

The effect of Ambient heat exposure early in pregnancy on the frequency of congenital heart defects: Systematic Review Protocol

Impact de l'exposition à la chaleur ambiante intense en début de grossesse sur la fréquence des cardiopathies congénitales : Protocole de revue systématique

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ABSTRACT

Introduction: Fetal development is highly sensitive to temperature extremes during pregnancy, partly due to the reduced thermoregulatory capacity of pregnant women. This vulnerability has been linked to an increased risk of congenital heart defects (CHD). With global warming expected to increase extreme heat events, understanding the relationship between maternal heat exposure and CHD risk has become increasingly urgent.

Objective: This systematic review aims to evaluate existing evidence on the impact of maternal high-temperature exposure on the incidence of CHD.

Methods: We will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Searches will be conducted in PubMed, Embase, Scopus, and Google Scholar databases using tested and validated search algorithms. We will include any type of study, published in English or French, involving pregnant women and/or neonates that directly evaluates the relationship between high-temperature exposure during pregnancy and CHD. Experimental or modelling studies involving animals and those examining the association between maternal fever and CHD will be excluded. Study selection, data extraction, and risk of bias assessment will be conducted by two independent reviewers. The quality and risk of bias will be assessed using the Newcastle-Ottawa Scale. The main outcomes are the incidence and types of CHD diagnosed in infant.

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Key-words: Hot Temperature, Extreme Heat, Pregnancy, Maternal Exposure, Congenital Abnormalities, Heart Defects Congenital, Infant, Newborn

RÉSUMÉ

Introduction : Le développement fœtal est particulièrement sensible aux températures ambiantes extrêmes pendant la grossesse, en partie en raison de la capacité réduite de thermorégulation chez la femme enceinte. Cette vulnérabilité a été associée à un risque accru de cardiopathies congénitales. Dans un contexte de réchauffement climatique susceptible d'augmenter la fréquence des vagues de chaleur extrême, il devient de plus en plus urgent de mieux comprendre la relation entre l'exposition maternelle à la chaleur et le risque de cardiopathies congénitales.

Objectif : Cette revue systématique vise à évaluer les données existantes concernant l'impact de l'exposition maternelle à des températures ambiantes élevées sur l'incidence des cardiopathies congénitales.

Méthodes : Nous suivons les recommandations PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Des recherches bibliographiques seront effectuées dans les bases de données PubMed, Embase, Scopus et Google Scholar à l'aide d'équations de recherche testées et validées. Nous inclurons tous types d'études, publiées en anglais ou en français, portant sur des femmes enceintes et/ou des nouveau-nés et évaluant directement la relation entre l'exposition à des températures élevées pendant la grossesse et les cardiopathies congénitales. Les études expérimentales ou de modélisation sur des animaux, ainsi que celles portant sur l'association entre la fièvre maternelle et les cardiopathies congénitales, seront exclues. La sélection des études, l'extraction des données et l'évaluation du risque de biais seront réalisées par deux évaluateurs indépendants. La qualité méthodologique et le risque de biais seront évalués à l'aide de l'échelle de Newcastle-Ottawa. Les principaux critères de jugement sont l'incidence et les types de cardiopathies congénitales diagnostiquées chez le nouveau-né.

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Mots-clés: Température élevée, chaleur extrême, grossesse, exposition maternelle, anomalies congénitales, malformations cardiaques congénitales, nourrisson, nouveau-né.

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INTRODUCTION

Background

Pregnancy is a complex and delicate period marked by significant physiological changes that make the developing foetus particularly vulnerable to environmental factors. Fetal development and organogenesis are influenced by a combination of genetic and environmental factors. While genetics, both inherited and de novo, play a primary role, environmental factors such as noise, heat and pollution also have a significant impact on this process. Of these, exposure to extreme temperatures during pregnancy is of particular concern, as elevated temperatures can disrupt fetal organ development, increasing the risk of congenital defects. This risk is compounded by the fact that pregnant women have a reduced thermoregulatory capacity, making them more vulnerable to heat stress. Heat exposure can lead to complications, including reduced placental blood flow, dehydration and inflammatory responses (1).

Research has linked extreme heat exposure during pregnancy to an increased risk of major maternal morbidity, preterm birth, low birth weight and a higher incidence of congenital birth defects (2-5). Congenital heart defects (CHD) is the most common birth defect worldwide, with a global prevalence of 8.22 per 1,000 live births (6). CHDs are particularly serious because of their unpredictable prognosis; in severe cases, these defects may require medical abortion or complex, multidisciplinary postnatal care that can be difficult to manage. Although published studies have examined the association between heat exposure and CHD (7-10), no systematic review has focused on this topic. Prevention of CHD requires the identification of modifiable risk factors, such as extreme heat and pollution, to reduce the prevalence of CHD.

