Effects of Wildfire Smoke Particulate Matter and Extreme Heat on the Risk of Congenital Heart Defects in Canada

Yijun Kim

Thesis submitted to the University of Ottawa in partial fulfillment of the requirements for the Master of Science degree in Epidemiology

School of Epidemiology and Public Health
Faculty of Medicine
University of Ottawa

© Yijun Kim, Ottawa, Canada, 2026

Preface

Ashley (Yijun) Kim was the primary author of all contents included in this thesis. Data curation for the study cohort was assembled by Ashley Kim and Qingyi Lan. Ashley Kim was responsible for the conceptualization of the study design, formal analysis, interpretation of findings and drafting the manuscript under the supervision of Dr. Éric Lavigne and Dr. Steven Hawken with guidance from the thesis advisory committee member, Dr. Piotr Wilk. All authors reviewed and provided critical feedback on the manuscript included in this thesis.

This thesis project utilized data accessed from the Federal Research Data Centre of Statistics Canada, and was approved by the Health Canada Research Ethics Board.

Acknowledgements

I would like to express my sincere gratitude to my co-supervisors, Dr. Éric Lavigne and Dr. Steven Hawken. Thank you for your guidance, expertise, and continued support throughout my thesis journey. I am deeply grateful for your mentorship, and it was a pleasure to have learned from you both during this graduate program. I would also like to thank my thesis advisory committee member, Dr. Piotr Wilk, for his meaningful insights and feedback.

To my colleagues in the MSc. Epidemiology program and at Health Canada, thank you for your guidance and for the many valuable lessons and experiences I have gained throughout the program.

To my friends, especially Chloe and Yerim, thank you for your endless encouragement and support. I could not have completed this degree without you all.

Lastly, I would like to thank my family for their unwavering support. To my parents, I am forever grateful for your unconditional love and providing me with the opportunity to continue my academic journey.

Table of Contents

Preface ..... *II*

Acknowledgements ..... *III*

List of Tables ..... *VI*

List of Figures ..... *VIII*

Abbreviations ..... *X*

Abstract ..... *XII*

Chapter 1. Introduction **1**

1.1 Background 1

1.2 Rationale 3

1.3 Thesis Objectives 4

1.4 Thesis Overview 5

1.5 References 6

Chapter 2. Literature Review **10**

2.1 Epidemiology of CHD 10

2.2 Etiology of CHD 11

2.3 Prenatal Exposure to $PM_{2.5}$, Wildfires, and CHD 18

2.4 Prenatal Heat Exposure and CHD 21

2.5 Interactive Effects of Wildfires and Heat on CHD 22

2.6 References 25

Chapter 3. Data Sources and Study Cohort **38**

3.1 Data Sources 38

3.2 Data Linkage 42

3.3 Study Cohort 43

3.4 References 48

Chapter 4. Wildfire Smoke $PM_{2.5}$, Extreme Heat Events and Congenital Heart Defects **50**

4.1 Preface 50

4.2 List of Authors 51

4.3 Acknowledgements 53

4.4 Abstract 54

4.5 Introduction 55

4.6 Methods 56
4.7 Statistical Analysis 61
4.8 Results 64
4.9 Discussion 67
4.10 Conclusions 72
4.11 Tables and Figures 73
4.12 Supplementary Materials 79
4.13 References 107
Chapter 5. Discussion 113
5.1 Summary of Findings 113
5.2 Integration of Findings 114
5.3 Strengths 117
5.4 Limitations 118
5.5 Recommendations for future wildfire seasons 119
5.6 Implications for future research 120
5.7 Conclusion 121
5.8 References 122
Appendix A – STROBE Statement Checklist 126

List of Tables

Table 3.1. List of ICD-10-CA codes used for identification of medical conditions. 39

Table 3.2. Baseline characteristics of the study cohort stratified by Congenital Heart Defect (CHD) outcome. 46

Table 4.1. Descriptive characteristics of the study cohort stratified by Congenital Heart Defect (CHD) outcome. 73

Supplementary Table S1. Pearson correlation coefficients of $PM_{2.5}$ pollutants and ambient temperature. 94

Supplementary Table S2. Cumulative Hazard Ratios (95% Confidence Intervals) associated with 1 $\mu g/m^3$ increase in $PM_{2.5}$ or presence of EHE during periconception on overall CHD and their corresponding Akaike Information Criterion (AIC) estimates. 95

Supplementary Table S3. Association between overall CHD and its subtypes per 1 $\mu g/m^3$ increase in all-source, WFS and non-WFS $PM_{2.5}$. 96

Supplementary Table S4. Association between overall CHD and its subtypes per 1 $\mu g/m^3$ increase in all-source, WFS and non-WFS $PM_{2.5}$ further adjusting for maternal comorbidities. . 97

Supplementary Table S5. Association between overall CHD and its subtypes per 1 $\mu g/m^3$ increase in all-source, WFS and non-WFS $PM_{2.5}$ using mixed-effects log-binomial models. 98

Supplementary Table S6. Association between overall CHD and its subtypes per 1 $\mu g/m^3$ increase in all-source, WFS and non-WFS $PM_{2.5}$ during first trimester. 99

Supplementary Table S7. Association between overall CHD per 1 $\mu g/m^3$ increase in all-source, WFS and non-WFS $PM_{2.5}$ in the subset of cohort with complete NO_2 data. 100

Supplementary Table S8. Association between overall CHD per 1 $\mu g/m^3$ increase in WFS $PM_{2.5}$ during periconception, adjusting for alternative specifications of seasonality. 101

Supplementary Table S9. Stratified analysis of associations between 1 $\mu g/m^3$ increase in WFS $PM_{2.5}$ concentration on CHD during periconception. 102

Supplementary Table S10. P-value of effect modification from stratified analyses of association between presence of EHE95 on CHD during periconception. 103

Supplementary Table S11. Hazard Ratios, Relative Excess Risk due to Interaction, Attributable Proportions and their 95% Confidence Intervals for the joint association of EHEs and WFS events on overall CHD during cardiogenesis. 104

Supplementary Table S12. Hazard Ratios, Relative Excess Risk due to Interaction, Attributable Proportions and their 95% Confidence Intervals for the joint association of EHEs and WFS events on overall CHD during cardiogenesis further adjusting for maternal comorbidities. 105

Supplementary Table S13. Hazard Ratios, Relative Excess Risk due to Interaction, Attributable Proportions and their 95% Confidence Intervals for the joint association of EHEs and high $PM_{2.5}$ stratified by presence of WFS on overall CHD during cardiogenesis. 106

List of Figures

Figure 2.1. Overview of CHD etiologic factors 12

Figure 3.1. Method of data linkage. 43

Figure 3.2. Flow chart of the study composition. 45

Figure 4.1. Association between overall Congenital Heart Defect (CHD) and its subtypes per 1 $\mu g/m^3$ increase in all-source, Wildfire smoke (WFS) and non-WFS $PM_{2.5}$ exposure during periconception. 75

Figure 4.2. Weekly Hazard Ratios (HRs) for overall Congenital Heart Defect (CHD) and its subtypes per 1 $\mu g/m^3$ increase in prenatal Wildfire smoke (WFS) $PM_{2.5}$ concentration. 76

Figure 4.3. Association between presence of Extreme Heat Events (EHEs) and overall Congenital Heart Defect (CHD) with its subtypes during periconception. 77

Figure 4.4. Relative Excess Risk due to Interaction for the joint association of Extreme Heat Events (EHEs) and Wildfire smoke (WFS) events on overall Congenital Heart Defect (CHD) during cardiogenesis. 78

Supplementary Figure S1. Flow chart of the inclusion and exclusion of the study population. .. 80

Supplementary Figure S2. Directed Acyclic Graph (DAG) representing the association between prenatal WFS $PM_{2.5}$ exposure during pregnancy and CHD in infants. 81

Supplementary Figure S3. Directed Acyclic Graph (DAG) representing the association between EHE exposure during pregnancy and CHD in infants. 82

Supplementary Figure S4. Spatial distribution of mean concentrations of all-source, WFS and non-WFS $PM_{2.5}$ across Canada by province (2013-2021). 83

Supplementary Figure S5. Weekly Hazard Ratios (HRs) for overall CHD per 1 $\mu g/m^3$ increase in prenatal WFS $PM_{2.5}$ concentration across different lag-response functions modelled using natural splines. 84

Supplementary Figure S6. Exposure-response curve of the association between WFS $PM_{2.5}$ and CHD during cardiogenesis. 85

Supplementary Figure S7. Association between presence of EHEs and overall CHD with its subtypes during periconception further adjusting for maternal comorbidities. 86

Supplementary Figure S8. Association between presence of EHE95 and overall CHD during periconception stratified by infant sex. 87

Supplementary Figure S9. Association between presence of EHE95 and overall CHD during periconception stratified by rurality of maternal residence at birth. 88

Supplementary Figure S10. Association between presence of EHE95 and overall CHD during periconception stratified by geographical regions. 89

Supplementary Figure S11. Association between presence of EHE95 and overall CHD during periconception stratified by residential instability quintiles. 90

Supplementary Figure S12. Association between presence of EHE95 and overall CHD during periconception stratified by ethno-cultural composition quintiles..... 91

Supplementary Figure S13. Association between presence of EHE95 and overall CHD during periconception stratified by economic dependency quintiles. 92

Supplementary Figure S14. Association between presence of EHE95 and overall CHD during periconception stratified by situational vulnerability quintiles..... 93

Abbreviations

AHAM	Association of Home Appliance Manufacturers
AP	Attributable Proportion
AQHI	Air Quality Health Index
ASD	Atrial Septal Defect
CanOSSEM	Canadian Optimized Statistical Smoke Exposure Model
CCASS	Canadian Congenital Anomalies Surveillance System
CCI	Canadian Classification of Health Interventions
CH_4	Methane
CHD	Congenital Heart Defect
CI	Confidence Interval
CIHI	Canadian Institute for Health Information
CIMD	Canadian Index of Multiple Deprivation
CO	Carbon Monoxide
COVID-19	Coronavirus Disease
CRA	Canada Revenue Agency
CVSBD	Canadian Vital Statistics Birth Database
CVSD	Canadian Vital Statistics Database
CVSDD	Canadian Vital Statistics Death Database
DA	Dissemination Area
DAD	Discharge Abstract Database
DAG	Directed Acyclic Graph
DLM	Distributed Lag Model
DLNM	Distributed Lag Non-Linear Model
EC	Elemental Carbon
EHE	Extreme Heat Event
FSA	Forward Sortation Area
GRID	Global Resource Information Database
HBV	Hepatitis B Virus
HCMV	Human Cytomegalovirus
HEPA	High-Efficiency Particulate Air
HLHS	Hypoplastic Left Heart Syndrome
HR	Hazard Ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
IQR	Interquartile Range
LMP	Last Menstrual Period
MERRA-2	Modern-Era Retrospective Analysis for Research and Applications
NAPS	National Air Pollution Surveillance

NASA	National Aeronautics and Space Administration
NO_2	Nitrogen Dioxide
O_3	Ozone
OC	Organic Carbon
OR	Odds Ratio
PAH	Polycyclic Aromatic Hydrocarbons
PCCF	Postal Code Conversion File
PM_1	Submicron Particulate Matter
PM_{10}	Inhalable Particulate Matter
$PM_{2.5}$	Fine Particulate Matter
RAQDPS	Regional Air Quality Deterministic Prediction System
RERI	Relative Excess Risk due to Interaction
RR	Relative Risk
SD	Standard Deviation
SES	Socioeconomic Status
SO_2	Sulphur Dioxide
T1FF	T1 Family File
UNEP	United Nations Environment Programme
VSD	Ventricular Septal Defect
WFS	Wildfire Smoke

Abstract

Background: Wildfire events and temperature anomalies have been increasing in frequency due to climate change. Prenatal exposures to resulting environmental stressors, including wildfire smoke (WFS) $PM_{2.5}$ and extreme heat events (EHEs) may be associated with adverse birth outcomes, specifically congenital heart defects (CHD).

Methods: The study cohort was developed using health administrative data across Canada, excluding the province of Quebec. Environmental exposures of $PM_{2.5}$ (all-source, WFS, and non-WFS) and ambient temperatures were assigned to each mother-infant pair based on the maternal residential history.

Results: No significant association between WFS $PM_{2.5}$ and CHD was observed. Similarly, no consistent association was identified for EHEs, and no significant additive interaction between WFS events and EHEs was observed.

Conclusion: Overall, no clear evidence of association between WFS $PM_{2.5}$ and EHEs on CHD risk was observed. Further research on the implications of wildfires on the relationship between environmental factors and adverse birth outcomes is warranted.

Chapter 1. Introduction

1.1 Background

Wildfires are destructive vegetation fires and a major natural hazard known to negatively affect the ecosystem and human health.[1] Over the recent years, record-breaking wildfire events have been increasing globally, resulting in devastating environmental and economic burden on society. Although fire is a natural and essential process of the ecosystem, climate change has led to amplified wildfire events, posing substantial risks to human health. According to the wildfire report released by the United Nations Environment Programme (UNEP) and Global Resource Information Database (GRID) - Arendal in 2022, global wildfire events are estimated to increase up to 20% by year 2040 compared to the reference period of 2010-2020.[2]

Canada has experienced escalated intensity and extension of wildfire seasons over the past decades.[3] Historically, typical wildfire seasons in Canada span from May to September,[4] but surges of fire events have been reported through November during the last few years.[5] With an annual average of 8,000 wildfires,[6] the wildfire response and suppression cost alone is estimated to exceed over $1 billion every year in Canada.[7] While most provinces and territories are susceptible to wildfires, extreme events are more frequently recorded in the western regions.[8] Notably, the Fort McMurray wildfire in 2016 has reported 589,000 hectares of land burned across Alberta and Saskatchewan,[9] with the largest record of wildfire related evacuation in history, displacing more than 88,000 residents.[10] British Columbia also experienced one of its most destructive wildfire seasons in 2017 and 2018, where over 1.2 million and 1.3 million hectares of lands were burned each year respectively.[11] More than half of the 2017-2018 British

Columbia wildfires were ignited by lightning, with an estimated fire suppression cost of $1.2 billion for the province over the two years.[11]

Wildfire occurrences and behaviours are associated with three major factors of fuel, weather and topography.[2] Increased human-produced emissions of greenhouse gases are one of the driving causes of climate change, which have resulted in a continuous rise of global surface temperature, further heightening weather anomalies.[12] Specifically, climate change has contributed to prolonged droughts and intensified heat events, creating hotter and drier conditions that, in turn, lead to more frequent and severe wildfire seasons.[13] Exposure to wildfire smoke (WFS) and heat exhibits a substantial health risk, particularly for pregnant individuals who are especially more vulnerable to these environmental stressors.[14] Notably, a recent systematic review suggests evidence of association between prenatal WFS exposure and increased risk of all-cause respiratory morbidity and reduced birth weight in infants,[15] whereas prenatal heat exposure was associated with preterm birth and congenital anomalies.[16]

Wildfire smoke (WFS) is composed of varying air pollutants including: fine particulate matter ($PM_{2.5}$), ozone (O_3), methane (CH_4), sulphur dioxide (SO_2), carbon monoxide (CO), polycyclic aromatic hydrocarbons (PAHs) and other volatile organic compounds.[17] Of these, $PM_{2.5}$ consists of particles with a diameter of less than or equal to 2.5μm, consisting of a mixture of smoke, aerosol particles and biological matters.[18] $PM_{2.5}$ is identified as the major component of wildfire smoke and is commonly used as a standard measure to assess the health effects imposed by air pollutants.[19–21] Exposure to these environmental stressors, including heat and $PM_{2.5}$, during pregnancy can prompt endothelial dysfunction and may lead to increased placental stress further affecting the health of infants.[22] A recent review conducted by Brew and colleagues in 2025 assessed the effects of prenatal landscape fire smoke exposure on perinatal health,

reporting associations with increased risk of adverse birth outcomes including preterm birth and low birth weight.[23] The same review also highlighted the knowledge gaps and the limited number of published studies investigating its effect on other birth outcomes, specifically congenital anomalies.[23]

Congenital Heart Defect (CHD) is a structural malformation of the heart or blood vessels present at birth.[24,25] It is the most prevalent congenital disorder around the world, with an estimated global mean prevalence of approximately 8.2 cases per 1,000 live births.[26] Varying in subtypes and severity, CHD disrupts normal cardiac circulation and predisposes patients to a range of complex comorbidities and long-term complications.[24,25,27] Notably, major complications associated with CHD include strokes, endocarditis, heart failures, pulmonary hypertension and arrhythmias.[28,29] Despite the improvement in survival rates due to enhancement in diagnostic and treatment capabilities, the disease still causes significant lifelong health complications and economic burdens for patients.[30–32]

1.2 Rationale

The association between ambient air pollutants, heat and congenital anomalies have been explored extensively in published studies and systematic reviews, but evidence on how wildfire affects this relationship remains unconfirmed.[16,33] Similarly, interactive effects of ambient air pollutants and heat exposure on perinatal outcomes have been examined in previous literature.[34,35] Nevertheless, the risk imposed by wildfire events on this potential synergistic effect is also an emerging field of study, where additional research is crucial given the growing co-occurrence of wildfire and heat events in North America.[36,37]

Furthermore, the majority of the studies examined the relationship between environmental factors and CHD through analysis of average exposures during specific trimesters

or predefined periods of gestation, typically ranging from one to three months of relatively wide exposure windows. In addition, exposure during preconception have generally been underexplored in previous research, despite being identified as a potential vulnerable window disrupting the early development of fetuses.[38] Therefore, this study will incorporate weekly exposures of environmental stressors throughout periconception, defined as 3 months window prior to start of pregnancy through the end of the first trimester, to allow for more precise detection of critical windows of susceptibility during early pregnancy. Overall, the findings of this study will contribute to the expanding body of literature on the health implications associated with wildfire and heat exposures, and provide a novel understanding of the CHD risk for future maternal health guidelines on wildfire events.

1.3 Thesis Objectives

The overall aim of this thesis is to examine the association between wildfire smoke (WFS) $PM_{2.5}$, heat and CHD in infants through analysis of a nationwide retrospective cohort data in Canada.

- Research Objective 1: To assess the association between prenatal exposure to heat, $PM_{2.5}$ arising from different sources (all-source, WFS, and non-WFS) and the risk of CHD through identification of sensitive windows of susceptibility during the periconception period.
- Research Objective 2: To assess the potential synergistic effect of WFS and heat on CHD.

1.4 Thesis Overview

This thesis analyzed existing datasets obtained from Statistics Canada, and falls under the University of Ottawa thesis category of secondary analysis. This thesis consists of five chapters and is written in "thesis by manuscript" format, in accordance with the School of Epidemiology and Public Health thesis guidelines. Chapter 1 introduced the background, rationale and objectives of the study. The subsequent chapters of the thesis are as follows:

- Chapter 2 includes a review of existing literature and current evidence on the epidemiology of CHD
- Chapter 3 includes an overview of the study cohort composition, description of different data sources and methods of data linkage.
- Chapter 4 includes a standalone manuscript, addressing research objectives 1 and 2.
- Chapter 5 includes a discussion chapter presenting the overall findings of the thesis along with implications of the results for future research.

1.5 References

1. United Nations Office for Disaster Risk Reduction. (2023, June 7). *Wildfires (EN0205) | UNDRR*. United Nations Office for Disaster Risk Reduction. https://www.undrr.org/understanding-disaster-risk/terminology/hips/en0205

2. Popescu, A., Paulson, A., Christianson, A., Sullivan, A., Tulloch, A., Bilbao, B., Mathison, C., Robinson, C., Ganz, D., Nangoma, D., Saah, D., Armenteras, D., Driscoll, D., Hankins, D., Kelley, D., Langer, E., Baker, E., Reisen, F., Robinne, F.-N., … Charlton, V. (2022). *Spreading like wildfire: The rising threat of extraordinary landscape fires—A rapid response assessment* (A. Sullivan, E. Baker, & T. Kurvits, Eds.). United Nations Environment Program (UNEP); USGS Publications Warehouse. https://pubs.usgs.gov/publication/70243263

3. Wang, W., Wang, X., Flannigan, M. D., Guindon, L., Swystun, T., Castellanos-Acuna, D., Wu, W., & Wang, G. (2025). Canadian forests are more conducive to high-severity fires in recent decades. *Science*, *387*(6729), 91–97. https://doi.org/10.1126/science.ado1006

4. Red Cross Canada. (n.d.). *Wildfires: Information & Facts*. Red Cross Canada. https://www.redcross.ca/how-we-help/emergencies-and-disasters-in-canada/types-of-emergencies/wildfires/wildfires-information-facts

5. Canadian Interagency Forest Fire Centre. (2025). *2024 Annual Report*. https://ciffc.ca/sites/default/files/2025-06/Canada_Report_2024_EN_Version.pdf

6. Natural Resources Canada. (n.d.). *Canadian Wildland Fire Information System | Canadian National Fire Database (CNFDB)*. Government of Canada. https://cwfis.cfs.nrcan.gc.ca/ha/nfdb

7. Natural Resources Canada. (2023, May 30). *Fighting and Managing Wildfires in a Changing Climate Program*. Government of Canada. https://natural-resources.canada.ca/forest-forestry/wildland-fires/fighting-managing-wildfires-changing-climate-program

8. Erni, S., Wang, X., Swystun, T., Taylor, S. W., Parisien, M.-A., Robinne, F.-N., Eddy, B., Oliver, J., Armitage, B., & Flannigan, M. D. (2024). Mapping wildfire hazard, vulnerability, and risk to Canadian communities. *International Journal of Disaster Risk Reduction*, *101*, 104221. https://doi.org/10.1016/j.ijdrr.2023.104221

9. Statistics Canada. (2017, March). *Infographic: Fort McMurray 2016 Wildfire – Economic Impact*. Statistics Canada. https://www150.statcan.gc.ca/n1/pub/11-627-m/11-627-m2017007-eng.htm

10. McGee, T. K. (2019). Preparedness and Experiences of Evacuees from the 2016 Fort McMurray Horse River Wildfire. *Fire*, *2*(1), 13. https://doi.org/10.3390/fire2010013

11. BC Wildfire Service. (2025, July). *Wildfire Averages—Province of British Columbia*. Government of British Columbia; Province of British Columbia. https://www2.gov.bc.ca/gov/content/safety/wildfire-status/about-bcws/wildfire-statistics/wildfire-averages

12. Lindsey, R., & Dahlman, L. (2025, May 29). *Climate change: Global temperature | NOAA Climate.gov*. National Oceanic and Atmospheric Administration. https://www.climate.gov/news-features/understanding-climate/climate-change-global-temperature

13. Xu, R., Yu, P., Abramson, M. J., Johnston, F. H., Samet, J. M., Bell, M. L., Haines, A., Ebi, K. L., Li, S., & Guo, Y. (2020). Wildfires, Global Climate Change, and Human Health. *New England Journal of Medicine*, *383*(22), 2173–2181. https://doi.org/10.1056/NEJMsr2028985

14. Amjad, S., Chojecki, D., Osornio-Vargas, A., & Ospina, M. B. (2021). Wildfire exposure during pregnancy and the risk of adverse birth outcomes: A systematic review. *Environment International*, *156*, 106644. https://doi.org/10.1016/j.envint.2021.106644

15. Zhang, Y., Tingting, Y., Huang, W., Yu, P., Chen, G., Xu, R., Song, J., Guo, Y., & Li, S. (2024). Health Impacts of Wildfire Smoke on Children and Adolescents: A Systematic Review and Meta-analysis. *Current Environmental Health Reports*, *11*(1), 46–60. https://doi.org/10.1007/s40572-023-00420-9

16. Lakhoo, D. P., Brink, N., Radebe, L., Craig, M. H., Pham, M. D., Haghighi, M. M., Wise, A., Solarin, I., Luchters, S., Maimela, G., & Chersich, M. F. (2025). A systematic review and meta-analysis of heat exposure impacts on maternal, fetal and neonatal health. *Nature Medicine*, *31*(2), 684–694. https://doi.org/10.1038/s41591-024-03395-8

