on nearest monitor to maternal residence	PM ₁₀ , PM _{2.5}	VSD • 1.16 (1.03, 1.30) in second month gestation • 1.21 (1.08, 1.36) in third month gestation All CHD • 1.10 (1.03, 1.18) in second month gestation • 1.08 (1.01, 1.16) in third month gestation

* Indicates an inverse and/or increased risk for cardiac anomalies linked to PM_{2.5} air pollutant. Results on other pollutants in the individual studies without significant associations were not included in the table.

[†] Adjusted odds ratio reported unless otherwise noted.

aOR = adjusted odds ratio; cOR = crude odds ratio; CI = confidence interval; CO = carbon monoxide; NO = nitrogen monoxide; NO₂ = nitrogen dioxide; PM_{2.5} = particulate matter with diameter less than 2.5µm; PM₁₀ = particulate matter with diameter less than 10µm; O₃ = ozone; SO₂ = sulfur dioxide; ASD = atrial septal defect; CHD = congenital heart defect; COA = coarctation of the aorta; DORV = double outlet right ventricle; dTGA = dextro-transposition of the great arteries; HLHS = hypoplastic left heart syndrome; IAA = interruption of the aortic arch; LTGA = levo-transposition of the great arteries; LVOT = left ventricular outflow tract; PA = pulmonary atresia; PDA = patent ductus arteriosus; RVOT = right ventricular outflow tract; TAPVR = total anomalous pulmonary venous return; TOF = tetralogy of fallot; VSD = ventricular septal defect; AVSD = atrioventricular septal defect; pVSD = perimembranous ventricular septal defect; mVSD = muscular ventricular septal defect.

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Figure 1:
Search results and study selection and inclusion process⁵¹

$Q=4.707$, $df=1$, $p=0.030$ $I-sq=78.757$, $T-sq=0.0136$, $T=0.369$

Figure 2:

Association between maternal exposure to pollutant particulate matter 2.5 and atrial septal defects in infants up to one year of age in two case-control studies (CI: confidence interval; CHD: congenital heart defect)

$Q=0.224$, $df=1$, $p=0.636$ $I-sq=0.00$, $T-sq=0.000$, $T=0.00$

Figure 3:

Association between maternal exposure to pollutant particulate matter 2.5 and ventricular septal defects in infants up to one year of age in two case-control studies (CI: confidence interval; CHD: congenital heart defect)

$Q=1.228$, $df=1$, $p=0.268$ $I-sq=18.597$, $T-sq=0.190$, $T=0.137$

Figure 4:

Association between maternal exposure to pollutant particulate matter 2.5 and tetralogy of fallot in infants up to one year of age in two case-control studies (CI: confidence interval; CHD: congenital heart defect)

Table 1:

Critical appraisal results of cohort studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Agay-Shay <i>et al.</i> ⁴⁸	Y	Y	Y	Y	Y	U	U	Y	Y	N/A	Y
Tanner <i>et al.</i> ¹⁴	Y	Y	Y	Y	Y	U	U	Y	Y	N/A	Y
Zhang <i>et al.</i> ⁴⁵	Y	Y	U	Y	Y	U	Y	Y	Y	N/A	Y
Total %	100	100	67	100	100	0	33	100	100	0	100

Y = yes; N = no; U = unclear; N/A not applicable

JBI critical appraisal checklist for cohort studies: Q1 = Were the two groups similar and recruited from the same population? Q2 = Were the exposures measured similarly to assign people to both exposed and unexposed groups? Q3 = Was the exposure measured in a valid and reliable way? Q4 = Were confounding factors identified? Q5 = Were strategies to deal with confounding factors stated? Q6 = Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? Q7 = Were the outcomes measured in a valid and reliable way? Q8 = Was the follow up time reported and sufficient to be long enough for outcomes to occur? Q9 = Was follow-up complete, and if not, were the reasons to loss of follow-up described and explores? Q10 = Were strategies to address incomplete follow-up utilized? Q11 = Was appropriate statistical analysis used?

Significant associations between congenital heart defects and pollutant particulate matter 2.5

Table 2:

Study	Significant associations with PM _{2.5}	Adjusted odds ratio* (95% confidence interval)
Agay-Shay <i>et al.</i> ⁴⁸	Patent ductus arteriosus	cOR = 0.77 [‡] (0.66, 0.99)
Padula <i>et al.</i> ⁴⁶	Dextro-transposition of the great arteries	2.6 (1.1, 6.5)
Stingone <i>et al.</i> ⁴⁷	Hypoplastic left heart syndrome	2.04 (1.07, 3.89)
	Septal [‡]	0.66 [‡] (0.53, 0.83) and 0.62 [‡] (0.45, 0.85) with increasing exposure
Tanner <i>et al.</i> ¹⁴	Atrial septal defect	0.50 [‡] (0.38, 0.65) and 0.54 [‡] (0.35, 0.81) with increasing exposure
	Non-isolated truncus arteriosus	8.80 (1.11, 69.50)
	Non-isolated total anomalous pulmonary venous return	5.00 (1.10, 22.84)
	Non-isolated coarctation of the aorta	1.60 (1.07, 2.41)
	Non-isolated interrupted aortic arch	5.50 (1.22, 24.82)
Zhang <i>et al.</i> ⁴⁵	Any critical congenital heart defect	1.33 (1.07, 1.65)
	Isolated, any critical congenital heart defect	1.13 (1.02, 1.25)
	Ventricular septal defect	1.16 (1.03, 1.30) in second month; 1.21 (1.08, 1.36) in third month
	All congenital heart defects	1.10 (1.03, 1.18) in second month; 1.08 (1.01, 1.16) in third month

cOR: crude odds ratio; PM_{2.5}: particulate matter with diameter less than 2.5 µm

* Adjusted odds ratio reported unless otherwise noted

[‡] Septal grouping refers to cases of muscular ventricular septal defects collected only in the first year of the study

[‡] Inverse association