In the context of ongoing climate change, the association between exposure to extreme heat and CHD is likely to become more important. Global warming, driven primarily by greenhouse gas emissions, is steadily increasing the average global temperature, which in turn is increasing the frequency, duration and severity of extreme heat events. Projections indicate that, without substantial efforts to reduce emissions, heatwaves will become more frequent and severe, posing increased risks to public health, including a potential rise in CHD rates, as well as broader impacts on agriculture and natural ecosystems (11,12).

Review question

In pregnant women of any age, health status and geographical location, how does exposure to high prenatal temperatures, especially during the first pregnancy trimester, compared with no exposure to high prenatal temperatures or exposure to temperatures considered to be within the normal range for the region, affect the incidence and types of CHD diagnosed in infants?

Objective

This systematic review aims to examine the existing evidence on the effects of maternal exposure to high temperatures on the incidence of CHD.

METHODS

Eligibility Criteria

Population

Mothers of any age, health status, and geographic location who were exposed to extreme heat during pregnancy and who gave birth to stillbirths or infants with CHD.

We excluded syndromic cases with genetic disorder and cases with history of CHD in parents or siblings.

Exposure

Exposure to high prenatal temperatures, specifically during first trimester of pregnancy.

We included any exposure to high external temperatures, regardless of its definition used (intensity, duration) or context (season, regional heat waves, artificially elevated temperatures like those in saunas, hot baths, etc.).

Exposure should be assessed during the first trimester of pregnancy in general, and particularly during the critical period of embryogenesis, between 3 and 8 weeks post-conception.

Control

No exposure to high prenatal temperatures in the first trimester of pregnancy or exposure to temperatures considered within the normal range.

Outcomes

The main outcomes are the incidence and types of CHD during pregnancy, neonatal period or infancy.

Inclusion and exclusion criteria

Studies to be included should met the following criteria:

- they involved pregnant women and/or offspring in the study population.
- they directly evaluated the relationship between high-temperature exposure during pregnancy and CHD or other birth defects.
- studies were published in English or French
- they utilised any type of study design
- there were no restrictions on publication dates.

We will exclude the following studies:

- Experimental or modelling studies involving animals.
- Studies evaluating the association between maternal fever and birth defects.
- Review papers that do not present original data

Search Strategy

We will perform a systematic search of Pubmed, Embase, Scopus and Google Scholar database using the following search terms:

To enhance the rigour of our search strategy, we will examine the reference lists of the included studies as well as the

Data base	Research query
Pubmed	<p>(«Hot Temperature»[Mesh] OR «Hot Temperature»[tiab] OR «Extreme Heat»[Mesh] OR «Extreme Heat»[tiab] OR «Extreme Hot Weather»[tiab] OR «Heat Exposure»[tiab] OR «Heatwave»[tiab] OR «High Temperature»[tiab] OR «Heat Stress»[tiab] OR «Hyperthermia»[Mesh] OR «Hyperthermia»[tiab])</p> <p>AND («Congenital Abnormalities»[Mesh] OR «Congenital Abnormalities»[tiab] OR «Heart Defects, Congenital»[Mesh] OR «Heart Defects, Congenital»[tiab] OR «Congenital Heart Defects»[tiab] OR «Congenital Heart Disease»[tiab] OR «Congenital Heart Anomalies»[tiab] OR «Birth Defects»[tiab] OR «Congenital Malformations»[tiab])</p> <p>AND («Pregnancy»[Mesh] OR «Pregnancy»[tiab] OR «Maternal Exposure»[Mesh] OR «Maternal Exposure»[tiab] OR «Maternal Health»[Mesh] OR «Maternal Health»[tiab] OR «Pregnant Women»[Mesh] OR «Pregnant Women»[tiab] OR «Prenatal Exposure»[tiab] OR «Prenatal Risk Factors»[tiab] OR «Gestational Exposure»[tiab]) AND (humans[Filter])</p>
Embase	<p>('high temperature'/exp OR 'hot temperature':ti,ab,kw OR 'extreme hot weather'/exp OR 'extreme heat':ti,ab,kw OR 'heat exposure':ti,ab,kw OR 'heatwave':ti,ab,kw OR 'heat stress':ti,ab,kw OR 'hyperthermia'/exp OR 'hyperthermia':ti,ab,kw)</p> <p>AND</p> <p>('congenital disorder'/exp OR 'congenital abnormalities':ti,ab,kw OR 'congenital heart malformation'/exp OR 'heart defects, congenital':ti,ab,kw OR 'congenital heart defects':ti,ab,kw OR 'congenital heart disease':ti,ab,kw OR 'congenital heart anomalies':ti,ab,kw OR 'birth defects':ti,ab,kw OR 'congenital malformations':ti,ab,kw)</p> <p>AND</p> <p>('pregnancy'/exp OR 'pregnancy':ti,ab,kw OR 'maternal exposure':ti,ab,kw OR 'maternal health':ti,ab,kw OR 'pregnant women':ti,ab,kw OR 'prenatal exposure':ti,ab,kw OR 'prenatal risk factors':ti,ab,kw OR 'gestational exposure':ti,ab,kw)</p> <p>AND</p> <p>[humans]/lim</p>
Scopus	<p>TITLE-ABS-KEY («Hot Temperature» OR «Extreme Heat» OR «Extreme Hot Weather» OR «Heat Exposure» OR «Heatwave» OR «High Temperature» OR «Heat Stress» OR «Hyperthermia»)</p> <p>AND TITLE-ABS-KEY («Congenital Abnormalities» OR «Congenital Heart Defects» OR «Congenital Heart Disease» OR «Heart Defects, Congenital» OR «Congenital Heart Anomalies» OR «Birth Defects» OR «Congenital Malformations»)</p> <p>AND TITLE-ABS-KEY («Pregnancy» OR «Maternal Exposure» OR «Maternal Health» OR «Pregnant Women» OR «Prenatal Exposure» OR «Prenatal Risk Factors» OR «Gestational Exposure»)</p>
Google Scholar	<p>(«maternal heat exposure» OR «high temperature» OR «extreme heat» OR «heat stress») AND («congenital heart defects» OR «congenital heart disease» OR «birth defects») AND («pregnancy» OR «prenatal exposure»)</p>