17. Health Canada. (2021, May 14). *Wildfire smoke and your health*. Government of Canada. https://www.canada.ca/en/health-canada/services/publications/healthy-living/wildfire-smoke-health.html

18. Health Canada. (2021, April 14). *Infographic: What is fine particulate matter (PM2.5)?* Government of Canada. https://www.canada.ca/en/health-canada/services/publications/healthy-living/infographic-fine-particulate-matter.html

19. Liu, J. C., Pereira, G., Uhl, S. A., Bravo, M. A., & Bell, M. L. (2015). A systematic review of the physical health impacts from non-occupational exposure to wildfire smoke. *Environmental Research*, *136*, 120–132. https://doi.org/10.1016/j.envres.2014.10.015

20. Reid, J. S., Koppmann, R., Eck, T. F., & Eleuterio, D. P. (2005). A review of biomass burning emissions part II: Intensive physical properties of biomass burning particles. *Atmospheric Chemistry and Physics*, *5*(3), 799–825. https://doi.org/10.5194/acp-5-799-2005

21. Lei, Y., Lei, T.-H., Lu, C., Zhang, X., & Wang, F. (2024). Wildfire Smoke: Health Effects, Mechanisms, and Mitigation. *Environmental Science & Technology*, *58*(48), 21097–21119. https://doi.org/10.1021/acs.est.4c06653

22. Thangavel, P., Park, D., & Lee, Y.-C. (2022). Recent Insights into Particulate Matter (PM2.5)-Mediated Toxicity in Humans: An Overview. *International Journal of Environmental Research and Public Health*, *19*(12), 7511. https://doi.org/10.3390/ijerph19127511

23. Brew, B. K., Murphy, V. E., Collison, A. M., Mattes, J., Karmaus, W., Morgan, G., Jalaludin, B., Zosky, G., Guo, Y., & Gibson, P. G. (2025). Approaches in landscape fire smoke pregnancy research and the impact on offspring: A review of knowledge gaps and recommendations. *Environmental Pollution*, *364*, 125348. https://doi.org/10.1016/j.envpol.2024.125348

24. U.S. Centers for Disease Control and Prevention. (2024, December 19). *About Congenital Heart Defects*. CDC. https://www.cdc.gov/heart-defects/about/index.html

25. National Health Service. (2017, October 19). *Congenital heart disease—Complications*. Nhs.Uk. https://www.nhs.uk/conditions/congenital-heart-disease/complications/

26. Liu, Y., Chen, S., Zühlke, L., Black, G. C., Choy, M., Li, N., & Keavney, B. D. (2019). Global birth prevalence of congenital heart defects 1970–2017: Updated systematic review and meta-analysis of 260 studies. *International Journal of Epidemiology*, *48*(2), 455–463. https://doi.org/10.1093/ije/dyz009

27. Canadian Congenital Heart Alliance. (2024, April 16). *About Congenital Heart Defects—Canadian Congenital Heart Alliance*. CCHA. https://cchaforlife.org/learn-about-chd/about-congenital-heart-defects/

28. National Health Service. (2017, October 19). *Congenital heart disease—Symptoms*. Nhs.Uk. https://www.nhs.uk/conditions/congenital-heart-disease/symptoms/

29. Sun, R., Liu, M., Lu, L., Zheng, Y., & Zhang, P. (2015). Congenital Heart Disease: Causes, Diagnosis, Symptoms, and Treatments. *Cell Biochemistry and Biophysics*, *72*(3), 857–860. https://doi.org/10.1007/s12013-015-0551-6

30. Van Der Bom, T., Zomer, A. C., Zwinderman, A. H., Meijboom, F. J., Bouma, B. J., & Mulder, B. J. M. (2011). The changing epidemiology of congenital heart disease. *Nature Reviews Cardiology*, *8*(1), 50–60. https://doi.org/10.1038/nrcardio.2010.166

31. GBD 2017 Congenital Heart Disease Collaborators. (2020). Global, regional, and national burden of congenital heart disease, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *The Lancet. Child & Adolescent Health*, *4*(3), 185–200. https://doi.org/10.1016/S2352-4642(19)30402-X

32. Krasuski, R. A., & Bashore, T. M. (2016). Congenital Heart Disease Epidemiology in the United States. *Circulation*, *134*(2), 110–113. https://doi.org/10.1161/CIRCULATIONAHA.116.023370

33. Ravindra, K., Chanana, N., & Mor, S. (2021). Exposure to air pollutants and risk of congenital anomalies: A systematic review and metaanalysis. *Science of The Total Environment*, *765*, 142772. https://doi.org/10.1016/j.scitotenv.2020.142772

34. Jiang, W., Liu, Z., Ni, B., Xie, W., Zhou, H., & Li, X. (2021). Independent and interactive effects of air pollutants and ambient heat exposure on congenital heart defects. *Reproductive Toxicology*, *104*, 106–113. https://doi.org/10.1016/j.reprotox.2021.07.007

35. Stingone, J. A., Luben, T. J., Sheridan, S. C., Langlois, P. H., Shaw, G. M., Reefhuis, J., Romitti, P. A., Feldkamp, M. L., Nembhard, W. N., Browne, M. L., & Lin, S. (2019). Associations between fine particulate matter, extreme heat events, and congenital heart defects. *Environmental Epidemiology*, *3*(6), e071. https://doi.org/10.1097/EE9.0000000000000071

36. Cleland, S. E., Paul, N., Coker, E. S., & Henderson, S. B. (2025). The Co-occurrence of Wildfire Smoke and Extreme Heat Events in British Columbia, 2010–2022: Evaluating Spatiotemporal Trends and Inequities in Exposure Burden. *ACS ES&T Air*, *2*(3), 319–330. https://doi.org/10.1021/acsestair.4c00219

37. Hu, J. K., Trišović, A., Bakshi, A., Braun, D., Dominici, F., & Casey, J. A. (2025). Coexposure to extreme heat, wildfire burn zones, and wildfire smoke in the Western US from 2006 to 2020. *Science Advances*, *11*(18), eadq6453. https://doi.org/10.1126/sciadv.adq6453

38. Grandjean, P., Barouki, R., Bellinger, D. C., Casteleyn, L., Chadwick, L. H., Cordier, S., Etzel, R. A., Gray, K. A., Ha, E.-H., Junien, C., Karagas, M., Kawamoto, T., Lawrence, B. P., Perera, F. P., Prins, G. S., Puga, A., Rosenfeld, C. S., Sherr, D. H., Sly, P. D., … Heindel, J. J. (2015). Life-Long Implications of Developmental Exposure to Environmental Stressors: New Perspectives. *Endocrinology*, *156*(10), 3408–3415. https://doi.org/10.1210/en.2015-1350

Chapter 2. Literature Review

2.1 Epidemiology of CHD

CHD is the most common congenital anomaly in newborns around the world, and a significant leading cause of infant mortality.[1] From 1970 to 2017, approximately 10% increase in global CHD prevalence was observed every five years, affecting over 1 million infants every year.[2] This upward trend is likely attributable to the advancement in medical diagnostic technologies, allowing more accurate detection of diseases. Accordingly, a plateau in CHD prevalence has been observed in high-income countries over the recent years.[3] A similar trend was also observed in Canada, where the prevalence rate of CHD has stabilized during the last several decades.[4] The estimated mean prevalence in Canada is approximately 12.3 CHD cases per 1,000 live births, affecting over 4,000 infants every year.[5]

Although enhancements in diagnostic and treatment capabilities have resulted in the reduction of mortality rates for CHD patients, the disease continues to pose significant long-term health complications and remains as one of the leading causes of infant mortality.[6,7] A Canadian study published in 2014 by Marelli and colleagues revealed approximately 60% of severe CHD population are comprised of adults, reflecting an increase in the median age of this population from 17 years in 2000 to 25 years in 2010.[8] Additionally, a study conducted in the province of Quebec has reported a 59% decrease in CHD-related childhood mortality rate during the 2002-2005 period compared to the 1987-1990 period.[9] Collectively, these findings highlight the improvement of CHD survival rate in children during the recent years, while simultaneously emphasizing the heightening severity of long-term comorbidities and economic burdens for the patients.[8–10] In Canada, the annual hospitalization rate of CHD patients has increased by an average of 1.1% each year from 2003 to 2012,[11] with common related cardiac complications of

atrial fibrillation, arrhythmias, ischemic heart disease, and coronary artery disease.[12,13] Consequently, the estimated annual cost of CHD-related hospitalization further increased from 2004 to 2013, reporting an estimated cost of $121.2 million among Canadian hospitals in 2013, excluding Quebec.[14] Given the escalating chronic complications and economic cost associated with CHD, further research examining the etiology of CHD is crucial.

2.2 Etiology of CHD

Formation of the heart tube occurs during the embryo's gastrulation process, which typically starts from embryonic week 3 in humans and continue to develop throughout the first trimester.[15] Following the fetal heart development, CHD can be diagnosed by fetal anomaly screening during the second trimester or through a combination with routine newborn physical examination after birth.[16] While over half of major CHD cases are diagnosed prenatally,[17] the disease is also commonly detected during infancy.[18] In Canada, the recommended reporting time frame of congenital anomalies is one year of age for most regions under the Canadian Congenital Anomalies Surveillance System (CCASS).[19]

Globally, Ventricular Septal Defects (VSD) have been identified as the most common CHD subtype followed by Atrial Septal Defects (ASD), collectively contributing to approximately 47% of total CHD cases.[20] VSDs result from defects occurring in the interventricular septum,[21] whereas ASDs result from abnormalities in the true septal membrane or disruption of the interatrial communications.[22] While both subtypes vary in severity of malformations, they are often associated with multiple chronic complications including pulmonary hypertension and congestive heart failure.[21,22]

Overall, approximately 55% of the CHD etiology is largely unclear, with 45% of the remaining CHD etiologic factors being attributable to multifactorial and interrelated

combinations of genetic and prenatal environmental factors.[23,24] Potential contributors identified to be associated with CHD etiology are summarized in Figure 2.1.

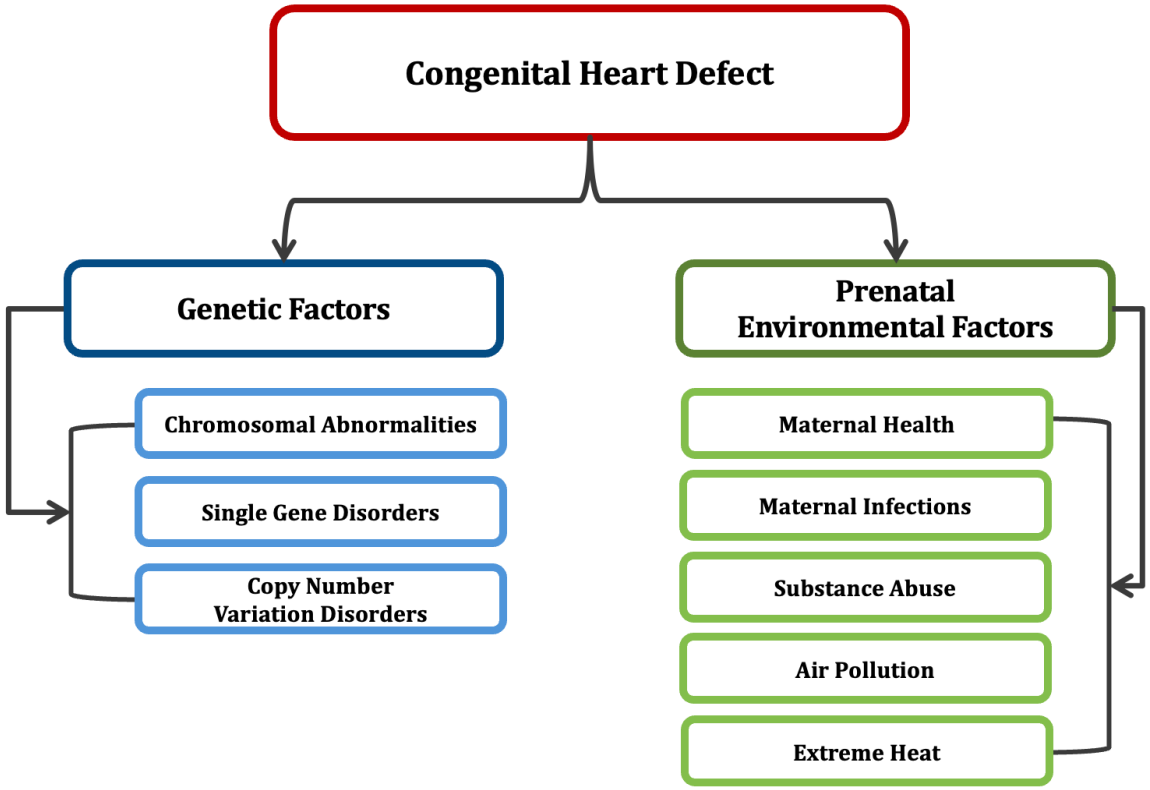


Figure 2.1. Overview of CHD etiologic factors

2.2.1 Genetic factors

Approximately 9 to 18% of CHD cases have been attributed to chromosomal abnormalities and aneuploidy conditions.[25] While patients with chromosomal disorders report varying incidence rates and subtypes of CHD, common syndromes resulting in the disease include: Trisomy 13, Trisomy 18, Trisomy 21, Monosomy X and XXY syndrome.[26] Moreover, the development of whole-genome sequencing in recent years has led to the identification of molecular pathways and genetic causes of CHD.[23,26] A complex gene regulatory network of transcription factors and downstream genes are orchestrated during the development of the heart.[27] Notably, GATA4, NKX2-5 and TBX5 are essential genes involved throughout cardiogenesis.[28] Mutations of these genes may disrupt crucial interactions between cardiac transcription factors during the embryonic stage, leading to the development of CHD.[29] Furthermore, copy number variations and microdeletions of 22q11.2 and 7q11.23 chromosomes have also been identified as contributors to cardiac malformations.[26,30] Evidence suggests the majority of these single gene disorders and copy number variation disorders are attributable to *de novo* mutations, accounting for approximately 10% of CHD cases.[31,32]

2.2.2 Prenatal environmental factors

Despite advancements in genomic technologies which allowed a discovery of potential genetic factors associated with CHD, substantial portion of its pathogenesis still remains unknown due to the complex nature of the disease. Throughout the recent years, various prenatal environmental factors have also been recognized to play a critical role in CHD etiology.

2.2.2.1 Maternal health

Maternal chronic diseases, notably obesity, hypertension and diabetes mellitus significantly influence the health of pregnant individuals and thus have been associated with

increased risks of CHD in offsprings. These pre-existing maternal health conditions are closely linked with an imbalance in adiponectin levels, insulin resistance and glycemic dysregulation.[33,34] The disruption of maternal glucose homeostasis, especially during embryogenesis, may lead to abnormal placental nutrient transport and vascularization, thereby negatively affecting fetal health.[33,35,36] A systematic review and meta-analysis conducted by Khalilipalandi and colleagues in 2024 investigated a range of prenatal risk factors of CHD through analysis of 170 eligible articles.[37] Across 15 studies, a positive association between maternal pregestational diabetes and CHD was reported with a pooled OR estimate of 3.48 (95% CI: 2.90, 4.18).[37] Furthermore, a dose-response relationship was observed between different categories of maternal obesity and increased risk of CHD, each reporting a pooled OR of 1.08 (95% CI: 1.05, 1.11) for maternal overweight, 1.16 (95% CI: 1.11, 1.22) for maternal obesity and 1.44 (95% CI: 1.35, 1.53) for morbid obesity across a total of 23 included studies.[37] Although considerable amount of heterogeneity was detected for both pooled ORs, the variation was largely due to the magnitude of the associations with estimates reporting persistently higher risk. Only two studies included in the meta-analysis examined the effects of maternal chronic hypertension, where both demonstrated an increased risk of CHD with estimated OR of 2.97 (95% CI: 2.61, 3.37) and 1.22 (95% CI: 1.06, 1.41).[37] However, this association became statistically non-significant for gestational hypertension with a pooled OR of 1.35 (95% CI: 0.65, 2.81) across five studies, as cardiogenesis occurs during the first trimester.[37]

Multiple gestations and parity are additional risk factors identified to affect maternal health and the development of CHD. While the exact underlying biological mechanism is still unclear, research suggests vascular anastomoses shared between the circulation of the monochorionic twins and nutrient depletion arising from short interpregnancy intervals may

increase the risk of adverse birth outcomes, including congenital anomalies.[38,39] Feng and colleagues investigated the association between maternal parity and CHD in 2014 through a meta-analysis.[40] A total of 14 case-control and cohort studies were examined for a potential dose-response relationship, where a 6% increase in CHD risk was observed per live birth (95% CI: 1.02, 1.09).[40] However, inconsistent evidence of association was observed when comparing nulliparous and multiparous births with a pooled RR of 1.01 (95% CI: 0.97, 1.06) across 16 studies.[40] This conflicting evidence underscores the multifaceted biological pathways linked to variation in multiparity. Although a notable I^2 value of 80.9% was detected for the dose-response estimate, the pooled RR remained consistent when excluding the seven studies identified as sources of heterogeneity.

Moreover, growing number of studies have investigated the effects of socioeconomic status (SES) on adverse birth outcomes over the recent years. SES includes a broad range of relevant social, environmental and economic factors that are closely interlinked with healthcare resources of individuals, and is a major contributor to health disparities.[41–43] A nationwide retrospective ecological study in Canada observed a higher prevalence of major CHD cases in the lowest quintile of maternal neighbourhood-level income compared to the national birth proportion, after adjusting for rurality of residence and household size.[44] Additionally, a 2023 retrospective cohort study conducted in Ontario found that neighbourhood-level maternal deprivation was positively associated with CHD (OR: 1.27, 95% CI: 1.18, 1.37), whereas higher ethnicity concentration was negatively associated (OR: 0.89, 95% CI: 0.82, 0.97).[45]

2.2.2.2 Maternal infections

Maternal bacterial or viral infections during pregnancy pose detrimental teratogenic risks, impairing fetal development.[46] *In utero* exposures to a wide range of pathogens may trigger an

inflammatory response of the placenta and subsequently interfere with embryonic heart development.[47,48] A 2022 prospective cohort study conducted in Central China found that the presence of varying maternal viral infections of HBV, coxsackievirus-B, HCMV and rubella during early pregnancy were associated with increased risks of CHD, with the highest RR of 3.12 observed for HCMV infection (95% CI: 2.44, 3.98).[49] Similarly, a case-control study done in Shandong province of China reported a positive association between overall maternal infections during pregnancy (rubella, influenza, hepatitis, etc.) and CHD (OR: 7.98, 95% CI: 2.14, 29.72).[50]

2.2.2.3 Substance abuse

Prenatal exposures to maternal substance abuse, including smoking, alcohol and illicit drug usage, pose a significant health risk on the fetal development. Although the precise underlying biological mechanism warrants further research, the accumulation of toxins through substance usage may disrupt the placental secretory activity and influence fetal development.[51] Some studies also suggest a potential presence of gene-environment interaction, where exposure to cigarette smoke may interrupt the regulation of GATA4 and TBX5 gene expressions, which play a crucial role during fetal heart development.[52,53] Moreover, an animal study found that ethanol exposure during early embryogenesis was linked with reduced cardiac cushions, potentially leading to increased risk of septal defects.[54]

Zhao and colleagues investigated the association between parental smoking and CHD through a meta-analysis in 2020.[55] The study found maternal passive smoking (pooled RR: 2.24, 95% CI: 1.81, 2.77) and paternal active smoking (pooled RR: 1.74, 95% CI: 1.48, 2.06) was associated with increased risks, each examined across 36 and 35 studies respectively.[55] Despite the high heterogeneity of pooled estimates, included studies reported consistent direction of

association. However, numerous studies have found conflicting effects of parental alcohol exposure on CHD. A meta-analysis in 2020 reported maternal alcohol consumption was associated with elevated risk of CHD (RR: 1.16, 95% CI: 1.05, 1.27) across 45 studies, yet majority of included articles found null associations with notable heterogeneity of the pooled estimate.[56]

2.2.2.4 Air pollution

Over the past decades, global industrialization and urbanization have resulted in growing concern about health hazards arising from air pollution.[57] Maternal exposure to ambient air pollutants induces placental oxidative stress, and thus has been identified as a significant risk factor of adverse birth outcomes.[58] Recent studies have investigated the potential association between CHD and prenatal exposure to various ambient air pollutants including: particulate matter (PM), nitrogen dioxide (NO_2), sulphur dioxide (SO_2), carbon monoxide (CO) and ozone (O_3).

A population-based case-control study in Taiwan examined the effects of prenatal exposure to ambient air pollutants, and found an interquartile range (IQR) increase in $PM_{2.5}$ exposure during weeks 3-8 of pregnancy was associated with greater odds of overall CHDs (OR: 1.21, 95% CI: 1.03, 1.42).[59] The study also assessed the effects of prenatal exposure to PM_{10}, O_3, SO_2, CO and NO_2, but no significant evidence of association was observed.[59] Similarly, Stingone and colleagues conducted a case-control study in Unites States, and observed higher $PM_{2.5}$ exposure during weeks 2-8 of pregnancy was linked with increased risk of hypoplastic left heart syndrome (HLHS).[60] In addition, their findings suggested a potential variation in the degree of susceptibility within the critical developmental window, further underscoring the importance of evaluating the effects of weekly associated exposure on the risk of CHD.

2.2.2.5 Heat exposure

Elevated frequency of temperature anomalies has been observed as a consequence of climate change over the past decades.[61] In Canada, for instance, the annual average temperature has experienced an approximate 2.0°C increase from 1948 to 2023.[62] The escalating occurrence of extreme temperature records around the globe poses an emerging concern of potential health impacts of climate change, particularly heat-related exposures. An expanding body of literature has indicated prenatal heat exposure may be associated with increased risks of adverse birth outcomes.[63] The proposed biological mechanism suggests heat exposure during pregnancy may induce maternal oxidative stress and influence fetal development, similar to ambient air pollutant exposures.[64]

A case-control study in the United States found that exposure to extreme heat events, defined as maximum daily temperature exceeding the 95th percentile of local temperature distribution for two or more consecutive days, during pregnancy weeks 3 to 8 was associated with increased risk of VSD in south and northeast regions.[65] The study also highlighted a substantial regional variability of the association, observing elevated risk within regions with larger daily temperature variability.[65] In addition, Xu and colleagues conducted a time-series study in China and observed a positive association between CHD risk per 1°C increase in temperature at the 95th percentile of the local temperature distribution during the first and second trimester.[66]

2.3 Prenatal Exposure to $PM_{2.5}$, Wildfires, and CHD

Ambient air pollutants consist of a diverse mixture of chemical substances emitted from both natural sources and human activities.[67] Inhalation of these pollutants have reported to pose a substantial public health hazard including all-cause mortality, respiratory and cardiovascular

complications, along with adverse pregnancy outcomes.[68] In Canada, potential health risks associated with ambient pollutant exposures are addressed by systematic monitoring of pollutant concentrations through the Air Quality Health Index (AQHI).[69] The AQHI incorporates measurements of $PM_{2.5}$, PM_{10}, O_3 at ground level, and NO_2 to evaluate the overall outdoor air quality and inform public health responses.[69,70] Of these $PM_{2.5}$ are a mixture of metals, organic compounds and fine particles with less than 2.5μm in diameter, that are mostly emitted from agriculture, dust and fire sources in Canada.[71,72] Although the annual mean $PM_{2.5}$ concentrations are relatively low in Canada compared to other regions in the globe including eastern and southern Asia and northern Africa,[73] an upward trend of peak $PM_{2.5}$ concentrations were observed in western Canada over the recent years.[70,74] This elevation in regional peak $PM_{2.5}$ levels are likely attributable to surges of extreme wildfire activities, where an annual increase of 0.8-0.9 $\mu g/m^3$ $PM_{2.5}$ concentrations were observed in the Prairies, British Columbia and northern Ontario regions from 2006 to 2020.[70] Overall, the intensifying severity of wildfire seasons, driven by climate change, has heightened concerns about the public health impacts of $PM_{2.5}$ exposure.

While wildfire smoke (WFS) is composed of varying pollutants, approximately 90% of the wildfire-specific PM mixture is estimated to be composed of $PM_{2.5}$.[75,76] Previous research found a major difference in the chemical composition of WFS $PM_{2.5}$, where higher concentrations of organic carbon (OC) and elemental carbon (EC) were observed in comparison to $PM_{2.5}$ arising from other sources.[77,78] In addition, WFS $PM_{2.5}$ tends to contain a greater proportion of smaller particles.[79] A recent study conducted in the urban areas of San Francisco reported that PM_1 accounted for approximately 80% of $PM_{2.5}$ distributions during wildfire events, compared with 52% during non-wildfire periods.[80] These variation in particle

composition of WFS $PM_{2.5}$ may lead to more detrimental health effects, with emerging evidence suggesting increased pulmonary toxicity in humans.[81,82] Multiple epidemiologic studies have explored the potential health hazards of WFS $PM_{2.5}$ over the recent years, and reported an elevated risk of health outcomes including respiratory hospitalizations[83] and all-cause mortality.[84,85] Specifically, pregnant individuals represent a particularly vulnerable population, where prenatal exposure to wildfire smoke may have adverse effects on infant health.

Although the underlying biological mechanism of prenatal WFS $PM_{2.5}$ on adverse birth outcomes warrants further investigation, substantial research has examined the broader effects of $PM_{2.5}$ exposure. A study examining normal human bronchial epithelial cells revealed a positive correlation between exposure to specific PM constituents and release of IL-6 and IL-8 inflammatory biomarkers.[86] The imbalance of such biomarkers may disrupt maternal inflammatory response and lead to placental inflammation.[87,88] Additionally, previous studies have found that exposure to $PM_{2.5}$ may increase 8-OHdG levels during pregnancy, which is a key biomarker that triggers oxidative stress.[89,90] Overall, prenatal $PM_{2.5}$ exposure may induce maternal oxidative stress and placental inflammation, further prompting endothelial dysfunction.[91] This crucial biological mechanism is recognized to influence fetal growth, and may consequently lead to abnormal fetal cardiac development.[92,93]

Numerous systematic reviews exploring the effects of WFS on adverse birth outcomes have been published, and reported associations with preterm birth and low birth weight. [94,95] Nonetheless, there is currently limited number of studies that have examined its effect on CHD. Requia and colleagues investigated the association between prenatal WFS exposure and birth defects in Brazil, and found an increased risk of cardiovascular congenital anomalies during the first trimester, specifically among the subgroup of females residing in the Southeast region (OR:

1.032, 95% CI: 1.003, 1.062).[96] Another study conducted by Park and colleagues in 2025 also examined the effects of prenatal wildfire exposure on CHD, reporting an OR of 1.12 (95% CI: 1.02, 1.23) for the subtype of ASD during pregnancy weeks 3-8.[97] A more recent case-control study conducted by Padula and colleagues in California, United States, incorporated source-specific $PM_{2.5}$ exposures and found maximum fire density $PM_{2.5}$ during the first 8 weeks of pregnancy was associated with increased risk of Coarctation of the aorta (OR: 2.26, 95% CI: 1.02, 4.99).[98] Although modest positive associations for all-source $PM_{2.5}$ were observed in this study, the magnitude was smaller and estimates were not statistically significant.[98] While these studies investigated the effects of WFS on CHD, their exposure assignment was within relatively broad windows of one to three months. Given the episodic nature of wildfires, incorporating weekly-level smoke exposure across gestation will allow capturing of intensity and duration of wildfire events on CHD.

2.4 Prenatal Heat Exposure and CHD

Climate change has led to elevated global mean annual surface temperatures and extreme weather events over the last century.[99] According to an assessment report released by the Intergovernmental Panel on Climate Change, a global increase in the frequency of extreme warm days, defined as daily maximum temperature exceeding the 90th percentile of its temperature distribution, has been observed since the 1950s.[100] In Canada, a rising trend of both annual and seasonal temperatures was observed over the past several decades, with most regions experiencing at least 1°C increase in mean annual temperature from 1948 to 2024.[101]

Although there is no standardized definition of heat exposure, common metrics include heatwaves or extreme heat events, which incorporate both the duration and intensity of heat exposure, temperature exceedance thresholds, typically defined at the 90th or 95th percentiles of

local temperature distribution or absolute temperature cutoffs, and per 1°C increase in ambient temperature within pre-defined temperature percentiles.[102] Similar to $PM_{2.5}$, previous research suggests prenatal heat exposures may negatively influence fetal development through maternal oxidative stress and placental inflammation.[103] Multiple animal studies explored the effects of *in utero* heat stress on cellular immunological functions and reported elevated levels of crucial biomarkers and hormones involved in the regulation of inflammatory responses, including IL-2 and IL-12 cytokines along with adrenocorticotropic hormone.[104–106] In addition, prenatal heat exposure may disrupt the homeostasis of heat shock proteins and impair fetal growth, where animal studies have reported significant adverse effects on cardiac development.[107,108]

While previous studies have found evidence of an association between prenatal heat exposure and CHD, a substantial spatial heterogeneity has been observed in this relationship. This is reflected in a recent meta-analysis published by Krishnakumar and colleagues on the effects of extreme heat events, defined using local temperature percentile thresholds, on CHD risk. Although the pooled OR across eight included studies was 1.12 (95% CI: 1.04, 1.34), high heterogeneity was observed with stronger effects reported in temperate climate zones, with null effect observed in North America.[109] A possible explanation for this conflicting evidence might be attributable to using relative thresholds instead of absolute temperatures for the heat exposure, limiting comparability between countries. Overall, the selection of appropriate heat metrics is highly dependent on the specific regional weather context to ensure meaningful interpretability for public health guidelines.

2.5 Interactive Effects of Wildfires and Heat on CHD

Increasing trends of $PM_{2.5}$ concentrations and extreme temperatures have been observed globally due to climate change during the last several decades.[61,73] Escalated temperatures and

heatwaves lead to more favourable meteorological conditions for lightning events, which are the most prevalent ignition factor for wildfires.[110] Consequently, wildfire and heat events often coincide, posing substantial health hazards. Over the recent years, a growing co-occurrence of wildfire and extreme heat has been found in North America. In western United States, an upward trajectory of coexposure has been observed from 2006 to 2020, where individuals residing in census tracts with higher social vulnerability were more prone to such hazards.[111] Moreover, a Canadian study observed an upward trend in British Columbia, with annual mean co-occurrence days per dissemination area rising from 1.0 day during the period of 2010-2014 to 4.5 days during 2018-2022.[112] This study also reported a notable increase in the magnitude of mean $PM_{2.5}$ concentrations during those two periods, further underscoring the intensifying severity of wildfire events.

While the potential synergistic effects of ambient air pollutants and heat exposure on perinatal outcomes have been explored in previous literature, the impact of wildfire on this interaction is an emerging field of study. A recent case-crossover study conducted by Ha and colleagues in 2024 examined the combined effects of heat and WFS on preterm birth, where higher odds were observed during co-occurrence of WFS $PM_{2.5}$ and extreme heat exposed days (OR_{lag4}: 1.24, 95% CI: 1.19, 1.29).[113] A key biological mechanism underlying this potential interaction between heat and air pollutants involves thermoregulatory responses to high ambient temperature, including elevated ventilation rate, vasodilation and skin permeability.[114,115] These physiological changes can lead to increased uptake of ambient air pollutants and thereby synergistically influence the health of humans. Nonetheless, there is currently a lack of robust evidence on the interactive effects of prenatal exposure to WFS $PM_{2.5}$ and heat on the health of newborns. Given the projected escalation of global temperature anomalies and wildfire activities

driven by climate change,[116] identification of associated health hazards, particularly for the vulnerable population of pregnant individuals, are imperative to strengthen public health preparedness and response for future wildfire seasons.

2.6 References

1. World Health Organization. (2023, February 27). *Congenital disorders*. WHO. https://www.who.int/news-room/fact-sheets/detail/birth-defects

2. Liu, Y., Chen, S., Zühlke, L., Black, G. C., Choy, M., Li, N., & Keavney, B. D. (2019). Global birth prevalence of congenital heart defects 1970–2017: Updated systematic review and meta-analysis of 260 studies. *International Journal of Epidemiology*, *48*(2), 455–463. https://doi.org/10.1093/ije/dyz009

3. Deng, L., Li, Q., & Cheng, Z. (2025). Evaluating the global, regional, and national burden of congenital heart disease in infants younger than 1 year: A 1990–2021 systematic analysis for the GBD study 2021. *Frontiers in Pediatrics*, *13*. https://doi.org/10.3389/fped.2025.1467914

4. Public Health Agency of Canada. (2024, January 16). *Congenital Anomalies in Canada*. Government of Canada. https://health-infobase.canada.ca/congenital-anomalies/data-tool/

5. Better Outcomes Registry & Network Ontario. (2024, February 13). *Research Highlights Health Disparities Related to Congenital Heart Disease and Socioeconomic Status*. BORN Ontario. https://www.bornontario.ca/en/news/research-highlights-health-disparities-related-to-congenital-heart-disease-and-socioeconomic-status.aspx

6. Van Der Bom, T., Zomer, A. C., Zwinderman, A. H., Meijboom, F. J., Bouma, B. J., & Mulder, B. J. M. (2011). The changing epidemiology of congenital heart disease. *Nature Reviews Cardiology*, *8*(1), 50–60. https://doi.org/10.1038/nrcardio.2010.166

7. Krasuski, R. A., & Bashore, T. M. (2016). Congenital Heart Disease Epidemiology in the United States. *Circulation*, *134*(2), 110–113. https://doi.org/10.1161/CIRCULATIONAHA.116.023370

8. Marelli, A. J., Ionescu-Ittu, R., Mackie, A. S., Guo, L., Dendukuri, N., & Kaouache, M. (2014). Lifetime Prevalence of Congenital Heart Disease in the General Population From 2000 to 2010. *Circulation*, *130*(9), 749–756. https://doi.org/10.1161/CIRCULATIONAHA.113.008396

9. Khairy, P., Ionescu-Ittu, R., Mackie, A. S., Abrahamowicz, M., Pilote, L., & Marelli, A. J. (2010). Changing Mortality in Congenital Heart Disease. *JACC*, *56*(14), 1149–1157. https://doi.org/10.1016/j.jacc.2010.03.085

10. Marelli, A. J., Mackie, A. S., Ionescu-Ittu, R., Rahme, E., & Pilote, L. (2007). Congenital Heart Disease in the General Population. *Circulation*, *115*(2), 163–172. https://doi.org/10.1161/CIRCULATIONAHA.106.627224

11. Islam, S., Yasui, Y., Kaul, P., Marelli, A. J., & Mackie, A. S. (2016). Congenital Heart Disease Hospitalizations in Canada: A 10-Year Experience. *Canadian Journal of Cardiology*, *32*(2), 197–203. https://doi.org/10.1016/j.cjca.2015.05.022

12. Zomer, A. C., Ionescu-Ittu, R., Vaartjes, I., Pilote, L., Mackie, A. S., Therrien, J., Langemeijer, M. M., Grobbee, D. E., Mulder, B. J. M., & Marelli, A. J. (2013). Sex Differences in Hospital Mortality in Adults With Congenital Heart Disease: The Impact of Reproductive Health. *Journal of the American College of Cardiology*, *62*(1), 58–67. https://doi.org/10.1016/j.jacc.2013.03.056

13. Verheugt, C. L., Uiterwaal, C. S. P. M., Velde, E. T. van der, Meijboom, F. J., Pieper, P. G., Sieswerda, G. T., Plokker, H. W. M., Grobbee, D. E., & Mulder, B. J. M. (2010). The emerging burden of hospital admissions of adults with congenital heart disease. *Heart*, *96*(11), 872–878. https://doi.org/10.1136/hrt.2009.185595

14. Mackie, A. S., Tran, D. T., Marelli, A. J., & Kaul, P. (2017). Cost of Congenital Heart Disease Hospitalizations in Canada: A Population-Based Study. *Canadian Journal of Cardiology*, *33*(6), 792–798. https://doi.org/10.1016/j.cjca.2017.01.024

15. Moorman, A., Webb, S., Brown, N. A., Lamers, W., & Anderson, R. H. (2003). Development of the Heart: (1) Formation of the Cardiac Chambers and Arterial Trunks. *Heart*, *89*(7), 806–814. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1767747/

16. Singh, Y. (2022). Diagnosis and management of critical congenital heart defects in infants. *Paediatrics and Child Health*, *32*(9), 332–338. https://doi.org/10.1016/j.paed.2022.07.003

17. Kaur, A., Hornberger, L. K., Fruitman, D., Ngwezi, D. P., Chandra, S., & Eckersley, L. G. (2022). Trends in the Prenatal Detection of Major Congenital Heart Disease in Alberta From 2008–2018. *Journal of Obstetrics and Gynaecology Canada*, *44*(8), 895–900. https://doi.org/10.1016/j.jogc.2022.03.020

18. Pavlicek, J., Klaskova, E., Kapralova, S., Palatova, A. M., Piegzova, A., Spacek, R., & Gruszka, T. (2021). Major heart defects: The diagnostic evaluations of first-year-olds. *BMC Pediatrics*, *21*, 528. https://doi.org/10.1186/s12887-021-02997-2

19. Public Health Agency of Canada. (2024, May 15). *Provincial and Territorial Congenital Anomalies Surveillance: A summary of surveillance programs across Canada, HPCDP: Vol 44(5), May 2024*. Government of Canada. https://www.canada.ca/en/public-health/services/reports-publications/health-promotion-chronic-disease-prevention-canada-research-policy-practice/vol-44-no-5-2024/provincial-territorial-congenital-anomalies-surveillance-summary-surveillance-programs.html

20. van der Linde, D., Konings, E. E. M., Slager, M. A., Witsenburg, M., Helbing, W. A., Takkenberg, J. J. M., & Roos-Hesselink, J. W. (2011). Birth Prevalence of Congenital

Heart Disease Worldwide. *JACC*, *58*(21), 2241–2247. https://doi.org/10.1016/j.jacc.2011.08.025

21. Alahmadi, M. H., & Oliver, T. I. (2025). Ventricular Septal Defect. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK470330/

22. Menillo, A. M., Alahmadi, M. H., & Pearson-Shaver, A. L. (2025). Atrial Septal Defect. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK535440/

23. Blue, G. M., Kirk, E. P., Sholler, G. F., Harvey, R. P., & Winlaw, D. S. (2012). Congenital heart disease: Current knowledge about causes and inheritance. *The Medical Journal of Australia*, *197*(3), 155–159. https://doi.org/10.5694/mja12.10811

24. Choudhury, T., Gilbert, B., & Garg, V. (2025). Genetic and Environmental Contributors To Congenital Heart Disease. *Current Treatment Options in Cardiovascular Medicine*, *27*. https://doi.org/10.1007/s11936-025-01091-5

25. Hartman, R. J., Rasmussen, S. A., Botto, L. D., Riehle-Colarusso, T., Martin, C. L., Cragan, J. D., Shin, M., & Correa, A. (2011). The Contribution of Chromosomal Abnormalities to Congenital Heart Defects: A Population-Based Study. *Pediatric Cardiology*, *32*(8), 1147–1157. https://doi.org/10.1007/s00246-011-0034-5

26. Richards, A. A., & Garg, V. (2010). Genetics of Congenital Heart Disease. *Current Cardiology Reviews*, *6*(2), 91–97. https://doi.org/10.2174/157340310791162703

27. Bruneau, B. G. (2013). Signaling and Transcriptional Networks in Heart Development and Regeneration. *Cold Spring Harbor Perspectives in Biology*, *5*(3), a008292. https://doi.org/10.1101/cshperspect.a008292

28. Jing-bin, H., Ying-long, L., Pei-wu, S., Xiao-dong, L., Ming, D., & Xiang-ming, F. (2010). Molecular mechanisms of congenital heart disease. *Cardiovascular Pathology*, *19*(5), e183–e193. https://doi.org/10.1016/j.carpath.2009.06.008

29. Fahed, A. C., Gelb, B. D., Seidman, J. G., & Seidman, C. E. (2013). Genetics of Congenital Heart Disease. *Circulation Research*, *112*(4), 707–720. https://doi.org/10.1161/CIRCRESAHA.112.300853

30. Simmons, M. A., & Brueckner, M. (2017). The Genetics of Congenital Heart Disease…Understanding and Improving Long Term Outcomes in Congenital Heart Disease: A Review for the General Cardiologist and Primary Care Physician. *Current Opinion in Pediatrics*, *29*(5), 520–528. https://doi.org/10.1097/MOP.0000000000000538

31. Jin, S. C., Homsy, J., Zaidi, S., Lu, Q., Morton, S., DePalma, S. R., Zeng, X., Qi, H., Chang, W., Sierant, M. C., Hung, W.-C., Haider, S., Zhang, J., Knight, J., Bjornson, R. D., Castaldi, C., Tikhonoa, I. R., Bilguvar, K., Mane, S. M., … Brueckner, M. (2017).

Contribution of rare inherited and de novo variants in 2,871 congenital heart disease probands. *Nature Genetics*, *49*(11), 1593–1601. https://doi.org/10.1038/ng.3970

32. Homsy, J., Zaidi, S., Shen, Y., Ware, J. S., Samocha, K. E., Karczewski, K. J., DePalma, S. R., McKean, D., Wakimoto, H., Gorham, J., Jin, S. C., Deanfield, J., Giardini, A., Porter, G. A., Kim, R., Bilguvar, K., López-Giráldez, F., Tikhonova, I., Mane, S., … Chung, W. K. (2015). De novo mutations in congenital heart disease with neurodevelopmental and other congenital anomalies. *Science*, *350*(6265), 1262–1266. https://doi.org/10.1126/science.aac9396

33. Helle, E., & Priest, J. R. (2020). Maternal Obesity and Diabetes Mellitus as Risk Factors for Congenital Heart Disease in the Offspring. *Journal of the American Heart Association*, *9*(8), e011541. https://doi.org/10.1161/JAHA.119.011541

34. Jones, H. N., Jansson, T., & Powell, T. L. (2010). Full-Length Adiponectin Attenuates Insulin Signaling and Inhibits Insulin-Stimulated Amino Acid Transport in Human Primary Trophoblast Cells. *Diabetes*, *59*(5), 1161–1170. https://doi.org/10.2337/db09-0824

35. Hedermann, G., Hedley, P. L., Thagaard, I. N., Krebs, L., Ekelund, C. K., Sørensen, T. I., & Christiansen, M. (2021). *Maternal obesity and metabolic disorders associate with congenital heart defects in the offspring: A systematic review* (p. 2020.06.25.20140186). medRxiv. https://doi.org/10.1101/2020.06.25.20140186

36. Chou, H.-H., Chiou, M.-J., Liang, F.-W., Chen, L.-H., Lu, T.-H., & Li, C.-Y. (2016). Association of maternal chronic disease with risk of congenital heart disease in offspring. *CMAJ*, *188*(17–18), E438–E446. https://doi.org/10.1503/cmaj.160061

37. Khalilipalandi, S., Lemieux, A., Lauzon-Schnittka, J., Perreault, L., Dubois, M., Tousignant, A., Watelle, L., Pratte, G., & Dallaire, F. (2024). Systematic Review and Meta-analysis of Prenatal Risk Factors for Congenital Heart Disease: Part 1, Maternal Chronic Diseases and Parental Exposures. *Canadian Journal of Cardiology*, *40*(12), 2476–2495. https://doi.org/10.1016/j.cjca.2024.07.004

38. Lewi, L., Deprest, J., & Hecher, K. (2013). The vascular anastomoses in monochorionic twin pregnancies and their clinical consequences. *American Journal of Obstetrics & Gynecology*, *208*(1), 19–30. https://doi.org/10.1016/j.ajog.2012.09.025

39. Grisaru-Granovsky, S., Gordon, E.-S., Haklai, Z., Samueloff, A., & Schimmel, M. M. (2009). Effect of interpregnancy interval on adverse perinatal outcomes—A national study. *Contraception*, *80*(6), 512–518. https://doi.org/10.1016/j.contraception.2009.06.006

40. Feng, Y., Yu, D., Chen, T., Liu, J., Tong, X., Yang, L., Da, M., Shen, S., Fan, C., Wang, S., & Mo, X. (2014). Maternal Parity and the Risk of Congenital Heart Defects in

Offspring: A Dose-Response Meta-Analysis of Epidemiological Observational Studies. *PLoS ONE*, *9*(10), e108944. https://doi.org/10.1371/journal.pone.0108944

41. Penman-Aguilar, A., Talih, M., Huang, D., Moonesinghe, R., Bouye, K., & Beckles, G. (2016). Measurement of Health Disparities, Health Inequities, and Social Determinants of Health to Support the Advancement of Health Equity. *Journal of Public Health Management and Practice*, *22*(Supplement 1), S33–S42. https://doi.org/10.1097/PHH.0000000000000373

42. Pérez-Stable, E. J., & Webb Hooper, M. (2023). The Pillars of Health Disparities Science—Race, Ethnicity, and Socioeconomic Status. *JAMA Health Forum*, *4*(12), e234463. https://doi.org/10.1001/jamahealthforum.2023.4463

43. Shavers, V. L. (2007). Measurement of socioeconomic status in health disparities research. *Journal of the National Medical Association*, *99*(9), 1013–1023. https://pmc.ncbi.nlm.nih.gov/articles/PMC2575866/

44. Smith, C., Olugbuyi, O., Kaul, P., Dover, D. C., Mackie, A. S., Islam, S., Eckersley, L., & Hornberger, L. K. (2024). Lower Socioeconomic Status is Associated with an Increased Incidence and Spectrum of Major Congenital Heart Disease and Associated Extracardiac Pathology. *Pediatric Cardiology*, *45*(2), 433–440. https://doi.org/10.1007/s00246-023-03310-x

45. Miao, Q., Dunn, S., Wen, S. W., Lougheed, J., Yang, P., Davies, M., Venegas, C. L., & Walker, M. (2023). Association between maternal marginalization and infants born with congenital heart disease in Ontario Canada. *BMC Public Health*, *23*(1), 790. https://doi.org/10.1186/s12889-023-15660-5

46. Adams Waldorf, K. M., & McAdams, R. M. (2013). Influence of Infection During Pregnancy on Fetal Development. *Reproduction (Cambridge, England)*, *146*(5), R151–R162. https://doi.org/10.1530/REP-13-0232

47. Ward, E. J., Bert, S., Fanti, S., Malone, K. M., Maughan, R. T., Gkantsinikoudi, C., Prin, F., Volpato, L. K., Piovezan, A. P., Graham, G. J., Dufton, N. P., Perretti, M., Marelli-Berg, F. M., & Nadkarni, S. (2023). Placental Inflammation Leads to Abnormal Embryonic Heart Development. *Circulation*, *147*(12), 956–972. https://doi.org/10.1161/CIRCULATIONAHA.122.061934

48. Megli, C. J., & Coyne, C. B. (2022). Infections at the maternal–fetal interface: An overview of pathogenesis and defence. *Nature Reviews. Microbiology*, *20*(2), 67–82. https://doi.org/10.1038/s41579-021-00610-y

49. Wang, T., Li, Q., Chen, L., Ni, B., Sheng, X., Huang, P., Zhang, S., & Qin, J. (2022). Maternal Viral Infection in Early Pregnancy and Risk of Congenital Heart Disease in

Offspring: A Prospective Cohort Study in Central China. *Clinical Epidemiology*, *14*, 71–82. https://doi.org/10.2147/CLEP.S338870

50. Liu, S., Liu, J., Tang, J., Ji, J., Chen, J., & Liu, C. (2009). Environmental Risk Factors for Congenital Heart Disease in the Shandong Peninsula, China: A Hospital-based Case–Control Study. *Journal of Epidemiology*, *19*(3), 122–130. https://doi.org/10.2188/jea.JE20080039