reference lists of any relevant reviews on the same topics.

Furthermore, to minimise the risk of publication bias, we will search for grey literature, such as theses and conference proceedings. Searches will be re-run prior to the final analysis.

Study Selection

Publications from the combined searches will be imported into Zotero for duplicate removal. Covidence will be used to facilitate the blinded selection of studies. Two reviewers will independently screen the titles and abstracts of all retrieved publications for inclusion, followed by an independent review of the full texts to determine eligibility. Any disagreements will be resolved through consultation with a third reviewer or through discussion between the two reviewers. Full details of the search results and study selections will be documented in a PRISMA flow diagram

Data Extraction

Data extraction will be undertaken onto a Microsoft Excel spreadsheet.

Data to be extracted will include:

- Study Identification: First author, publication year, country of study, and study period
- Study Design and Methodology: Type of study, data

collection methods, and analytical approach

- Population Characteristics: Total number of participants, age range, ethnicity, relevant medical history, and presence of gestational diabetes
- Exposure Details: Definition and criteria for high temperature, gestational age at time of exposure
- Control Group: Number of control subjects and selection criteria
- Outcomes Assessed: Incidence of CHD and other birth defects
- Confounding Variables: Factors controlled for in the analysis.

Study investigators will be contacted for unreported data or additional details.

Two reviewers will independently screen records for data extraction. Disagreements will be resolved by a third reviewer consultation, or through discussion between the two reviewers.

Risk of Bias Assessment

Two reviewers will independently assess the quality and risk of bias in the included studies. Disagreements will be resolved either through discussion between the two reviewers or by consulting a third reviewer.

All studies meeting the selection criteria were appraised for methodological quality using the MINORS scale. The quality and risk of bias will be assessed using the

Newcastle-Ottawa Scale.

Data Synthesis

The data synthesis will be conducted using a narrative approach. We will systematically summarize the findings from the included studies, focusing on the relationship between ambient heat exposure early in pregnancy and the risk of CHD. The synthesis will include a detailed description of study characteristics, methodologies, and outcomes.

We will identify patterns and inconsistencies in the results, exploring factors such as study design, population, timing and measurement of heat exposure, and types of CHD. The quality and potential biases of the studies will also be assessed to provide a comprehensive understanding of the existing evidence.

If the necessary data are available, subgroup analyses will be conducted based on the type of heat exposure, the duration of heat exposure, or the specific type of CHD.

It is important to consider several confounding factors, including the mother's pre-existing conditions (such as hypertension and diabetes), lifestyle behaviors (such as diet, physical activity, and medication use), as well as other environmental factors (such as pollution, noise, and other exposures).

Ethics and Dissemination

Ethical considerations will be addressed by adhering to established guidelines for conducting systematic reviews. Findings will be communicated through publication in peer-reviewed journals. There are no conflicts of interest or collaborators associated with this study.

CONCLUSION

This systematic review will synthesize current evidence on the impact of high temperature exposure during pregnancy on the prevalence of CHD. By clarifying this relationship, our findings aim to inform both individual and collective preventive strategies to protect maternal and fetal health in a warming climate.

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