51. Ross, E. J., Graham, D. L., Money, K. M., & Stanwood, G. D. (2015). Developmental Consequences of Fetal Exposure to Drugs: What We Know and What We Still Must Learn. *Neuropsychopharmacology*, *40*(1), 61–87. https://doi.org/10.1038/npp.2014.147

52. Cheng, W., Zhou, R., Feng, Y., & Wang, Y. (2016). Mainstream smoke and sidestream smoke affect the cardiac differentiation of mouse embryonic stem cells discriminately. *Toxicology*, *357–358*, 1–10. https://doi.org/10.1016/j.tox.2016.05.017

53. Jiang, X.-Y., Feng, Y.-L., Ye, L.-T., Li, X.-H., Feng, J., Zhang, M.-Z., Shelat, H. S., Wassler, M., Li, Y., Geng, Y.-J., & Yu, X.-Y. (2017). Inhibition of Gata4 and Tbx5 by Nicotine-Mediated DNA Methylation in Myocardial Differentiation. *Stem Cell Reports*, *8*(2), 290–304. https://doi.org/10.1016/j.stemcr.2016.12.016

54. Karunamuni, G., Gu, S., Doughman, Y. Q., Peterson, L. M., Mai, K., McHale, Q., Jenkins, M. W., Linask, K. K., Rollins, A. M., & Watanabe, M. (2014). Ethanol exposure alters early cardiac function in the looping heart: A mechanism for congenital heart defects? *American Journal of Physiology-Heart and Circulatory Physiology*, *306*(3), H414–H421. https://doi.org/10.1152/ajpheart.00600.2013

55. Zhao, L., Chen, L., Yang, T., Wang, L., Wang, T., Zhang, S., Chen, L., Ye, Z., Zheng, Z., & Qin, J. (2020). Parental smoking and the risk of congenital heart defects in offspring: An updated meta-analysis of observational studies. *European Journal of Preventive Cardiology*, *27*(12), 1284–1293. https://doi.org/10.1177/2047487319831367

56. Zhang, S., Wang, L., Yang, T., Chen, L., Zhao, L., Wang, T., Chen, L., Ye, Z., Zheng, Z., & Qin, J. (2020). Parental alcohol consumption and the risk of congenital heart diseases in offspring: An updated systematic review and meta-analysis. *European Journal of Preventive Cardiology*, *27*(4), 410–421. https://doi.org/10.1177/2047487319874530

57. Fowler, D., Brimblecombe, P., Burrows, J., Heal, M. R., Grennfelt, P., Stevenson, D. S., Jowett, A., Nemitz, E., Coyle, M., Liu, X., Chang, Y., Fuller, G. W., Sutton, M. A., Klimont, Z., Unsworth, M. H., & Vieno, M. (2020). A chronology of global air quality. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*, *378*(2183), 20190314. https://doi.org/10.1098/rsta.2019.0314

58. Gorini, F., & Tonacci, A. (2025). Ambient Air Pollution and Congenital Heart Disease: Updated Evidence and Future Challenges. *Antioxidants*, *14*(1), 48. https://doi.org/10.3390/antiox14010048

59. Huang, C., Chen, B., Pan, S., Ho, Y., & Guo, Y. L. (2019). Prenatal exposure to PM2.5 and Congenital Heart Diseases in Taiwan. *Science of The Total Environment*, *655*, 880–886. https://doi.org/10.1016/j.scitotenv.2018.11.284

60. Stingone, J. A., Luben, T. J., Daniels, J. L., Fuentes, M., Richardson, D. B., Aylsworth, A. S., Herring, A. H., Anderka, M., Botto, L., Correa, A., Gilboa, S. M., Langlois, P. H., Mosley, B., Shaw, G. M., Siffel, C., Olshan, A. F., & the National Birth Defects Prevention Study. (2014). Maternal Exposure to Criteria Air Pollutants and Congenital Heart Defects in Offspring: Results from the National Birth Defects Prevention Study. *Environmental Health Perspectives*, *122*(8), 863–872. https://doi.org/10.1289/ehp.1307289

61. United Nations. (n.d.). *1.5°C: What it means and why it matters*. United Nations. United Nations. https://www.un.org/en/climatechange/science/climate-issues/degrees-matter

62. Environment and Climate Change Canada. (2016, April 28). *Temperature change in Canada*. https://www.canada.ca/en/environment-climate-change/services/environmental-indicators/temperature-change.html

63. Nyadanu, S. D., Dunne, J., Tessema, G. A., Mullins, B., Kumi-Boateng, B., Bell, M. L., Duko, B., & Pereira, G. (2024). Maternal exposure to ambient air temperature and adverse birth outcomes: An umbrella review of systematic reviews and meta-analyses. *Science of The Total Environment*, *917*, 170236. https://doi.org/10.1016/j.scitotenv.2024.170236

64. Ferguson, K. K., Kamai, E. M., Cantonwine, D. E., Mukherjee, B., Meeker, J. D., & McElrath, T. F. (2018). Associations between repeated ultrasound measures of fetal growth and biomarkers of maternal oxidative stress and inflammation in pregnancy. *American Journal of Reproductive Immunology (New York, N.Y. : 1989)*, *80*(4), e13017. https://doi.org/10.1111/aji.13017

65. Lin, S., Lin, Z., Ou, Y., Soim, A., Shrestha, S., Lu, Y., Sheridan, S., Luben, T. J., Fitzgerald, E., Bell, E., Shaw, G. M., Reefhuis, J., Langlois, P. H., Romitti, P., Feldkamp, M. L., Malik, S., Pantea, C., Nayak, S., Hwang, S.-A., & Browne, M. (2018). Maternal ambient heat exposure during early pregnancy in summer and spring and congenital heart defects – A large US population-based, case-control study. *Environment International*, *118*, 211–221. https://doi.org/10.1016/j.envint.2018.04.043

66. Xu, W., Li, D., Shao, Z., You, Y., Pan, F., Lou, H., Li, J., Jin, Y., Wu, T., Pan, L., An, J., Xu, J., Cheng, W., Tao, L., Lei, Y., Huang, C., & Shu, Q. (2023). The prenatal weekly temperature exposure and neonatal congenital heart disease: A large population-based

observational study in China. *Environmental Science and Pollution Research International*, *30*(13), 38282–38291. https://doi.org/10.1007/s11356-022-24396-5

67. United Nations Office for Disaster Risk Reduction (UNDRR), & International Science Council (ISC). (2025). *UNDRR–ISC Hazard Information Profiles – 2025 Update: OUTDOOR Ambient*. United Nations Office for Disaster Risk Reduction. https://www.undrr.org/understanding-disaster-risk/terminology/hips/en0103

68. Manisalidis, I., Stavropoulou, E., Stavropoulos, A., & Bezirtzoglou, E. (2020). Environmental and Health Impacts of Air Pollution: A Review. *Frontiers in Public Health*, *8*. https://doi.org/10.3389/fpubh.2020.00014

69. Environment and Climate Change Canada. (2021, April 28). *About the Air Quality Health Index*. Government of Canada. https://www.canada.ca/en/environment-climate-change/services/air-quality-health-index/about.html

70. Environment and Climate Change Canada. (2024). *Canadian environmental sustainability indicators: Air quality*. www.canada.ca/en/environment-climate-change/services/environmental-indicators/air-quality.html

71. United States Environmental Protection Agency. (2016, April 19). *Particulate Matter (PM) Basics* [Overviews and Factsheets]. https://www.epa.gov/pm-pollution/particulate-matter-pm-basics

72. Environment and Climate Change Canada. (2025). *Canadian Environmental Sustainability Indicators: Air pollutant emissions*. http://www.canada.ca/en/environment-climate-change/services/environmental-indicators/air-pollutant-emissions.html

73. Yu, W., Ye, T., Zhang, Y., Xu, R., Lei, Y., Chen, Z., Yang, Z., Zhang, Y., Song, J., Yue, X., Li, S., & Guo, Y. (2023). Global estimates of daily ambient fine particulate matter concentrations and unequal spatiotemporal distribution of population exposure: A machine learning modelling study. *The Lancet Planetary Health*, *7*(3), e209–e218. https://doi.org/10.1016/S2542-5196(23)00008-6

74. Environment and Climate Change Canada. (2024). *Canadian Environmental Sustainability Indicators: International comparison : air pollutant emissions in selected countries*. Environment and Climate Change Canada = Environnement et changement climatique Canada. https://www.canada.ca/en/environment-climate-change/services/environmental-indicators/international-comparison-air-pollutant-emissions.html

75. Groß, S., Esselborn, M., Weinzierl, B., Wirth, M., Fix, A., & Petzold, A. (2013). Aerosol classification by airborne high spectral resolution lidar observations. *Atmospheric Chemistry and Physics*, *13*(5), 2487–2505. https://doi.org/10.5194/acp-13-2487-2013

76. Vicente, A., Alves, C., Calvo, A. I., Fernandes, A. P., Nunes, T., Monteiro, C., Almeida, S. M., & Pio, C. (2013). Emission factors and detailed chemical composition of smoke particles from the 2010 wildfire season. *Atmospheric Environment*, *71*, 295–303. https://doi.org/10.1016/j.atmosenv.2013.01.062

77. Krasovich Southworth, E., Qiu, M., Gould, C. F., Kawano, A., Wen, J., Heft-Neal, S., Kilpatrick Voss, K., Lopez, A., Fendorf, S., Burney, J. A., & Burke, M. (2025). The Influence of Wildfire Smoke on Ambient PM2.5 Chemical Species Concentrations in the Contiguous US. *Environmental Science & Technology*, *59*(6), 2961–2973. https://doi.org/10.1021/acs.est.4c09011

78. Spracklen, D. V., Logan, J. A., Mickley, L. J., Park, R. J., Yevich, R., Westerling, A. L., & Jaffe, D. A. (2007). Wildfires drive interannual variability of organic carbon aerosol in the western U.S. in summer. *Geophysical Research Letters*, *34*(16). https://doi.org/10.1029/2007GL030037

79. Xu, R., Yu, P., Abramson, M. J., Johnston, F. H., Samet, J. M., Bell, M. L., Haines, A., Ebi, K. L., Li, S., & Guo, Y. (2020). Wildfires, Global Climate Change, and Human Health. *New England Journal of Medicine*, *383*(22), 2173–2181. https://doi.org/10.1056/NEJMsr2028985

80. Sparks, T. L., & Wagner, J. (2021). Composition of particulate matter during a wildfire smoke episode in an urban area. *Aerosol Science and Technology*, *55*(6), 734–747. https://doi.org/10.1080/02786826.2021.1895429

81. Kim, Y. H., Warren, S. H., Krantz, Q. T., King, C., Jaskot, R., Preston, W. T., George, B. J., Hays, M. D., Landis, M. S., Higuchi, M., DeMarini, D. M., & Gilmour, M. I. (2018). Mutagenicity and Lung Toxicity of Smoldering vs. Flaming Emissions from Various Biomass Fuels: Implications for Health Effects from Wildland Fires. *Environmental Health Perspectives*, *126*(1), 017011. https://doi.org/10.1289/EHP2200

82. Wegesser, T. C., Pinkerton, K. E., & Last, J. A. (2009). California Wildfires of 2008: Coarse and Fine Particulate Matter Toxicity. *Environmental Health Perspectives*, *117*(6), 893–897. https://doi.org/10.1289/ehp.0800166

83. Aguilera, R., Corringham, T., Gershunov, A., & Benmarhnia, T. (2021). Wildfire smoke impacts respiratory health more than fine particles from other sources: Observational evidence from Southern California. *Nature Communications*, *12*(1), 1493. https://doi.org/10.1038/s41467-021-21708-0

84. Chen, G., Guo, Y., Yue, X., Tong, S., Gasparrini, A., Bell, M. L., Armstrong, B., Schwartz, J., Jaakkola, J. J. K., Zanobetti, A., Lavigne, E., Saldiva, P. H. N., Kan, H., Royé, D., Milojevic, A., Overcenco, A., Urban, A., Schneider, A., Entezari, A., … Li, S. (2021). Mortality risk attributable to wildfire-related PM2·5 pollution: A global time

series study in 749 locations. *The Lancet Planetary Health*, *5*(9), e579–e587. https://doi.org/10.1016/S2542-5196(21)00200-X

85. Jegasothy, E., Hanigan, I. C., Van Buskirk, J., Morgan, G. G., Jalaludin, B., Johnston, F. H., Guo, Y., & Broome, R. A. (2023). Acute health effects of bushfire smoke on mortality in Sydney, Australia. *Environment International*, *171*, 107684. https://doi.org/10.1016/j.envint.2022.107684

86. Becker, S., Dailey, L. A., Soukup, J. M., Grambow, S. C., Devlin, R. B., & Huang, Y.-C. T. (2005). Seasonal Variations in Air Pollution Particle-Induced Inflammatory Mediator Release and Oxidative Stress. *Environmental Health Perspectives*, *113*(8), 1032–1038. https://doi.org/10.1289/ehp.7996

87. Chiarello, D. I., Ustáriz, J., Marín, R., Carrasco-Wong, I., Farías, M., Giordano, A., Gallardo, F. S., Illanes, S. E., & Gutiérrez, J. (2023). Cellular mechanisms linking to outdoor and indoor air pollution damage during pregnancy. *Frontiers in Endocrinology*, *14*. https://doi.org/10.3389/fendo.2023.1084986

88. Craig, E. A., Lin, Y., Ge, Y., Wang, X., Murphy, S. K., Harrington, D. K., Miller, R. K., Thurston, S. W., Hopke, P. K., Barrett, E. S., O'Connor, T. G., Rich, D. Q., & Zhang, J. (2024). Associations of Gestational Exposure to Air Pollution and Polycyclic Aromatic Hydrocarbons with Placental Inflammation. *Environment & Health*, *2*(9), 672–680. https://doi.org/10.1021/envhealth.4c00077

89. Meng, Q., Liu, J., Shen, J., Del Rosario, I., Janzen, C., Devaskar, S. U., Lakey, P. S. J., Shiraiwa, M., Weichenthal, S., Zhu, Y., Oroumiyeh, F., Banerjee, S., Paulson, S. E., Jerrett, M., Paul, K. C., & Ritz, B. (2024). Ambient exposure to fine particulate matter with oxidative potential affects oxidative stress biomarkers in pregnancy. *American Journal of Epidemiology*, *194*(1), 27–34. https://doi.org/10.1093/aje/kwae152

90. Marsal, A., Sauvain, J.-J., Thomas, A., Lyon-Caen, S., Borlaza, L. J. S., Philippat, C., Jaffrezo, J.-L., Boudier, A., Darfeuil, S., Elazzouzi, R., Lepeule, J., Chartier, R., Bayat, S., Slama, R., Siroux, V., & Uzu, G. (2024). Effects of personal exposure to the oxidative potential of PM2.5 on oxidative stress biomarkers in pregnant women. *Science of The Total Environment*, *911*, 168475. https://doi.org/10.1016/j.scitotenv.2023.168475

91. Thangavel, P., Park, D., & Lee, Y.-C. (2022). Recent Insights into Particulate Matter (PM2.5)-Mediated Toxicity in Humans: An Overview. *International Journal of Environmental Research and Public Health*, *19*(12), 7511. https://doi.org/10.3390/ijerph19127511

92. Gangwar, R. S., Bevan, G. H., Palanivel, R., Das, L., & Rajagopalan, S. (2020). Oxidative stress pathways of air pollution mediated toxicity: Recent insights. *Redox Biology*, *34*, 101545. https://doi.org/10.1016/j.redox.2020.101545

93. Vilas-Boas, V., Chatterjee, N., Carvalho, A., & Alfaro-Moreno, E. (2024). Particulate matter-induced oxidative stress – Mechanistic insights and antioxidant approaches reported in in vitro studies. *Environmental Toxicology and Pharmacology*, *110*, 104529. https://doi.org/10.1016/j.etap.2024.104529

94. Amjad, S., Chojecki, D., Osornio-Vargas, A., & Ospina, M. B. (2021). Wildfire exposure during pregnancy and the risk of adverse birth outcomes: A systematic review. *Environment International*, *156*, 106644. https://doi.org/10.1016/j.envint.2021.106644

95. Foo, D., Stewart, R., Heo, S., Dhamrait, G., Choi, H. M., Song, Y., & Bell, M. L. (2024). Wildfire smoke exposure during pregnancy and perinatal, obstetric, and early childhood health outcomes: A systematic review and meta-analysis. *Environmental Research*, *241*, 117527. https://doi.org/10.1016/j.envres.2023.117527

96. Requia, W. J., Kill, E., Papatheodorou, S., Koutrakis, P., & Schwartz, J. D. (2022). Prenatal exposure to wildfire-related air pollution and birth defects in Brazil. *Journal of Exposure Science & Environmental Epidemiology*, *32*(4), 596–603. https://doi.org/10.1038/s41370-021-00380-y

97. Park, B. Y., Vedhanayagam, K., Ortiz-Luis, J., Basu, R., Gheorghe, C. P., Govindappagari, S., Abinader, R., & Yao, R. (2025). Living Near Wildfires and the Risk of Fetal Congenital Heart Defects: Evaluating Critical Windows of Vulnerability. *AJP Reports*, *15*(1), e18–e24. https://doi.org/10.1055/a-2528-3588

98. Padula, A. M., Mayo, J. A., Lurmann, F. W., Pavlovic, N. R., & Shaw, G. M. (2026). Wildland fire smoke and birth defects in California. *Journal of Exposure Science & Environmental Epidemiology*. https://doi.org/10.1038/s41370-026-00885-4

99. Bush, E., Gillett, N., Watson, E., Fyfe, J., Vogel, F., & Swart, N. (2019). *Understanding Observed Global Climate Change; Chapter 2 in Canada's Changing Climate Report* (pp. 24–72). Government of Canada.

100. *IPCC, 2014: Climate Change 2014: Synthesis Report. Contribution of Working Groups I, II and III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change*. (2014). Intergovernmental Panel on Climate Change.

101. Environment and Climate Change Canada. (2025, July 31). *Temperature change in Canada*. Government of Canada. https://www.canada.ca/en/environment-climate-change/services/environmental-indicators/temperature-change.html

102. Chersich, M. F., Pham, M. D., Areal, A., Haghighi, M. M., Manyuchi, A., Swift, C. P., Wernecke, B., Robinson, M., Hetem, R., Boeckmann, M., Hajat, S., Nakstad, B., Wright, C. Y., Harvey, C., Wang, C., Durusu, D., Scorgie, F., Rees, H., Harden, L., … Roux, T. (2020). Associations between high temperatures in pregnancy and risk of preterm birth,

low birth weight, and stillbirths: Systematic review and meta-analysis. *The BMJ*, *371*, m3811. https://doi.org/10.1136/bmj.m3811

103. Konkel, L. (2019). Taking the Heat: Potential Fetal Health Effects of Hot Temperatures. *Environmental Health Perspectives*, *127*(10), 102002. https://doi.org/10.1289/EHP6221

104. Wang, L., Liu, F., Luo, Y., Zhu, L., & Li, G. (2015). Effect of acute heat stress on adrenocorticotropic hormone, cortisol, interleukin-2, interleukin-12 and apoptosis gene expression in rats. *Biomedical Reports*, *3*(3), 425–429. https://doi.org/10.3892/br.2015.445

105. Han, A. Y., Zhang, M. H., Zuo, X. L., Zheng, S. S., Zhao, C. F., Feng, J. H., & Cheng, C. (2010). Effect of acute heat stress on calcium concentration, proliferation, cell cycle, and interleukin-2 production in splenic lymphocytes from broiler chickens. *Poultry Science*, *89*(10), 2063–2070. https://doi.org/10.3382/ps.2010-00715

106. Popovska-Perčinić, F., Manojlović-Stojanoski, M., Pendovski, L., Dinevska Kjovkarovska, S., Miova, B., Grubin, J., Milošević, V., & Ajdžanović, V. (2021). A Moderate Increase in Ambient Temperature Influences The Structure and Hormonal Secretion of Adrenal Glands in Rats. *Cell Journal (Yakhteh)*, *22*(4), 415–424. https://doi.org/10.22074/cellj.2021.6827

107. Hanafi, S. A., Zulkifli, I., Ramiah, S. K., Chung, E. L. T., Awad, E. A., & Sazili, A. Q. (2022). Prenatal thermal stress affects acute-phase proteins, heat shock protein 70, and circulating corticosterone in developing broiler embryos and neonates. *Journal of Thermal Biology*, *109*, 103328. https://doi.org/10.1016/j.jtherbio.2022.103328

108. Xie, J., Tang, L., Lu, L., Zhang, L., Xi, L., Liu, H.-C., Odle, J., & Luo, X. (2014). Differential Expression of Heat Shock Transcription Factors and Heat Shock Proteins after Acute and Chronic Heat Stress in Laying Chickens (Gallus gallus). *PLOS ONE*, *9*(7), e102204. https://doi.org/10.1371/journal.pone.0102204

109. Krishnakumar, M., Hari, A., Gutjahr, G., Bendapudi, P., Ahamed, H., Prabhakaran, P., Kumar, R. K., & Raj, M. (2024). Impact of exposure to extreme heat events during pregnancy on the incidence of congenital heart disease in offspring: A meta-analysis. *BMJ Paediatrics Open*, *8*(1), e002848. https://doi.org/10.1136/bmjpo-2024-002848

110. Pérez-Invernón, F. J., Gordillo-Vázquez, F. J., Huntrieser, H., & Jöckel, P. (2023). Variation of lightning-ignited wildfire patterns under climate change. *Nature Communications*, *14*(1), 739. https://doi.org/10.1038/s41467-023-36500-5

111. Hu, J. K., Trišović, A., Bakshi, A., Braun, D., Dominici, F., & Casey, J. A. (2025). Coexposure to extreme heat, wildfire burn zones, and wildfire smoke in the Western US from 2006 to 2020. *Science Advances*, *11*(18), eadq6453. https://doi.org/10.1126/sciadv.adq6453

112. Cleland, S. E., Paul, N., Coker, E. S., & Henderson, S. B. (2025). The Co-occurrence of Wildfire Smoke and Extreme Heat Events in British Columbia, 2010–2022: Evaluating Spatiotemporal Trends and Inequities in Exposure Burden. *ACS ES&T Air*, *2*(3), 319–330. https://doi.org/10.1021/acsestair.4c00219

113. Ha, S., Abatzoglou, J. T., Adebiyi, A., Ghimire, S., Martinez, V., Wang, M., & Basu, R. (2024). Impacts of heat and wildfire on preterm birth. *Environmental Research*, *252*, 119094. https://doi.org/10.1016/j.envres.2024.119094

114. Grigorieva, E., & Lukyanets, A. (2021). Combined Effect of Hot Weather and Outdoor Air Pollution on Respiratory Health: Literature Review. *Atmosphere*, *12*(6), 790. https://doi.org/10.3390/atmos12060790

115. Castro, E., Healy, J., Liu, A., Wei, Y., Kosheleva, A., & Schwartz, J. (2025). Interactive effects between extreme temperatures and PM2.5 on cause-specific mortality in thirteen U.S. states. *Environmental Research Letters*, *20*(1), 014011. https://doi.org/10.1088/1748-9326/ad97d1

116. Popescu, A., Paulson, A., Christianson, A., Sullivan, A., Tulloch, A., Bilbao, B., Mathison, C., Robinson, C., Ganz, D., Nangoma, D., Saah, D., Armenteras, D., Driscoll, D., Hankins, D., Kelley, D., Langer, E., Baker, E., Reisen, F., Robinne, F.-N., … Charlton, V. (2022). *Spreading like wildfire: The rising threat of extraordinary landscape fires—A rapid response assessment* (A. Sullivan, E. Baker, & T. Kurvits, Eds.). United Nations Environment Program (UNEP). USGS Publications Warehouse. https://pubs.usgs.gov/publication/70243263

Chapter 3. Data Sources and Study Cohort

3.1 Data Sources

This thesis includes a population-based retrospective cohort study composed of singleton live births in Canada from 2013 to 2021, excluding the province of Quebec. The study cohort was computed through linkage of various health administrative datasets and environmental data accessed through Statistics Canada, the central statistical agency that is responsible for governing vital social and economic data for provinces and territories of Canada.[1]

3.1.1 Canadian Vital Statistics Database (CVSD)

The primary source cohort included mother-infant pairs registered in the Canadian Vital Statistics Birth Database (CVSBD). The CVSBD is an administrative database regulated by Statistics Canada, which extracts birth-related data collected from Vital Statistics Registries at both provincial and territorial levels across Canada.[2] The following information reported in CVSBD was obtained for analysis: date of birth of infants, infant sex, birth weight, pregnancy duration of infants at birth, multiple births, maternal age, maternal place of residence, and parity. The maternal place of residence at birth was recorded as a six-character postal code, allowing the individuals to be linked with the associated regional environmental and social characteristics.

Moreover, the Canadian Vital Statistics Death Database (CVSDD) was utilized to capture death records of infants, where the reported date of death was incorporated into the calculation of the follow-up period of the study cohort. The CVSDD, similar to the CVSBD, collects death-related data of the individuals across Canada through Vital Statistics Registries.[3]

3.1.2 Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD)

The Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) is a health administrative database, which directly collects clinical and demographic data of hospital discharge records from regional health authorities across Canada, with the exception of Quebec.[4] It classifies and records clinical procedures and diagnoses through the usage of standardized codes including International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada (ICD-10-CA) and Canadian Classification of Health Interventions (CCI).[4] The records of DADs were available for both the mothers and infants, allowing extraction of relevant medical conditions. The outcome of CHD cases and its subtypes, chromosomal abnormalities, as well as information on different maternal comorbidities were identified through the following ICD-10-CA codes listed below (Table 3.1).

Table 3.1. List of ICD-10-CA codes used for identification of medical conditions.

Medical conditions	ICD-10-CA code
Congenital heart defect (CHD)	Q20-Q26
Atrial septal defect (ASD)	Q21.1
Ventricular septal defect (VSD)	Q21.0
Chromosomal abnormalities	Q90-Q99
Pre-existing maternal diabetes mellitus	O24.5, O24.6, O24.7
Pre-existing maternal hypertension	O10

3.1.3 T1 Family File (T1FF) and Postal Code Conversion File (PCCF)

Postal Code Conversion File (PCCF), which consists of records of six-character postal codes across Canada and their associated dissemination areas (DAs) and forward sortation areas (FSAs) were obtained from Statistics Canada. FSAs are geographical units defined by the first three characters of postal codes, with 1,669 FSAs recorded across Canada according to the 2021

Census,[5] whereas DAs are the smallest census geographic unit, composed of an average population of 400-700 individuals.[6] The PCCF was utilized to assign DAs and FSAs corresponding to the maternal codes within the cohort for further linkage with the exposures and relevant neighbourhood-level SES characteristics, along with classification of the rurality of each postal code according to Statistics Canada definitions.

In addition, T1 Family file (T1FF), which contains income related data from T1 Income Tax and Benefit Return forms received from Canada Revenue Agency (CRA), was obtained from Statistics Canada. Three-year history of maternal residential addresses, documented using a six-character postal code, were extracted from the following files to construct maternal residential history. These records were an essential requirement for the assignment of $PM_{2.5}$ exposures, where this information was then utilized to determine the baseline exposure level for each mother-infant pair.

3.1.4 All-source, WFS and Non-WFS $PM_{2.5}$ Data

Data on all-source $PM_{2.5}$ exposure during preconception and pregnancy were derived using the Canadian Optimized Statistical Smoke Exposure Model (CanOSSEM) based on the six-character residential postal codes of mother-infant pairs. The CanOSSEM is a machine learning model designed to estimate daily all-source $PM_{2.5}$ concentrations across Canada at a 5 km x 5 km resolution.[7] It integrates regulatory air quality monitoring network observations with remotely sensed data, enabling prediction of exposure in populated areas where national air quality monitoring data is not available.[7]

All-source $PM_{2.5}$ concentrations acquired from CanOSSEM were further separated into WFS $PM_{2.5}$ and non-WFS $PM_{2.5}$ concentrations following a data-driven methodology developed by Cleland and colleagues.[8] Gestational age at birth, recorded as completed gestational weeks at

birth on CVSBD based on last menstrual period (LMP), was subtracted from each infant's date of birth to obtain the estimated start date of pregnancy. Daily all-source $PM_{2.5}$ concentrations were then aggregated into weekly level estimates for each gestational week throughout pregnancy and preconception period for each individual. The weekly all-source $PM_{2.5}$ concentration history of each mother-infant pair, aggregated at the DA-level, was collected from three years prior to the date of birth, based on each mother's residential history obtained from T1FF. Modified z-scores were then assigned to each weekly sum of all-source $PM_{2.5}$ concentrations throughout each mother infant pair's exposure history. A week was further defined as smoke-impacted when both of the following criteria were satisfied:

1) Falls under the wildfire season (spanning from May 1st to October 31st)
2) Modified z-score of weekly all-source $PM_{2.5}$ exceeds the value of +2

The median weekly all-source $PM_{2.5}$ concentrations across smoke-free weeks of each mother infant pair's exposure history was then defined as the counterfactual $PM_{2.5}$ estimate, representing the baseline level of all-source $PM_{2.5}$ exposure in the absence of WFS events. Weekly all-source $PM_{2.5}$ concentrations were further separated into WFS and non-WFS $PM_{2.5}$ components using the formulas shown below.

For smoke-impacted weeks:

- Non-WFS $PM_{2.5}$ = Counterfactual $PM_{2.5}$
- WFS $PM_{2.5}$ = All-source $PM_{2.5}$ – Non-WFS $PM_{2.5}$

For smoke-free weeks:

- Non-WFS $PM_{2.5}$ = All-source $PM_{2.5}$
- WFS $PM_{2.5}$ = 0 $\mu g/m^3$

3.1.5 Ambient Temperature Data

Daily estimates of ambient mean and maximum temperatures were extracted from the NASA Modern-Era Retrospective Analysis for Research and Applications, Version 2 (MERRA-2).[9] MERRA-2 provides estimations of varying meteorological parameters at a 0.5° x 0.625° resolution, corresponding to approximately 50 km x 50 km resolution, through analysis of satellite observations computed on a cubed-spheric grid.[9] Daily estimates of temperature exposures at the FSA level were then aggregated at a weekly level, similarly to the $PM_{2.5}$ exposure, to assign the weekly mean temperature exposure history and extreme heat event (EHE) history throughout pregnancy and preconception period. Detailed information on the EHE definition used for analysis is described in Chapter 4.

3.1.6 Canadian Index of Multiple Deprivation (CIMD)

Relevant DA-level SES characteristics were obtained from the Canadian Index of Multiple Deprivation (CIMD). The CIMD assigns each DA with quintiles of varying SES components including residential instability, situational vulnerability, economic dependency and ethno-cultural composition across Canada at the national level.[10] This information was available for most regions in Canada, excluding the territories of Yukon, Nunavut and the Northwest Territories. Therefore, those with missing CIMD quintiles were combined as a separate missing category for analysis in Chapter 4.

3.2 Data Linkage

The linkage of administrative datasets, including CVSD, CIHI-DAD and T1FF, were completed by Statistics Canada through individual-level identification of mother-infant pairs based on the unique combination of registration numbers, province of residence and year of birth of infants. Furthermore, environmental and SES data were linked based on the DA and FSA

associated with the six-character postal codes obtained from maternal residential history. The detailed method of data linkage is illustrated in Figure 3.1.

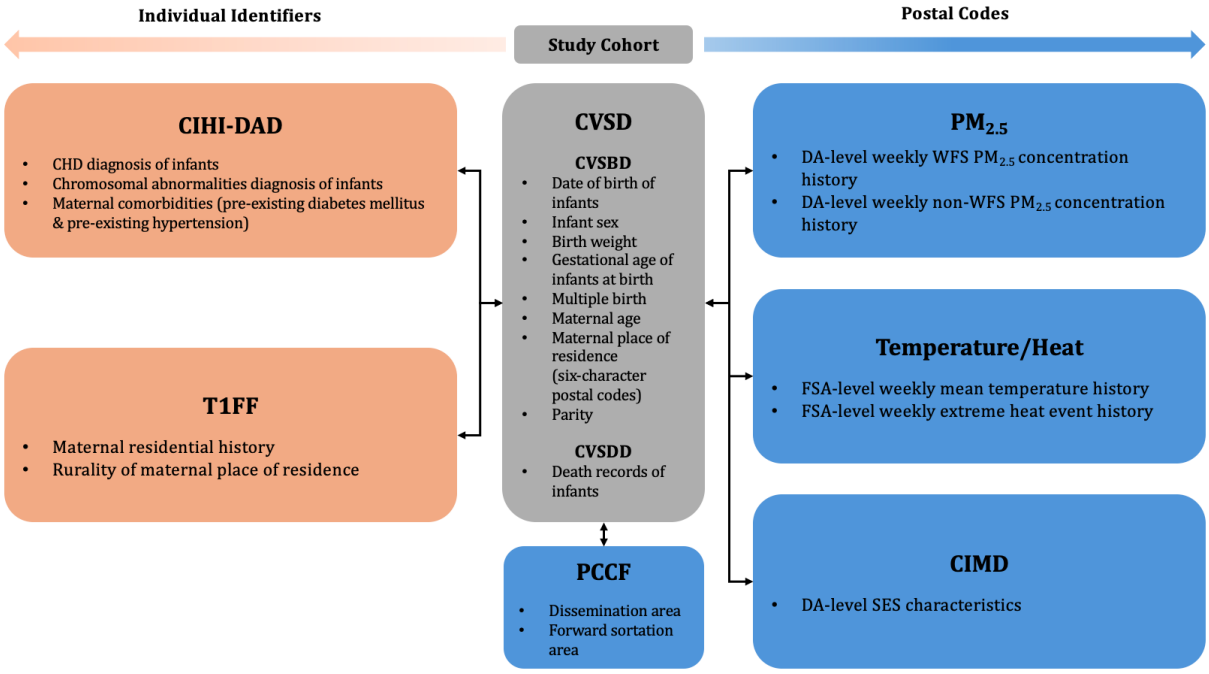


Figure 3.1. Method of data linkage.

3.3 Study Cohort

There were 3,389,335 mother-infant pairs recorded in CVSBD from 2013 to 2021. To be included in the study cohort, at least one hospitalization record for each infant was required from CIHI-DAD to identify the outcome of CHD cases. Consequently, 1,058,870 mother-infant pairs were excluded from the CVSBD cohort, where approximately 71% of these excluded infants were due to the limited data availability of DADs for the province of Quebec. Note that all frequencies were randomly rounded to base five, in accordance with Statistics Canada disclosure rules.

As a result, 2,330,465 mother-infant pairs of the source cohort had at least one DAD record, where the following exclusion criteria were then applied:

1) Missing gestational age at birth, n = 1,300 (0.06%) – Records of gestational age at birth was vital for estimation of the conception date and assignment of environmental exposures during each gestational week. Hence, infants with missing information on gestational age at birth were excluded.
2) Invalid DAD records, n = 1,210 (0.05%) – DAD records were utilized to estimate the date of CHD diagnosis, which were used as the time scale of the Cox proportional hazard model for statistical analyses. Thus, DAD records with invalid information or errors in the identifiers or discharge dates were excluded.
3) Multiple births, n = 28,075 (1.20%) – Infants from multiple pregnancies often have vastly different maternal and neonatal characteristics compared to singleton births.[11,12] Therefore, the study cohort was limited to singleton births for comparability.
4) Chromosomal abnormalities, n = 4,070 (0.17%) – Infants with chromosomal abnormalities and single gene defects, which are significant genetic risk factors of CHD,[13] were excluded to focus on the risk imposed by environmental factors.
5) Gestational age at birth < 20 weeks, n = 75 (< 0.01%) – Deliveries prior to 20 weeks of gestation are commonly associated with non-viable pregnancies. Due to the high fatality rate of such live births within a day of birth,[14] prior to ascertainment of CHD cases, these infants were excluded from the study cohort.
6) Missing environmental exposures, n = 458,095 (19.66%) – Infants with missing $PM_{2.5}$ and ambient temperature exposure history during the periconception period were excluded. These cases were mostly due to invalid records of maternal residential history obtained from T1FF, or residing in remote areas lacking coverage by environmental monitoring stations.

Following exclusions, the final study cohort was comprised of 1,837,635 infants. Detailed distribution of each exclusion criteria is illustrated in the flow chart shown below (Figure 3.2).

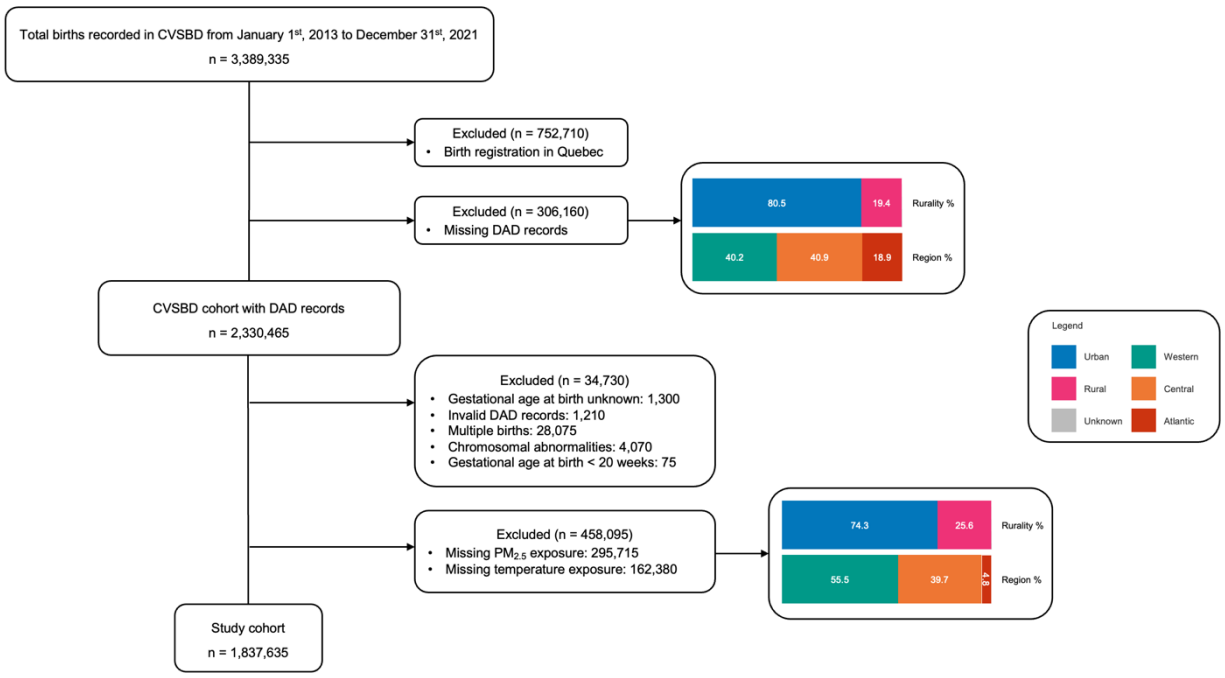


Figure 3.2. Flow chart of the study composition.

Note: In accordance with Statistics Canada disclosure rules, all frequencies were randomly rounded to base five. As a result, there may be discrepancies between totals by each exclusion characteristic.

Baseline characteristics of the study cohort, stratified by the outcome of CHD cases, is presented below in Table 3.2.

Table 3.2. Baseline characteristics of the study cohort stratified by Congenital Heart Defect (CHD) outcome.

Characteristics	CHD cases (N = 23,005)	No CHD cases (N = 1,814,630)	Total (N = 1,837,635)
Gestational age at birth in weeks, mean (SD)	35.5 (5.2)	38.8 (1.7)	38.8 (1.8)
Birth weight in grams, mean (SD)	2,731.1 (1,137.9)	3,365.1 (534.7)	3,357.1 (550.9)
Maternal age at delivery, n (%)			
< 18	140 (0.6)	9,070 (0.5)	9,210 (0.5)
18-29	8,840 (38.4)	698,070 (38.5)	706,905 (38.5)
30-39	12,770 (55.5)	1,031,110 (56.8)	1,043,880 (56.8)
> 39	1,255 (5.5)	76,380 (4.2)	77,635 (4.2)
Parity, n (%)			
None	10,330 (44.9)	785,705 (43.3)	796,035 (43.3)
1	7,295 (31.7)	641,065 (35.3)	648,360 (35.3)
2+	5,335 (23.2)	386,645 (21.3)	391,980 (21.3)
Missing	40 (0.2)	1,215 (0.1)	1,260 (0.1)
Infant sex, n (%)			
Male	12,545 (54.5)	932,825 (51.4)	945,370 (51.4)
Female	10,460 (45.5)	881,810 (48.6)	892,265 (48.6)
Rurality of maternal residence, n (%)			
Urban	19,900 (86.5)	1,567,225 (86.4)	1,587,130 (86.4)
Rural	3,060 (13.3)	244,810 (13.5)	247,870 (13.5)
Missing	40 (0.2)	2,595 (0.1)	2,635 (0.1)
Maternal pre-existing hypertension, n (%)			
Yes	400 (1.7)	13,570 (0.7)	13,970 (0.8)
No	19,145 (83.2)	1,534,135 (84.5)	1,553,275 (84.5)
Missing	3,460 (15.0)	266,925 (14.7)	270,385 (14.7)
Maternal pre-existing diabetes, n (%)			
Yes	990 (4.3)	16,730 (0.9)	17,720 (1.0)
No	18,550 (80.6)	1,530,970 (84.4)	1,549,525 (84.3)
Missing	3,460 (15.0)	266,925 (14.7)	270,385 (14.7)
Region, n (%)			
Central	11,880 (51.6)	933,005 (51.4)	944,885 (51.4)
Western	9,645 (41.9)	781,625 (43.1)	791,265 (43.1)
Atlantic	1,475 (6.4)	100,005 (5.5)	101,480 (5.5)
Residential instability quintiles, n (%)			
1 (least marginalized)	3,450 (15.0)	299,400 (16.5)	302,850 (16.5)
2	3,975 (17.3)	329,840 (18.2)	333,810 (18.2)
3	4,000 (17.4)	314,995 (17.4)	319,000 (17.4)
4	4,440 (19.3)	337,510 (18.6)	341,950 (18.6)
5 (most marginalized)	4,325 (18.8)	321,210 (17.7)	325,535 (17.7)
Missing	2,810 (12.2)	211,680 (11.7)	214,490 (11.7)
Ethno-cultural composition quintiles, n (%)			
1 (least marginalized)	1,705 (7.4)	136,355 (7.5)	138,060 (7.5)
2	3,315 (14.4)	255,630 (14.1)	258,950 (14.1)
3	4,150 (18.0)	314,780 (17.3)	318,930 (17.4)
4	4,665 (20.3)	372,110 (20.5)	376,780 (20.5)
5 (most marginalized)	6,355 (27.6)	524,075 (28.9)	530,425 (28.9)
Missing	2,810 (12.2)	211,680 (11.7)	214,490 (11.7)
Economic dependency quintiles, n (%)			
1 (least marginalized)	4,425 (19.2)	374,905 (20.7)	379,325 (20.6)
2	4,665 (20.3)	369,570 (20.4)	374,235 (20.4)
3	4,330 (18.8)	333,990 (18.4)	338,320 (18.4)
4	3,810 (16.6)	298,355 (16.4)	302,165 (16.4)
5 (most marginalized)	2,965 (12.9)	226,130 (12.5)	229,100 (12.5)

Missing	2,805 (12.2)	211,675 (11.7)	214,485 (11.7)
Situational vulnerability quintiles, n (%)			
1 (least marginalized)	3,410 (14.8)	318,900 (17.6)	322,310 (17.5)
2	4,035 (17.5)	338,170 (18.6)	342,205 (18.6)
3	3,980 (17.3)	311,955 (17.2)	315,935 (17.2)
4	3,870 (16.8)	300,745 (16.6)	304,615 (16.6)
5 (most marginalized)	4,900 (21.3)	333,185 (18.4)	338,085 (18.4)
Missing	2,810 (12.2)	211,680 (11.7)	214,485 (11.7)

Abbrev. CHD, Congenital Heart Defect; SD, Standard Deviation.

Note: In accordance with Statistics Canada disclosure rules, all frequencies were randomly rounded to base five. As a result, there may be discrepancies between column totals and totals by infant/maternal characteristic. Statistical analyses employed unrounded data.

Infants diagnosed with CHD were delivered earlier with lower gestational age at birth (mean = 35.5 weeks, SD = 5.2 weeks) compared to those without CHD (mean = 38.8 weeks, SD = 1.7 weeks). In addition, birthweight of infants was considerably lower with higher variability observed for CHD cases (mean = 2,731.1g, SD = 1,137.9g) compared to non-CHD cases (mean = 3,365.1g, SD = 534.7g). A slightly higher proportion of males were diagnosed with CHD cases (54.5%) compared to those without CHD (51.4%). Moreover, consistent with evidence from previous literature, higher percentages of pre-existing maternal comorbidities of hypertension and diabetes were identified for infants with CHD.[15] Lastly, the distributions of SES characteristics were generally similar across the cohorts, although slightly higher proportion of infants residing in areas with most marginalized situational vulnerability index were observed for CHD cases.

3.4 References

1. Statistics Canada. (2025, October 20). *Mandate and role: Who we are and what we do*. Statistics Canada. https://www.statcan.gc.ca/en/about/mandate

2. Statistics Canada. (2024, September 10). *Statistics Canada, Canadian Vital Statistics—Birth database (CVSB)*. https://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&Id=1544655

3. Statistics Canada. (2025, April 9). *Statistics Canada, Canadian Vital Statistics—Death database (CVSD)*. Statistics Canada. https://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=3233

4. Canadian Institute for Health Information. (2025, May 5). *Discharge Abstract Database (DAD) metadata | CIHI*. Canadian Institute for Health Information. https://www.cihi.ca/en/discharge-abstract-database-dad-metadata

5. Statistics Canada. (2021, November 17). *Dictionary, Census of Population, 2021—Figure 1.1 Hierarchy of standard geographic areas for dissemination, 2021 Census*. Government of Canada. https://www12.statcan.gc.ca/census-recensement/2021/ref/dict/fig/index-eng.cfm?ID=F1_1

6. Government of Canada, S. C. (2021, November 17). *Dictionary, Census of Population, 2021 – Dissemination area (DA)*. Statistics Canada. https://www12.statcan.gc.ca/census-recensement/2021/ref/dict/az/definition-eng.cfm?ID=geo021

7. Paul, N., Yao, J., McLean, K. E., Stieb, D. M., & Henderson, S. B. (2022). The Canadian Optimized Statistical Smoke Exposure Model (CanOSSEM): A machine learning approach to estimate national daily fine particulate matter (PM2.5) exposure. *Science of The Total Environment*, *850*, 157956. https://doi.org/10.1016/j.scitotenv.2022.157956

8. Cleland, S. E., Hamilton, O. P. X.-Q., Brauer, M., & Henderson, S. B. (2026). Multiyear wildfire smoke exposure (MultiWiSE) metrics: A data-driven approach to characterizing episodic PM2.5 exposures for epidemiologic research. *Journal of Exposure Science & Environmental Epidemiology*. https://doi.org/10.1038/s41370-026-00876-5

9. Gelaro, R., McCarty, W., Suárez, M. J., Todling, R., Molod, A., Takacs, L., Randles, C. A., Darmenov, A., Bosilovich, M. G., Reichle, R., Wargan, K., Coy, L., Cullather, R., Draper, C., Akella, S., Buchard, V., Conaty, A., Silva, A. M. da, Gu, W., … Zhao, B. (2017). The Modern-Era Retrospective Analysis for Research and Applications, Version 2 (MERRA-2). *Journal of Climate*, *30*(14), 5419–5454. https://doi.org/10.1175/JCLI-D-16-0758.1

10. Government of Canada, S. C. (2024, November 28). *The Canadian Index of Multiple Deprivation (CIMD)*. Government of Canada. https://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=5274

11. Heino, A., Gissler, M., Hindori-Mohangoo, A. D., Blondel, B., Klungsøyr, K., Verdenik, I., Mierzejewska, E., Velebil, P., Ólafsdóttir, H. S., Macfarlane, A., Zeitlin, J., & Committee, E.-P. S. (2016). Variations in Multiple Birth Rates and Impact on Perinatal Outcomes in Europe. *PLOS ONE*, *11*(3), e0149252. https://doi.org/10.1371/journal.pone.0149252

12. Su, R.-N., Zhu, W.-W., Wei, Y.-M., Wang, C., Feng, H., Lin, L., & Yang, H.-X. (2015). Maternal and neonatal outcomes in multiple pregnancy: A multicentre study in the Beijing population. *Chronic Diseases and Translational Medicine*, *1*(4), 197–202. https://doi.org/10.1016/j.cdtm.2015.08.004

13. Richards, A. A., & Garg, V. (2010). Genetics of Congenital Heart Disease. *Current Cardiology Reviews*, *6*(2), 91–97. https://doi.org/10.2174/157340310791162703

14. Macfarlane, P. I., Wood, S., & Bennett, J. (2003). Non-viable delivery at 20–23 weeks gestation: Observations and signs of life after birth. *Archives of Disease in Childhood - Fetal and Neonatal Edition*, *88*(3), F199–F202. https://doi.org/10.1136/fn.88.3.F199

15. Gomersall, J. C., Moore, V. M., Fernandez, R. C., Giles, L. C., Grzeskowiak, L. E., Davies, M. J., & Rumbold, A. R. (2024). Maternal modifiable factors and risk of congenital heart defects: Systematic review and causality assessment. *BMJ Open*, *14*(8), e082961. https://doi.org/10.1136/bmjopen-2023-082961

Chapter 4. Wildfire Smoke $PM_{2.5}$, Extreme Heat Events and Congenital Heart Defects

4.1 Preface

This chapter includes a manuscript titled "*Association between Periconception Exposure to Wildfire Smoke $PM_{2.5}$, Extreme Heat Events and Congenital Heart Defects in Canada*". This study addresses both objectives 1 and 2 of the thesis, and investigates both the independent effects of $PM_{2.5}$ arising from different sources (all-source, WFS, and non-WFS) and EHEs along with their potential synergistic effect on the risk of CHD. This manuscript will be further edited and submitted to the journal of BMC Global and Public Health. Ethical approval for this study was obtained from the Health Canada Research Ethics Board.

4.2 List of Authors

Yijun Kim[1,2], Steven Hawken[2,3], Piotr Wilk[4,5], Stephanie E. Cleland[6,7], Qingyi Lan[1,8], Naman Paul[9], Annalise Ferro[1], Hong Chen[1,10], Scott Weichenthal[11], Jean-Nicolas Côté[12], Lulu Gao[1], Jessica Evans[1], Éric Lavigne[1,2]

[1] Environmental Health Science and Research Bureau, Health Canada, Ottawa, Canada

[2] School of Epidemiology and Public Health, University of Ottawa, Ottawa, Canada

[3] The Ottawa Hospital Research Institute, Ottawa, Canada

[4] Department of Epidemiology and Biostatistics, Western University, London, Canada

[5] Department of Epidemiology and Population Studies, Institute of Public Health, Jagiellonian University, Kraków, Poland

[6] Faculty of Health Sciences, Simon Fraser University, Burnaby, Canada

[7] Legacy for Airway Health, Vancouver Coastal Health Research Institute, Vancouver, Canada

[8] School of Population and Public Health, University of British Columbia, Vancouver, Canada

[9] Environmental Health Services, British Columbia Centre for Disease Control, Canada

[10] Dalla Lana School of Public Health, University of Toronto, Toronto, Canada

[11] Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada

[12] Department of Geomatics, University of Sherbrooke, Sherbrooke, Canada

Author's Contributions: Yijun Kim: Writing – original draft, Formal Analysis, Data Curation, Conceptualization. Steven Hawken: Writing – review & editing, Supervision, Conceptualization. Piotr Wilk: Writing – review & editing. Stephanie E. Cleland: Writing – review & editing. Qingyi Lan: Writing – review & editing, Data Curation. Naman Paul: Writing – review & editing. Annalise Ferro: Writing – review & editing. Hong Chen: Writing – review & editing. Scott Weichenthal: Writing – review & editing. Jean-Nicolas Côté: Writing – review & editing. Lulu Gao: Writing – review & editing. Jessica Evans: Writing – review & editing. Éric Lavigne: Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

4.3 Acknowledgements

Parts of this material are based on data and information provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions and statements expressed herein are those of the authors and not necessarily those of the CIHI. The linkage of databases was computed by Statistics Canada, the national statistical office of Canada, through the Federal Research Data Centre. This study is based in part on data provided by the Federal Research Data Centre of Statistics Canada. The analyses, conclusions, opinions and statements expressed herein are those of the authors and not necessarily those of Statistics Canada.

This study was supported by a research grant from Health Canada, and Heart and Stroke Foundation of Canada (Heart & Stroke; Project Grant ID: G-23-0035099)

4.4 Abstract

Background: Exposure to wildfire smoke (WFS) and extreme heat events (EHEs) during pregnancy may affect fetal cardiovascular development. This study examined the association between prenatal exposure to wildfire smoke fine particulate matter (WFS $PM_{2.5}$), EHEs, and their interactive effects on the risk of congenital heart defects (CHD) in infants.

Methods: We conducted a population-based cohort study of singleton live births in Canada from 2013 to 2021. Maternal residential histories were linked to weekly WFS and non-WFS $PM_{2.5}$ estimates during the periconception period. CHD diagnoses were identified from hospitalization records through first year of life. Distributed lag Cox proportional hazards models were used to examine week-specific associations. Potential synergistic effects between wildfire smoke and EHEs were examined through relative excess risk due to interaction (RERI).

Results: Among 1,837,635 births, 23,005 infants (1.3%) were diagnosed with CHD. The adjusted hazard ratio for overall CHD was 1.007 (95% CI: 0.993, 1.022) per 1 $\mu g/m^3$ increase in WFS $PM_{2.5}$ during the periconception period. In stratified analysis by regions, a small positive association was observed in Western region (HR: 1.023, 95% CI: 1.007, 1.040), although no significant evidence of effect modification was identified. We found no consistent evidence of an association with EHE nor any consistent additive interaction between wildfire smoke and EHE.

Conclusions: Overall, no clear evidence of association between WFS $PM_{2.5}$ and EHEs on CHD risk was observed. Further research on the implications of wildfires on the association between ambient air pollutants and adverse birth outcomes is warranted.

4.5 Introduction

In recent years, increased heat events and prolonged droughts due in part to climate change have led to an escalation in the intensity and duration of wildfire seasons around the globe.[1] These wildfire events have substantially elevated human exposure to wildfire smoke, posing significant public health concerns, particularly for disproportionately impacted populations such as pregnant individuals and their developing fetuses.[2] Fine particulate matter ($PM_{2.5}$) is a major constituent of wildfire smoke, with emerging evidence suggesting $PM_{2.5}$ from wildfire smoke (WFS) may have amplified health effects compared to $PM_{2.5}$ originating from other sources.[3] Prenatal exposure to environmental stressors, including extreme heat and ambient air pollutants, may induce placental inflammation and oxidative stress during pregnancy, and further influence the health of newborns.[4,5]

Congenital heart defects (CHD) are the most prevalent congenital anomalies in newborns, and a leading cause of infant mortality.[6] CHD can lead to the disruption of normal cardiac blood flow and predispose infants to a range of complex comorbidities and chronic cardiovascular complications.[7] Aside from defects attributed to genetic disorders, the etiology of CHD remains incompletely understood, with multifactorial combinations of environmental exposures and non-genetic risk factors reported to affect its development.[8] While numerous studies have examined associations between prenatal exposure to both $PM_{2.5}$ and heat on CHD risks,[9,10] a notable gap persists in the current literature regarding the implication of wildfires on this relationship. Given the increasing co-occurrence of wildfire smoke events and extreme heat events (EHE),[11,12] understanding the potential synergistic effects of prenatal exposure to WFS $PM_{2.5}$ and heat on fetal health is especially crucial.

To address these knowledge gaps, we conducted a population-based retrospective cohort study of mother-infant pairs in Canada from 2013 to 2021 using health administrative data. The independent associations between periconception exposure to EHEs, $PM_{2.5}$ from wildfire smoke, non-wildfire sources and all-sources, as well as their interactive effects on CHD were investigated. Potential effect modification by infant sex, rurality, geographic regions and socioeconomic characteristics was further examined. Sensitive windows of susceptibility were examined through the analysis of week-specific risk during the periconception period. Notably, preconception exposures represent a relatively underexplored window in existing literature, despite being recognized as a vulnerable period for epigenetic changes which may influence fetal development.[13] By examining windows of susceptibility and CHD risk associated with wildfire smoke and extreme heat, the findings of this study may provide meaningful evidence for future maternal health guidelines during wildfire seasons.

4.6 Methods

Study Design and Population

This retrospective cohort study included all singleton live births from January 1st, 2013 to December 31st, 2021 in Canada, excluding the province of Quebec. Linked mother-infant data was obtained from the Canadian Vital Statistics Birth Database (CVSBD), which extracts birth-related administrative data from provincial and territorial vital statistics registries.[14] The maternal place of residence at birth, recorded as six-character residential postal codes in CVSBD, was linked to their associated forward sortation area (FSA) and dissemination area (DA) for the exposure assignment. FSAs are geographic districts defined by the first three characters of postal codes which can range from small city blocks to designated rural regions, whereas DAs are the smallest census geographic unit, each composed of approximately 400-700 persons.[15] Mother-

infant pairs with missing or invalid information affecting linkage of exposure and outcome data, multiple births, infants born with < 20 weeks of gestation, and those with chromosomal abnormalities were excluded from the study (Supplementary Figure S1). There were a total of 3,389,335 recorded live births during the study period. Approximately 31.2% of mother-infant pairs (n = 1,058,870) were excluded due to missing hospitalization records. This included 752,710 infants born in Quebec, where hospitalization data were unavailable, and 306,160 infants with no hospitalization records or linkage failure. Of the remaining cohort with linked hospitalization records (n = 2,330,465), 19.7% of mother-infant pairs were excluded due to missing environmental exposures (n = 458,095).

The exposure window was restricted to the periconception period, defined as 13 weeks before and after the start of pregnancy, encompassing both preconception (weeks 1-13 prior to start of pregnancy) and first trimester (gestational weeks 1-13) windows. Although the first two weeks of gestation are biologically considered as part of the preconception period, they were incorporated into the first trimester window for comparability with existing literature. In particular, gestational weeks 5-10, corresponding to embryonic weeks 3-8 post-conception, represent a critical period of cardiogenesis.[16] Even though cardiac maturation continues throughout pregnancy, structural morphogenesis of the heart is largely complete by the end of first trimester.[17] Therefore, exposure definition was restricted to the periconception period to examine the cumulative effects during a biologically relevant developmental window.

All-source, WFS and Non-WFS $PM_{2.5}$ Exposure Assessment

Daily all-source $PM_{2.5}$ exposure estimates were derived based on DAs associated with the residential history of each mother-infant pair. Maternal residential history was constructed using address of residence recorded in CVSBD and tax records from previous years (T1 Family File).

Within the study cohort, approximately 15.1% of mothers moved during the periconception period. All-source $PM_{2.5}$ estimates were obtained using the Canadian Optimized Statistical Smoke Exposure Model (CanOSSEM), which is a machine learning model that estimates daily mean concentrations of all-source $PM_{2.5}$ at a 5 km x 5 km spatial resolution across all populated regions of Canada.[18] CanOSSEM integrates regulatory air quality monitoring network observations with remotely sensed data, enabling prediction of population exposure in areas where national air quality monitoring data is not available.[18] Overall, the model performs well, with approximately 96% of the predicted $PM_{2.5}$ estimates falling within 5 $\mu g/m^3$ of the monitored measurements.[18]

Daily all-source $PM_{2.5}$ estimates from CanOSSEM were subsequently used to derive estimates of weekly mean wildfire smoke (WFS) and non-WFS $PM_{2.5}$ exposure estimates using the Multiyear Wildfire Smoke Exposure (MultiWiSE) approach developed by Cleland and colleagues.[19] This data-driven approach establishes a baseline counterfactual value representing the weekly $PM_{2.5}$ concentrations expected in the absence of WFS, for each geographic area. The counterfactual value for each mother-infant pair was calculated using the distribution of weekly all-source $PM_{2.5}$ concentrations in the three years prior to birth. Modified z-scores were then calculated from the weekly all-source $PM_{2.5}$ concentrations, to identify whether a given week during the periconception period was affected by wildfire smoke. Each week that fell within the wildfire season (May 1st to October 31st) with modified z-scores exceeding +2 was identified as smoke-impacted. For these weeks, the WFS $PM_{2.5}$ concentrations was estimated by setting non-WFS $PM_{2.5}$ to the counterfactual value and then subtracting non-WFS $PM_{2.5}$ concentrations from the all-source $PM_{2.5}$ concentrations.

For smoke-impacted weeks:

- Non-WFS $PM_{2.5}$ = Counterfactual value
- WFS $PM_{2.5}$ = All-source $PM_{2.5}$ – Non-WFS $PM_{2.5}$

Ambient Temperature and EHE Exposure Assessment

Daily estimates of mean (T_{mean}) and maximum (T_{max}) ambient temperatures in °C were extracted from the National Aeronautics and Space Administration's Modern-Era Retrospective Analysis for Research and Applications, Version 2 (MERRA-2). MERRA-2 provides varying meteorological estimates at approximately 50 km resolution, through analysis of satellite observations computed on a cubed-sphere grid.[20] The estimates were derived across Canada using FSA regions linked to maternal residential FSAs of each mother-infant pair. Similar to the $PM_{2.5}$ exposure, the covariate of weekly T_{mean} exposure was assigned for each mother-infant pair during the periconception period.

EHEs were defined using relative thresholds of 90^{th} and 95^{th} percentiles of daily maximum temperature (T_{max}) based on local T_{max} distribution of the FSA region during spring and summer, following definition used by Lin and colleagues[21]: (a) $T_{max} \geq 90^{th}$ percentile for three or more consecutive days of the T_{max} distribution for the season of year (EHE90), and (b) $T_{max} \geq 95^{th}$ percentile for two or more consecutive days of the T_{max} distribution for the season of year (EHE95). Binary indicators denoting the presence of each EHE definition were then assigned during each week of periconception for all infants.

Congenital Heart Defects Outcome

CHDs were identified through International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada (ICD-10-CA) codes obtained from the Canadian Institute for Health Information - Discharge Abstract Database (CIHI-DAD).[22] CIHI-DAD is a health administrative database which collects clinical and demographic data of hospital

discharge records from regional authorities across Canada, with the exception of the province of Quebec. The linkage of DAD with CVSBD was conducted by Statistics Canada based on unique identifier variables of mother-infant pairs, allowing both maternal and infant hospitalization records to be linked with the study cohort. CHD was defined as hospitalizations for congenital anomalies identified with ICD-10-CA codes of Q20-Q26 from birth to one year of age, which is the recommended reporting time frame under the Canadian Congenital Anomalies Surveillance System (CCASS).[23] Hospitalization data were available through 2022, providing at least one complete year of records for all infants. Major CHD subtypes including Atrial Septal Defect (ASD; ICD-10-CA code of Q21.1), and Ventricular Septal Defect (VSD; ICD-10-CA code of Q21.0), were also analyzed. The subtypes of ASD and VSD were not mutually exclusive.

Covariates

Covariates were selected *a priori* based on evidence from the existing literature as identified in the Directed Acyclic Graphs (DAGs) (Supplementary Figures S2 & S3). These included: maternal age at delivery (<18, 18-29, 30-39, >39), sex of infant, parity (none, 1, ≥2, missing), seasonality (first-harmonic sine and cosine terms of day-of-year of conception),[24,25] year of conception, maternal place of residence (urban, rural, missing), weekly mean temperatures, and socioeconomic status (SES) characteristics obtained from the Canadian Index of Multiple Deprivation (CIMD).[26] The CIMD uses census data to derive area-based quintiles of residential instability, ethno-cultural composition, economic dependency and situational vulnerability across Canada, and were assigned to each mother-infant pair at the DA level.[24] Based on the DAG, weekly mean ambient temperature was adjusted as a covariate when analyzing the independent effect of WFS $PM_{2.5}$ (Supplementary Figure S2). Conversely, air pollutant variables were considered mediators in analyses of EHEs and CHD, and were not

adjusted in those models (Supplementary Figure S3).[27,28] Random intercepts at the FSA level were also included in the models to account for spatial variability. Given the smaller number of cases co-exposed to both WFS and EHEs, random intercepts were not included in the analyses of interactive effect to ensure stable estimates.

4.7 Statistical Analysis

Independent Effects of All-source, WFS, Non-WFS $PM_{2.5}$ and EHEs

Cox proportional hazards models were used to analyze the independent effects of $PM_{2.5}$ from different sources and EHEs on the risk of CHD. The time scale of the model was the infant's age in days, where the follow-up period was limited from birth until the diagnosis of CHD, death or one year of age. Since CHD develops in utero but is ascertained after birth,[29] the time scale served to capture time to clinical diagnosis of disease. The effect of all-source $PM_{2.5}$ was examined using a single-pollutant model, while WFS and non-WFS $PM_{2.5}$ were examined jointly using a two-pollutant model that simultaneously adjusted for both exposures. The Pearson correlation between WFS and non-WFS $PM_{2.5}$ during periconception was weak (r = -0.021, 95% CI: -0.023, -0.020) with acceptable variance inflation factors (VIF_{WFS} = 1.93, $VIF_{Non\text{-}WFS}$ = 2.39), allowing us to examine the independent effects using a two-pollutant model (Supplementary Table S1). The Cox models were integrated with a distributed lag model (DLM) to identify sensitive windows of susceptibility during periconception, while adjusting for pre-selected covariates.[30]

Weekly mean concentrations of WFS, non-WFS and all-source $PM_{2.5}$ during periconception were each modelled as cross-basis functions. A linear exposure-response model was used to calculate the overall effect estimates. Potential non-linear effects were also examined through a secondary model parametrizing the exposure-response using natural cubic splines. For

each cross-basis function, multiple lag-response models (natural cubic splines with 2 to 5 dfs) were compared. The model with the lowest Akaike information criterion (AIC) was selected, where natural cubic splines with 3 dfs provided the optimal fit for all $PM_{2.5}$ metrics (Supplementary Table S2).

Using a similar approach, binary indicators of EHEs during each week of periconception were modelled using the same cross-basis framework with a linear exposure-response relationship. Based on AIC, natural cubic splines with 4 dfs were selected for the lag-response models of EHE90, and 3 dfs for EHE95 (Supplementary Table S2). Weekly mean ambient temperature was modelled assuming a non-linear exposure-response relationship with natural cubic splines of 4 dfs (knots placed at 5^{th}, 75^{th} and 95^{th} percentiles), and natural cubic splines with 3 dfs for its lag structure.

Week-specific hazard ratios (HR) for overall CHD and its subtypes were examined per 1 $\mu g/m^3$ increase in weekly mean WFS, non-WFS and all-source $PM_{2.5}$ concentrations, and for the presence of EHEs. Cumulative estimates were further obtained for the preconception (1-13 weeks prior to pregnancy), first trimester (gestational weeks 1-13), period of cardiogenesis (gestational weeks 5-10), entire periconception (preconception and first trimester) and sensitive exposure windows. The sensitive window was defined based on the statistical significance of week-specific HR, indicated by 95% CI excluding the value of 1.

Sensitivity analyses were conducted to assess the robustness of results, which included: 1) additional adjustment for risk factors of maternal pre-existing diabetes or hypertension as a binary variable (yes/no). These conditions were identified using ICD-10-CA codes recorded in the DAD (O10 for hypertension; O24.5-24.7 for diabetes) during pregnancy. Due to a relatively high proportion of mothers with no hospitalization records, adjustment of this

covariate was restricted to sensitivity analysis; 2) mixed-effects log-binomial models were employed to examine the $PM_{2.5}$ associations to account for potential postnatal factors that may influence the underlying time scale of the primary Cox models; 3) limiting the exposure window to first trimester only; 4) additional adjustment for the cross-basis of NO_2 concentrations for the $PM_{2.5}$ models. Due to limited data availability, this sensitivity analysis was conducted in a subset of the cohort with complete NO_2 data; and 5) adjusting for alternative specifications of seasonality.

Stratified analyses were also performed to assess potential effect modification by infant sex, rurality of residence, SES characteristics, and geographical regions. Geographical regions included Western (British Columbia, Prairies and Territories), Central (Ontario) and Atlantic regions. Due to small sample sizes, the Territories were grouped with the Western region for analysis. A multiplicative interaction term between the cross-basis functions of exposure and modifier was included in each model, where p-value < 0.05 indicated evidence of effect modification.

Interactive Effects of Wildfire Smoke and EHE

The interactive effects of WFS and EHE were investigated through incorporation of Relative Excess Risk due to Interaction (RERI) and Attributable Proportion due to Interaction (AP), following approach developed by Hosmer and Lemeshow.[31,32] Each exposure variable was dichotomized during the cardiogenesis window. WFS events were defined as the presence of weekly mean WFS $PM_{2.5} > 0$ or 5 $\mu g/m^3$, based on the MultiWiSE metrics.[19] Heat events were defined as the presence of weekly EHE90 or EHE95.

RERI was assessed using the following formula of: $RERI = HR_{11} - HR_{10} - HR_{01} + 1$, where a statistically significant value of RERI or AP > 0 indicates evidence of additive

interaction.[31] Each HR variable in the equation was defined as: HR_{10} = presence of a WFS event but absence of an EHE, HR_{01} = absence of a WFS event but presence of an EHE, HR_{11} = presence of both a WFS event and an EHE. The reference group was HR_{00}, which represents infants with the absence of both a WFS event and an EHE.

To further examine whether the observed interaction is driven specifically by wildfire event or elevated $PM_{2.5}$ concentration, stratified analyses were also conducted. All-source $PM_{2.5}$ concentration during the cardiogenesis was dichotomized, where weekly mean all-source $PM_{2.5}$ estimates exceeding 80th percentile of the FSA-specific concentration distribution was defined as high $PM_{2.5}$ exposure, consistent with a previous study.[33] The RERI and AP between high $PM_{2.5}$ and EHEs were then analyzed separately within strata defined by the presence or absence of WFS event during the exposure window.

All statistical analyses were conducted using R (version 4.5.0), and the *survival* (version 3.8-3) and *dlnm* (version 2.4.7) packages.

4.8 Results

Descriptive Statistics

Descriptive characteristics of the study cohort stratified by CHD outcome are presented in Table 1. Our study included a total of 1,837,635 singleton live births identified between 2013 and 2021 across Canada. Among the cohort, 23,005 (1.3%) infants were diagnosed with CHD during the follow-up period, including 9,880 cases of ASD (0.5%) and 5,085 cases of VSD (0.3%). On average, infants diagnosed with CHDs were delivered earlier, with mean gestational age at birth of 35.5 weeks (SD = 5.2) compared to 38.8 weeks (SD = 1.7) for infants without CHD. Furthermore, there was a slightly higher proportion of males among CHD cases (54.5%) compared to those without CHD (51.4%).

The mean WFS $PM_{2.5}$ concentration during the periconception period was 0.57 $\mu g/m^3$ (SD = 1.08), while the mean non-WFS $PM_{2.5}$ concentration was 6.52 $\mu g/m^3$ (SD = 0.50). Higher concentrations of WFS $PM_{2.5}$ were observed in the Western region (Supplementary Figure S4). Within the cohort, 62.5% of mother-infant pairs experienced at least one week of the periconception period affected by WFS (weekly mean WFS $PM_{2.5} > 0$ $\mu g/m^3$). For EHEs, 59.3% and 61.4% of mother-infant pairs experienced at least one EHE90 and EHE95 during the periconception period, respectively. Heat events characterized by higher maximum temperatures over shorter durations were more frequent in the cohort, as indicated by slightly higher proportion of EHE95 observed compared to EHE90.

Association between All-source, WFS, Non-WFS $PM_{2.5}$ concentration and CHD

No significant association between WFS $PM_{2.5}$ and overall CHD risk was observed during the periconception period (HR: 1.007, 95% CI: 0.993, 1.022 per 1 $\mu g/m^3$ increase) (Figures 1 & 2). Although point estimates were consistently positive for the preconception, first trimester and cardiogenesis windows, confidence intervals included unity. Similarly, no significant associations were observed for all-source and non-WFS $PM_{2.5}$ with overall CHD (Figure 1 & Supplementary Table S3). For the subtype of ASD, an inverse association with WFS and all-source $PM_{2.5}$ was observed during the preconception window (HR: 0.979, 95% CI: 0.963, 0.995 per 1 $\mu g/m^3$ increase, and HR: 0.980, 95% CI: 0.966, 0.994 per 1 $\mu g/m^3$ increase respectively), whereas no significant association was identified for VSD (Figure 2 & Supplementary Table S3).

We additionally provided the lag curves by employing multiple lag-response functions (Supplementary Figure S5). Similar curves were observed except for the ns (df = 2) model which produced a monotonic curve. The exposure-response curve of WFS $PM_{2.5}$ concentration during

cardiogenesis is presented in Supplementary Figure S6. A gradual increase in the estimated CHD risk was observed at concentrations above 2 $\mu g/m^3$, although the CIs included unity.

In sensitivity analyses, estimates were largely unchanged when further adjusting for maternal comorbidities, employing the mixed-effects log-binomial model, and when restricting the exposure to first trimester (Supplementary Tables S4-S6). In the cohort subset with complete NO_2 data, additional adjustment for NO_2 did not materially change the estimate, although the WFS $PM_{2.5}$ estimates were attenuated relative to the full cohort (Supplementary Table S7). When adjusting for alternative specifications of seasonality, a small positive association was observed in the model adjusting for the categorical covariate of season of conception (HR: 1.014, 95% CI: 1.000, 1.029 per 1 $\mu g/m^3$ increase) (Supplementary Table S8).

In stratified analysis, a positive significant association was observed within the Western region (HR: 1.023, 95% CI: 1.007, 1.040 per 1 $\mu g/m^3$ increase, $P_{Interaction} = 0.61$) (Supplementary Table S9), although the p-value of effect modification was not statistically significant. Point estimates were lower in Central (HR: 0.939, 95% CI: 0.868, 1.015 per 1 $\mu g/m^3$ increase) and Atlantic (HR: 0.996, 95% CI: 0.795, 1.248 per 1 $\mu g/m^3$ increase) strata, likely reflecting low exposure contrast of WFS $PM_{2.5}$ distribution within these regions.

Association between EHEs and CHD

No significant associations were observed between EHEs and overall CHD or its subtypes during periconception (Figure 3). Results remained consistent when further adjusting for maternal comorbidities (Supplementary Figure S7). A statistically significant interaction with infant sex was present for EHE95 and overall CHD ($P_{Interaction} = 0.04$), with elevated risk observed for female infants (Supplementary Table S10). Gestational weeks 5 to 13 were identified as a sensitive window among females, with the highest estimate observed at

gestational week 13 (HR: 1.052, 95% CI: 1.009, 1.098) (Supplementary Figure S8). No significant effect modification was observed when stratified by rurality of residence, geographical regions or different dimensions of SES characteristics (Supplementary Figures S9-S14 & Supplementary Table S10).

Interactive Effects of WFS and EHE on CHD

Overall, no significant additive interaction was observed between EHEs and WFS on CHD risk during cardiogenesis (Figure 4 & Supplementary Table S11). Results were consistent when further adjusting for maternal comorbidities (Supplementary Table S12). In exploratory analyses stratified by the presence of a WFS event during cardiogenesis, high all-source $PM_{2.5}$ was associated with elevated CHD risk within WFS-impacted windows (HR: 1.121, 95% CI: 1.039, 1.209 in the EHE90 model, and HR: 1.120, 95% CI: 1.039, 1.208 in the EHE95 model) but not within non-WFS-impacted windows (HR: 0.934, 95% CI: 0.848, 1.028, and HR: 0.952, 95% CI: 0.866, 1.046, respectively) (Supplementary Table S13). Co-exposure to EHEs and high $PM_{2.5}$ within WFS-impacted windows was associated with a similar increase in risk (HR: 1.093, 95% CI: 1.009, 1.183 for EHE90, and HR: 1.089, 95% CI: 1.008, 1.177 for EHE95) and the corresponding RERIs and APs were negative.

4.9 Discussion

In this large population-based retrospective cohort study, we investigated the associations between prenatal exposure to WFS $PM_{2.5}$ and EHEs during periconception, and their joint effects on the risk of CHD. Positive point estimates were observed between WFS $PM_{2.5}$ and overall CHD risk during periconception, but no clear evidence of association was found. No consistent associations were observed for EHEs. Similarly, no significant additive interaction was identified between WFS and EHEs on the risk of CHD.

A limited number of peer-reviewed studies have examined the effects of wildfire smoke on CHD. A large retrospective cohort study conducted in California, United States, observed that prenatal wildfire exposure was associated with an increased risk of ASD during the first trimester (OR: 1.11, 95% CI: 1.04, 1.18).[34] However, this study used the presence of wildfire events during each trimester as the exposure rather than the concentration of $PM_{2.5}$, limiting direct comparability with the estimates from our findings. A more recent case-control study in California also found that exposure to wildfire smoke during the first 8 weeks of pregnancy was associated with elevated risk of coarctation of the aorta, though they did not assess overall CHD or septal defects.[35] Another retrospective cohort study in Brazil reported positive association between first trimester exposure to wildfire smoke and circulatory congenital anomalies only within the subgroup of females in the Southeast region (OR: 1.032, 95% CI: 1.003, 1.062), with no clear association observed across the full cohort.[36] However, their main exposure was number of wildfire records, which may also limit direct comparability with our results.

Overall, these mixed findings are likely attributable to variation in analytical methodologies including exposure assessment of wildfire smoke and confounder adjustments, combined with differences in baseline $PM_{2.5}$ concentration distribution between countries. This was also reflected in our sensitivity analyses, where the association between WFS $PM_{2.5}$ and overall CHD reached statistical significance only when seasonality was modelled as a categorical season-of-conception term, a specification with poorer fit than the sinusoidal terms used in the primary model (Supplementary Table S8). Moreover, lower levels of absolute $PM_{2.5}$ concentration and exposure heterogeneity across Canada, compared to other study regions, may have led to limited exposure contrast to detect associations. Notably, we observed a positive association in the Western region in stratified analysis, which had higher levels of mean WFS

$PM_{2.5}$ concentrations. The lower exposure heterogeneity within other Canadian regions may have also led to higher exposure misclassification of WFS $PM_{2.5}$ estimates, and consequently attenuated the associations across the full cohort.[37]

We also observed an inverse association between WFS and all-source $PM_{2.5}$ with ASD during the preconception window. Although a few previous studies have reported a negative association with all-source $PM_{2.5}$ and ASD during pregnancy,[38,39] this inverse association more plausibly reflects chance among the many estimates examined, instability of distributed lag estimates at the boundary of the exposure window, residual confounding, or live birth bias than a protective effect. Given that both air pollutants and severe cases of CHD may lead to pregnancy losses, this may have contributed to the observed inverse association.[40,41]

Evidence on the association between prenatal exposure to EHEs and CHD has been mixed with notable heterogeneity by climate zone, as demonstrated by a recent systematic review and meta-analysis.[10] The pooled estimate indicated a positive association among 8 included studies, but the estimate was attenuated within a subgroup of studies conducted in the continental climate zone (OR: 1.07, 95% CI: 0.97, 1.19).[10] In our study, no consistent association between EHEs and CHD was identified, although a sex-specific EHE95 signal was observed in stratified analyses. While prior research has highlighted potential sex-specific variation in fetal growth trajectories and epigenetic mechanisms,[42] this finding should be interpreted cautiously. Effect modification was assessed across 7 different characteristics in our study, where this observed interaction may be an artifact of multiple testing, especially considering the null associations observed in our overall EHE findings.

To the best of our knowledge, this is the first study to examine the potential additive interaction between WFS and heat exposure on CHD. No significant additive interaction

between WFS and EHEs on CHD risk was found. In exploratory analyses, however, high all-source $PM_{2.5}$ during cardiogenesis was associated with an elevated CHD hazard within WFS-impacted windows but not within non-WFS-impacted windows, with or without co-exposure to EHEs. This contrast may reflect a smoke-specific or threshold effect that linear per-unit models may not fully capture, consistent with the shape of our exposure-response curve (Supplementary Figure S6). However, this analysis was post hoc and based on dichotomized exposures, and thus should be regarded as hypothesis-generating. More generally, our interaction findings are preliminary and cautious interpretations are warranted given that the CIs of our RERI and AP estimates included the null, and relatively smaller number of cases were co-exposed to both events. Further research examining this potential additive interaction on CHD is recommended.

While no clear association was found in our study, biological mechanisms linking the effects of environmental stressors on adverse birth outcomes remain plausible. Previous evidence has highlighted prenatal exposure to ambient air pollutants and heat may increase the release of key biomarkers and hormones involved in the regulation of inflammatory responses.[43-45] The resulting homeostatic imbalance of the immune system during pregnancy may induce placental inflammation and oxidative stress, and lead to dysregulation of complex cellular signaling pathways involved in the formation and maturation of critical organs.[46,47] In particular, previous research has also highlighted variation in particle composition of WFS $PM_{2.5}$, containing higher concentrations of organic and elemental carbon along with a greater proportion of smaller particles, which may exert increased toxicity in humans.[2,48,49] Moreover, heat exposure has been associated with increased ventilation in humans, which may further increase the deposition of ambient air pollutants and thus lead to synergistic effects.[50] Further research examining the effects of WFS $PM_{2.5}$ and heat on CHD is warranted considering this biological plausibility.

This study has several strengths. The large sample size of our study cohort, encompassing over 1.8 million mother-infant pairs, provided robust statistical power to explore potential effect modification by a wide range of characteristics. We also incorporated weekly exposures of environmental stressors through the employment of distributed lag models, allowing examination of potential sensitive windows of susceptibility during periconception. Furthermore, the methodology of wildfire smoke exposure assessment in our study, through the analysis of WFS $PM_{2.5}$ concentrations, enabled us to account for the temporal dynamics and intensity of wildfire smoke events on CHD.

There are also a few limitations in this study worth noting. Although our study cohort included mother-infant pairs across majority of regions in Canada, our sample excluded infants born in the province of Quebec due to unavailability of health administrative data, which may limit the generalizability of our findings. The study cohort was also restricted to live births delivered at ≥ 20 weeks of gestation. Exclusion of stillbirths and early pregnancy losses, which are often associated with more severe CHDs,[51] may have underestimated the association. In addition, approximately 20% of otherwise eligible births were excluded due to missing exposure data (Supplementary Figure S1). Compared with the study cohort, a higher proportion of excluded mother-infant pairs were residing in rural and Western regions, which may further limit generalizability. Moreover, we were unable to adjust for several maternal risk factors of CHD including obesity, tobacco smoke exposure and other teratogenic substance usage due to limited data. CHD cases were identified from hospitalization records during the first year of life. Milder defects that do not lead to hospitalization, notably small ASDs that close spontaneously, would not have been captured, so the ASD outcome likely represents more clinically significant cases. A large number of associations were also examined across exposure metrics, windows, subtypes

and subgroups without adjustment for multiple comparisons, and isolated statistically significant findings should be interpreted in that context. Furthermore, the timescale of the Cox models served to capture the clinical diagnostic timing rather than the biological onset of the disease, which may be influenced by postnatal factors including variability in healthcare access and neonatal screening protocols. However, the estimates remained consistent in mixed-effects log-binomial models, suggesting minimal influence of timescale. Exposures were assigned at the DA or FSA level rather than at individual residences, which may introduce misclassification of exposures. Lastly, it is important to note that the isolation of WFS $PM_{2.5}$ was computed based on the concentration distribution of all-source $PM_{2.5}$ during the pre-specified 3-year period. This may lead to potential exposure misclassification of smoke-impacted weeks, especially when the concentration of all-source $PM_{2.5}$ is low.

4.10 Conclusions

In this large population-based cohort, no clear association between periconception exposure to WFS $PM_{2.5}$ and CHD was observed. Neither EHEs nor wildfire smoke-heat co-exposure showed consistent associations with CHD. Further research on the implications of prenatal exposure to wildfire smoke on congenital anomalies is warranted.

4.11 Tables and Figures

Table 4.1. Descriptive characteristics of the study cohort stratified by Congenital Heart Defect (CHD) outcome.

Characteristics	CHD cases (N = 23,005)	No CHD cases (N = 1,814,630)	Total (N = 1,837,635)
Gestational age at birth in weeks, mean (SD)	35.5 (5.2)	38.8 (1.7)	38.8 (1.8)
Birth weight in grams, mean (SD)	2,731.1 (1,137.9)	3,365.1 (534.7)	3,357.1 (550.9)
Maternal age at delivery, n (%)			
< 18	140 (0.6)	9,070 (0.5)	9,210 (0.5)
18-29	8,840 (38.4)	698,070 (38.5)	706,905 (38.5)
30-39	12,770 (55.5)	1,031,110 (56.8)	1,043,880 (56.8)
> 39	1,255 (5.5)	76,380 (4.2)	77,635 (4.2)
Parity, n (%)			
None	10,330 (44.9)	785,705 (43.3)	796,035 (43.3)
1	7,295 (31.7)	641,065 (35.3)	648,360 (35.3)
2+	5,335 (23.2)	386,645 (21.3)	391,980 (21.3)
Missing	40 (0.2)	1,215 (0.1)	1,260 (0.1)
Infant sex, n (%)			
Male	12,545 (54.5)	932,825 (51.4)	945,370 (51.4)
Female	10,460 (45.5)	881,810 (48.6)	892,265 (48.6)
Rurality of maternal residence, n (%)			
Urban	19,900 (86.5)	1,567,225 (86.4)	1,587,130 (86.4)
Rural	3,060 (13.3)	244,810 (13.5)	247,870 (13.5)
Missing	40 (0.2)	2,595 (0.1)	2,635 (0.1)
Maternal pre-existing hypertension, n (%)			
Yes	400 (1.7)	13,570 (0.7)	13,970 (0.8)
No	19,145 (83.2)	1,534,135 (84.5)	1,553,275 (84.5)
Missing	3,460 (15.0)	266,925 (14.7)	270,385 (14.7)
Maternal pre-existing diabetes, n (%)			
Yes	990 (4.3)	16,730 (0.9)	17,720 (1.0)
No	18,550 (80.6)	1,530,970 (84.4)	1,549,525 (84.3)
Missing	3,460 (15.0)	266,925 (14.7)	270,385 (14.7)
Region, n (%)			
Central	11,880 (51.6)	933,005 (51.4)	944,885 (51.4)
Western	9,645 (41.9)	781,625 (43.1)	791,265 (43.1)
Atlantic	1,475 (6.4)	100,005 (5.5)	101,480 (5.5)
Residential instability quintiles, n (%)			
1 (least marginalized)	3,450 (15.0)	299,400 (16.5)	302,850 (16.5)
2	3,975 (17.3)	329,840 (18.2)	333,810 (18.2)
3	4,000 (17.4)	314,995 (17.4)	319,000 (17.4)
4	4,440 (19.3)	337,510 (18.6)	341,950 (18.6)
5 (most marginalized)	4,325 (18.8)	321,210 (17.7)	325,535 (17.7)
Missing	2,810 (12.2)	211,680 (11.7)	214,490 (11.7)
Ethno-cultural composition quintiles, n (%)			
1 (least marginalized)	1,705 (7.4)	136,355 (7.5)	138,060 (7.5)
2	3,315 (14.4)	255,630 (14.1)	258,950 (14.1)
3	4,150 (18.0)	314,780 (17.3)	318,930 (17.4)
4	4,665 (20.3)	372,110 (20.5)	376,780 (20.5)
5 (most marginalized)	6,355 (27.6)	524,075 (28.9)	530,425 (28.9)
Missing	2,810 (12.2)	211,680 (11.7)	214,490 (11.7)
Economic dependency quintiles, n (%)			
1 (least marginalized)	4,425 (19.2)	374,905 (20.7)	379,325 (20.6)
2	4,665 (20.3)	369,570 (20.4)	374,235 (20.4)
3	4,330 (18.8)	333,990 (18.4)	338,320 (18.4)

4	3,810 (16.6)	298,355 (16.4)	302,165 (16.4)
5 (most marginalized)	2,965 (12.9)	226,130 (12.5)	229,100 (12.5)
Missing	2,805 (12.2)	211,675 (11.7)	214,485 (11.7)
Situational vulnerability quintiles, n (%)			
1 (least marginalized)	3,410 (14.8)	318,900 (17.6)	322,310 (17.5)
2	4,035 (17.5)	338,170 (18.6)	342,205 (18.6)
3	3,980 (17.3)	311,955 (17.2)	315,935 (17.2)
4	3,870 (16.8)	300,745 (16.6)	304,615 (16.6)
5 (most marginalized)	4,900 (21.3)	333,185 (18.4)	338,085 (18.4)
Missing	2,810 (12.2)	211,680 (11.7)	214,485 (11.7)
Average exposure during periconception			
WFS $PM_{2.5}$, $\mu g/m^3$ (SD)	0.59 (1.10)	0.57 (1.08)	0.57 (1.08)
Non-WFS $PM_{2.5}$, $\mu g/m^3$ (SD)	6.49 (0.49)	6.52 (0.50)	6.52 (0.50)
All-source $PM_{2.5}$, $\mu g/m^3$ (SD)	7.07 (1.19)	7.09 (1.18)	7.09 (1.18)
Ambient temperature, °C (SD)	6.70 (6.73)	6.90 (6.75)	6.90 (6.75)

Abbrev. SD, Standard Deviation; WFS, Wildfire Smoke.

Note: In accordance with Statistics Canada disclosure rules, all frequencies were randomly rounded to base five. As a result, there may be discrepancies between column totals and totals by infant/maternal characteristic. Statistical analyses employed unrounded data.

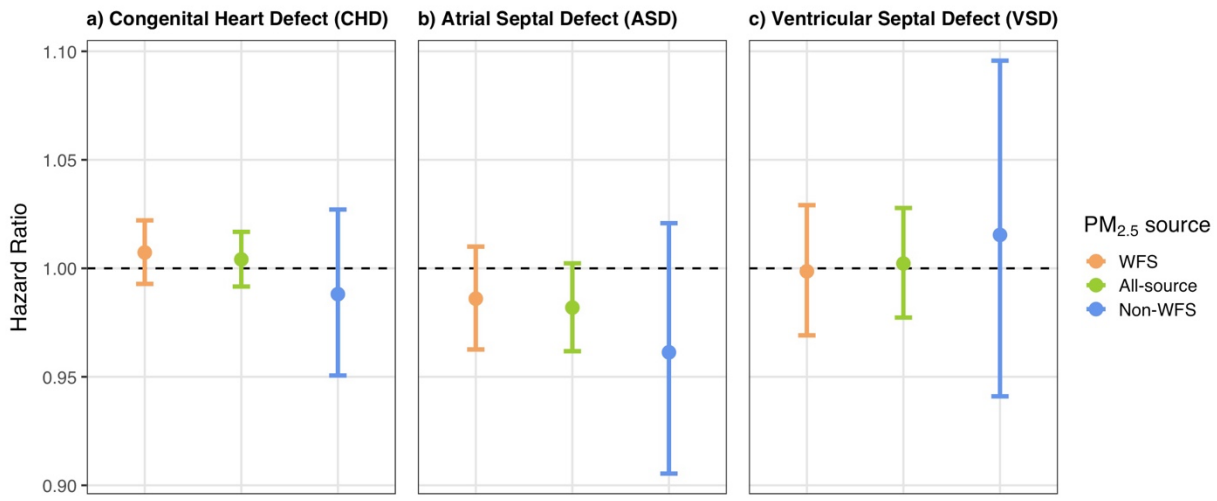


Figure 4.1. Association between overall Congenital Heart Defect (CHD) and its subtypes per 1 μg/m^3 increase in all-source, Wildfire smoke (WFS) and non-WFS $PM_{2.5}$ exposure during periconception.

Note: All-source $PM_{2.5}$ was examined in a single pollutant model, while WFS and non-WFS $PM_{2.5}$ were examined in a two-pollutant model adjusting for the cross-basis of both exposures. All models were adjusted for weekly mean ambient temperature (cross-basis), maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability with random intercepts at FSA level.

Abbrev. FSA, Forward Sortation Areas.

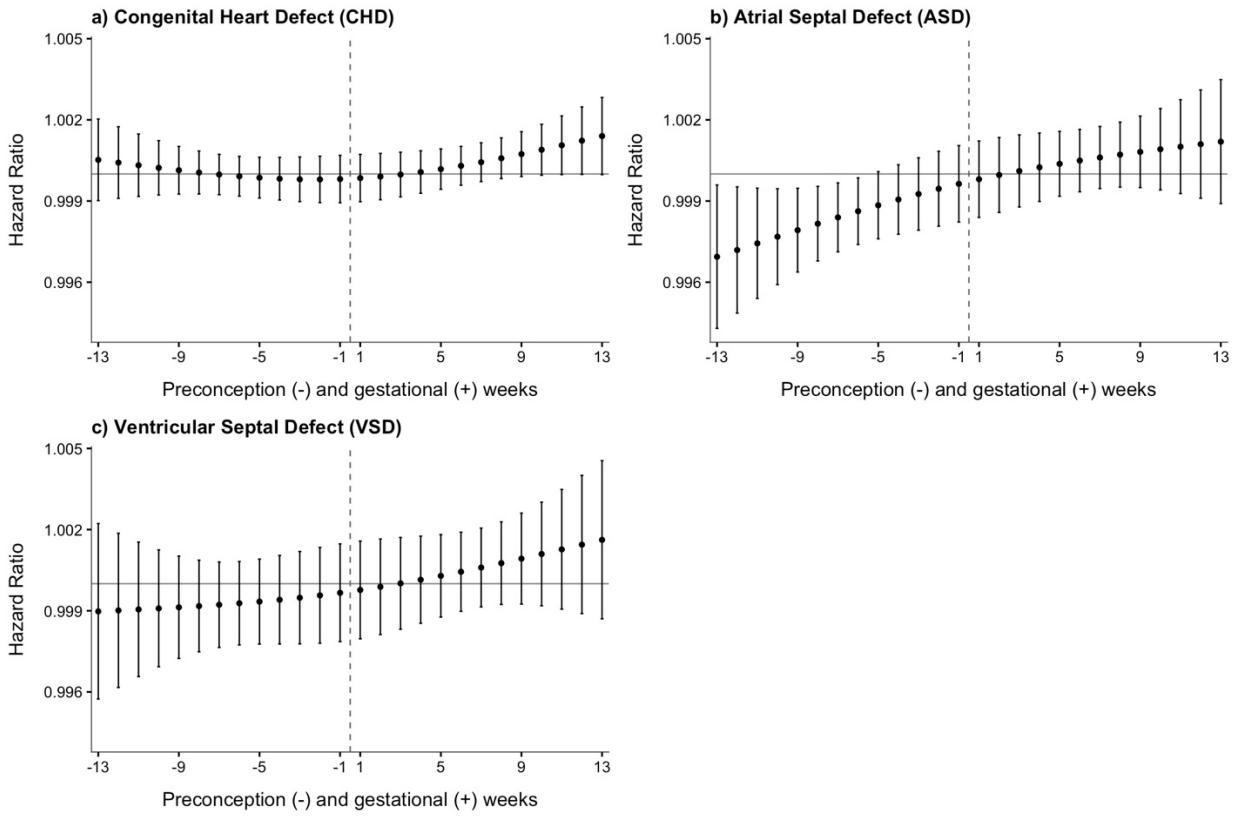


Figure 4.2. Weekly Hazard Ratios (HRs) for overall Congenital Heart Defect (CHD) and its subtypes per 1 μg/m^3 increase in prenatal Wildfire smoke (WFS) $PM_{2.5}$ concentration.

Note: The model was adjusted for weekly non-WFS $PM_{2.5}$ concentrations (cross-basis), weekly mean ambient temperature (cross-basis), maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability with random intercepts at FSA level.

Abbrev. FSA, Forward Sortation Areas.

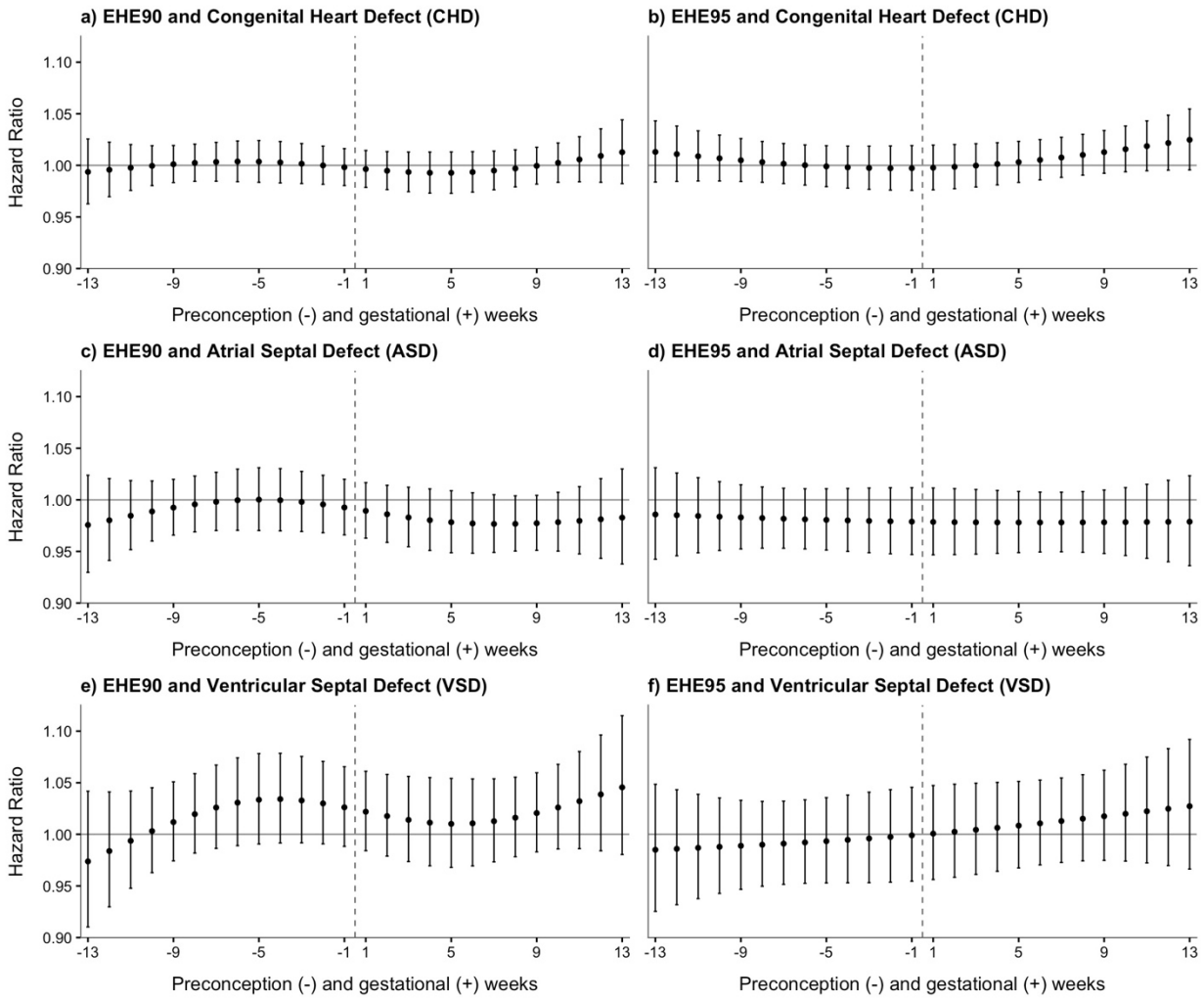


Figure 4.3. Association between presence of Extreme Heat Events (EHEs) and overall Congenital Heart Defect (CHD) with its subtypes during periconception.

Note: EHEs were defined as daily maximum temperature exceeding threshold percentiles of regional temperature distribution for number of consecutive days (EHE90 - 90th percentile for at least 3 consecutive days, EHE95 - 95th percentile for at least 2 consecutive days). All models were adjusted for maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability with random intercepts at FSA level.

Abbrev. FSA, Forward Sortation Areas.

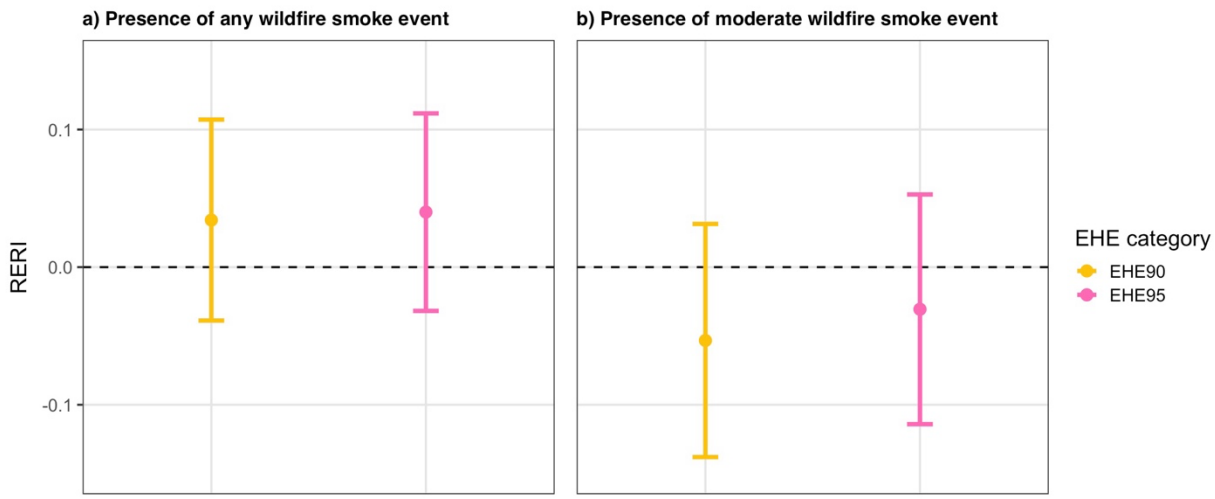


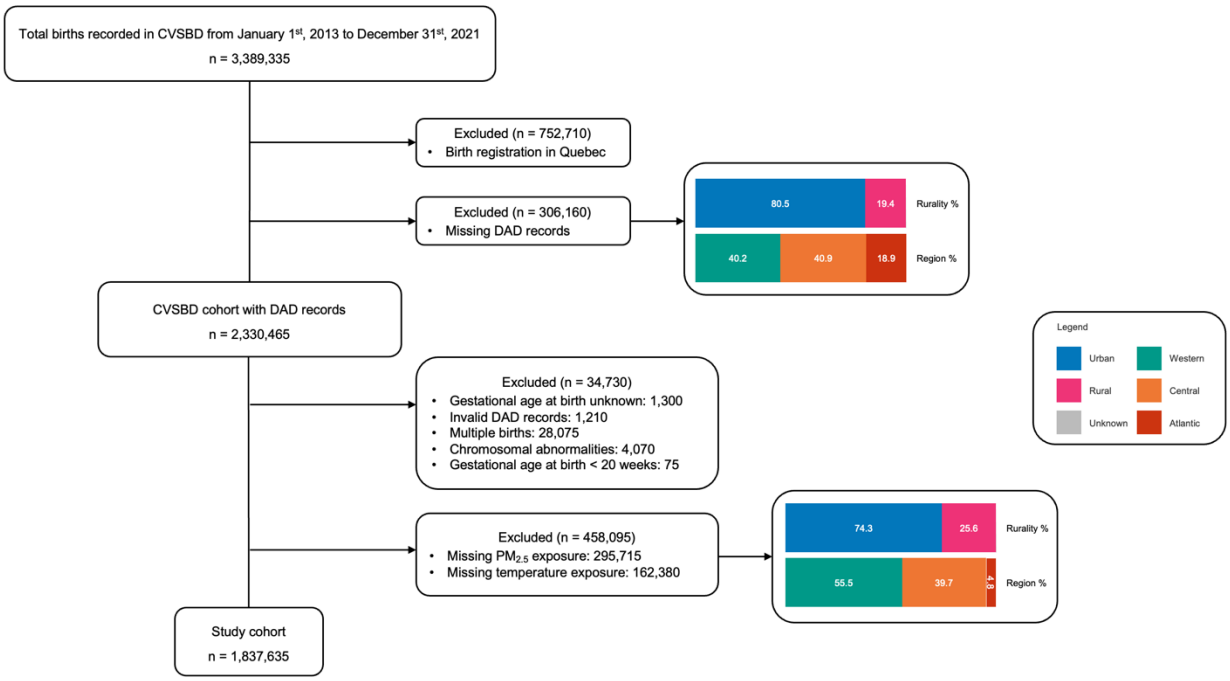
Figure 4.4. Relative Excess Risk due to Interaction for the joint association of Extreme Heat Events (EHEs) and Wildfire smoke (WFS) events on overall Congenital Heart Defect (CHD) during cardiogenesis.

Note: EHEs were defined as daily maximum temperature exceeding threshold percentiles of the regional temperature distribution for number of consecutive days (EHE90 - 90th percentile for at least 3 consecutive days, EHE95 - 95th percentile for at least 2 consecutive days). Wildfire smoke events were defined using two thresholds of any wildfire smoke (weekly WFS $PM_{2.5} > 0$ μg/m^3) and moderate wildfire smoke (weekly WFS $PM_{2.5} > 5$ μg/m^3). All models were adjusted for maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability.

4.12 Supplementary Materials

NO_2 Exposure Assessment

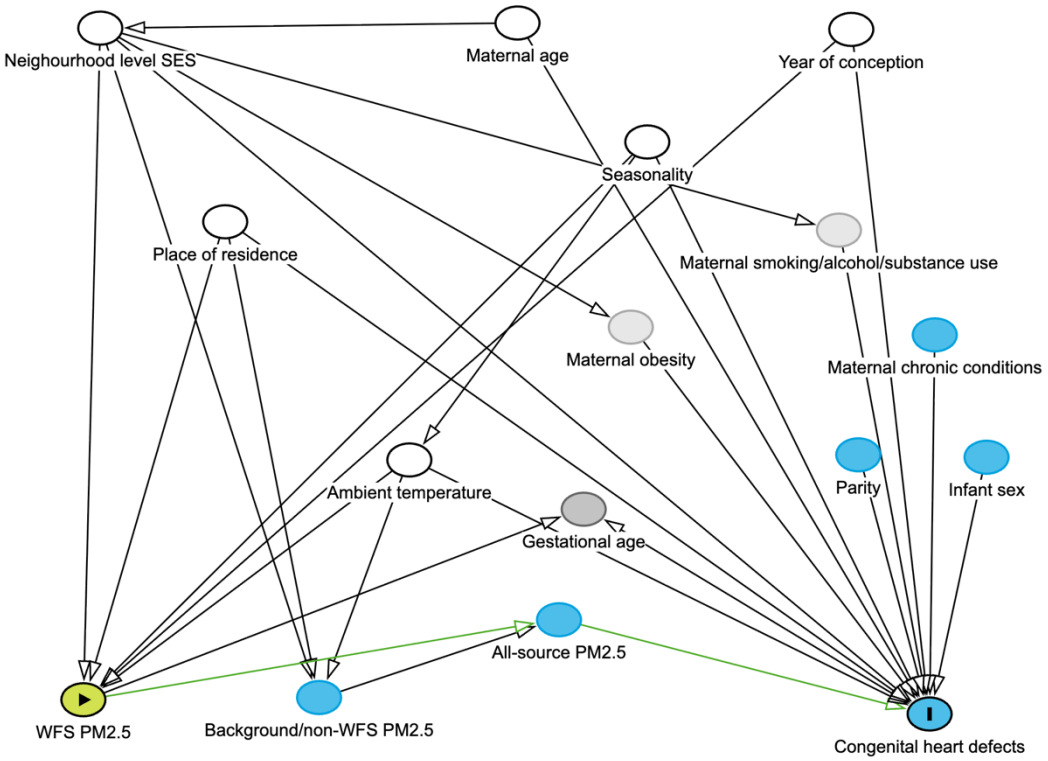
Weekly estimates of NO_2 exposures were obtained from Health Canada, which were derived using a national land-use regression (LUR) model. The LUR model incorporates ground-based estimates from National Air Pollution Surveillance (NAPS) stations, satellite-derived estimates, land use patterns of industrial land use within 2 km and road lengths within 10 km, along with summer rainfall estimates.[52] Deterministic gradients derived from previous literature were then incorporated into the LUR model, using scaling factors of 1.65 near highways and 1.2 near major roads, assumed to decay to background levels at distances of 300m and 100m for each road.[52] This LUR model was developed based on data from 2006, and was applied to NO_2 estimates observed from NAPS stations in subsequent years. Similar to $PM_{2.5}$ exposures, weekly estimates of NO_2 were assigned to each mother infant-pair during the periconception period. As this data was only available up to 2020, the sensitivity analysis adjusting for NO_2 concentrations were only analyzed among the subset of 1,271,785 infants who had complete NO_2 data. Within this cohort subset, 15,695 infants were diagnosed with congenital heart defects (CHD). Results of the following analyses are presented in Supplementary Table S7.



Supplementary Figure S1. Flow chart of the inclusion and exclusion of the study population.

Note: In accordance with Statistics Canada disclosure rules, all frequencies were randomly rounded to base five. As a result, there may be discrepancies between totals by each exclusion criteria.

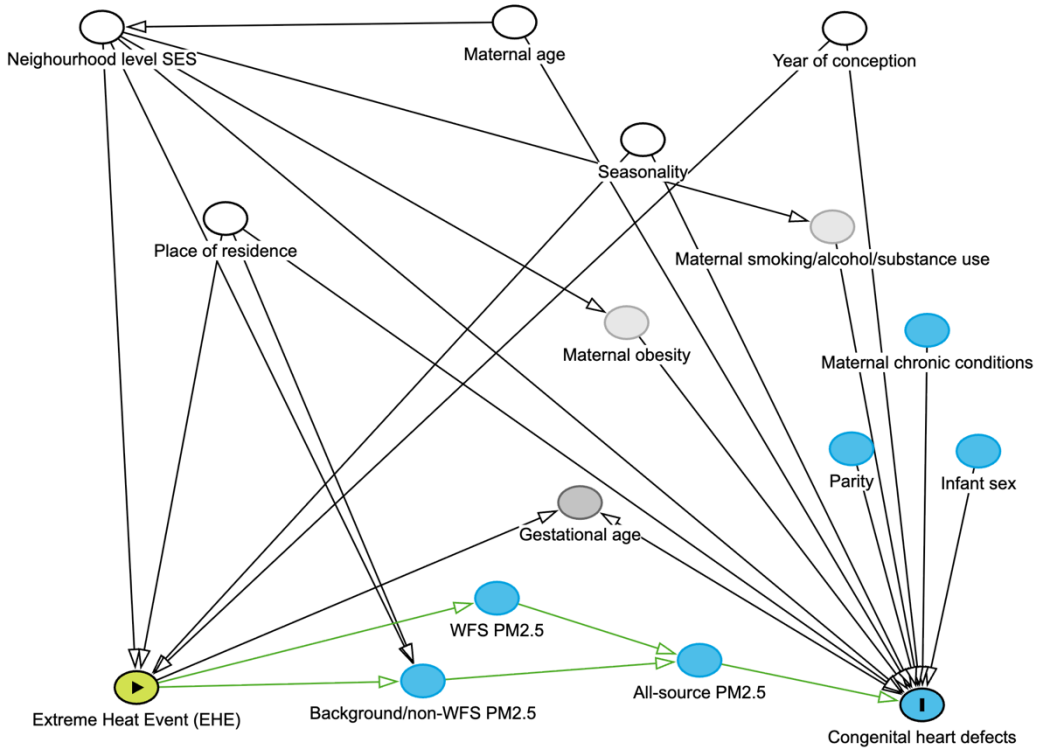
Abbrev. CVSBD, Canadian Vital Statistics Birth Database; DAD, Discharge Abstract Database.



Supplementary Figure S2. Directed Acyclic Graph (DAG) representing the association between prenatal WFS $PM_{2.5}$ exposure during pregnancy and CHD in infants.

Note: Variables in white bubbles represent adjusted covariates, light grey bubbles represent unmeasured variables, and the dark grey bubble represents a collider.

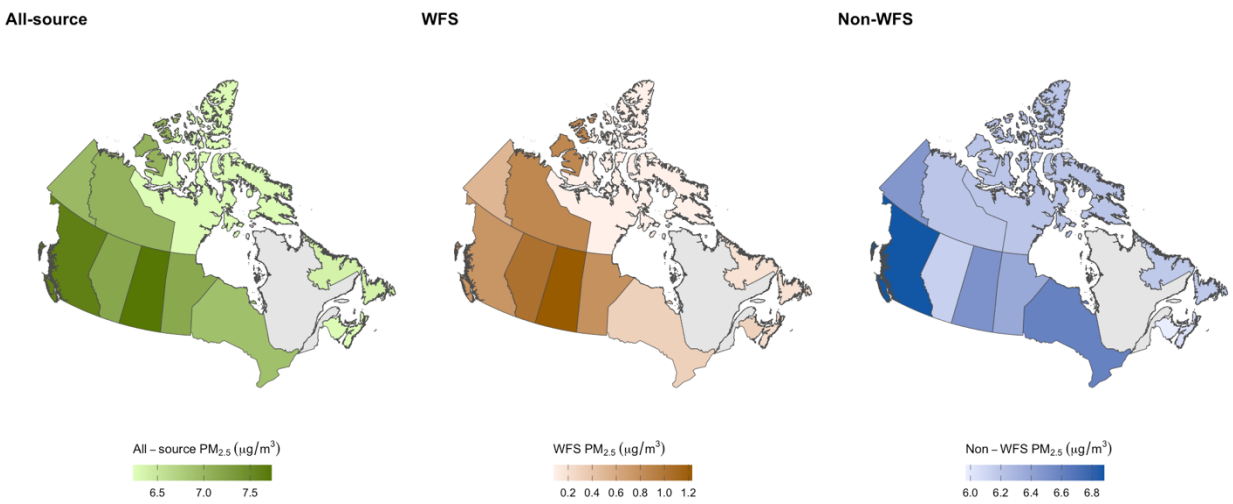
Abbrev. CHD, Congenital Heart Defect; WFS, Wildfire Smoke.



Supplementary Figure S3. Directed Acyclic Graph (DAG) representing the association between EHE exposure during pregnancy and CHD in infants.

Note: Variables in white bubbles represent adjusted covariates, light grey bubbles represent unmeasured variables and dark grey bubble represents a collider. The bubble connected by green line represents a mediator, which was not included in the model.

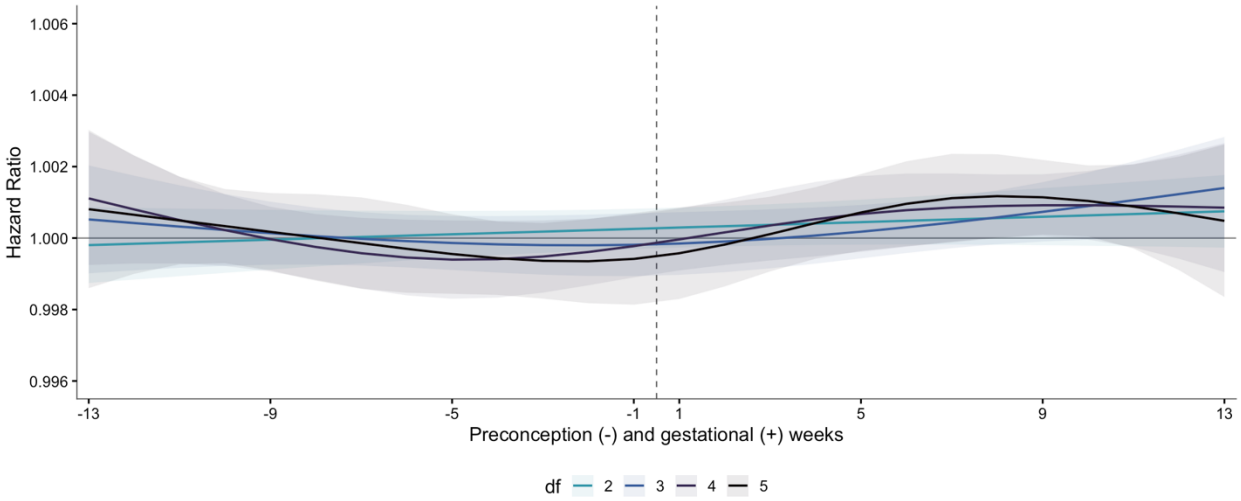
Abbrev. CHD, Congenital Heart Defect; EHE, Extreme Heat Event; WFS, Wildfire Smoke.



Supplementary Figure S4. Spatial distribution of mean concentrations of all-source, WFS and non-WFS $PM_{2.5}$ across Canada by province (2013-2021).

Note: Region shaded in grey corresponds to the province of Quebec.

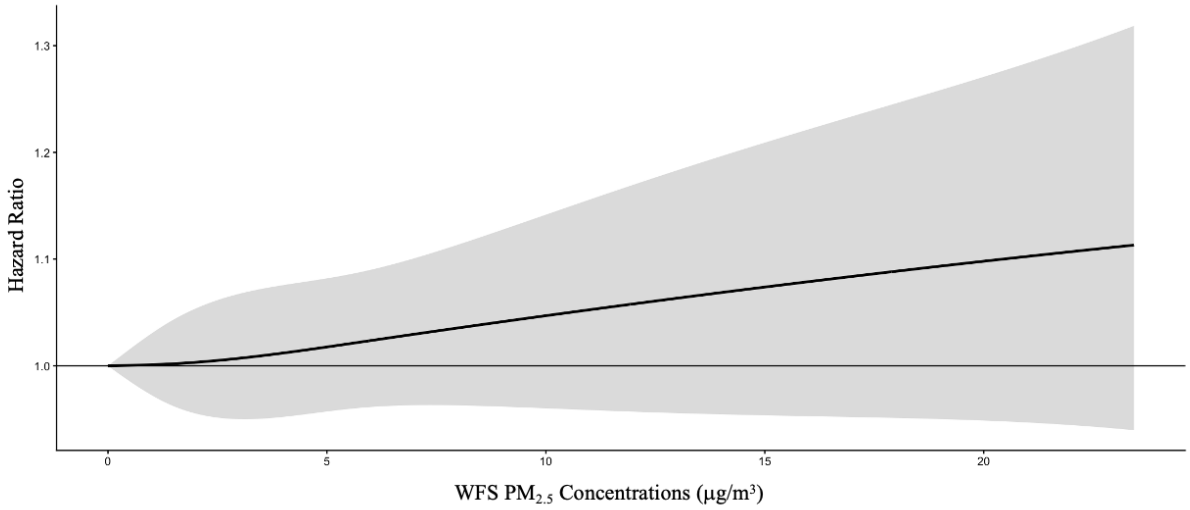
Abbrev. WFS, Wildfire Smoke.



Supplementary Figure S5. Weekly Hazard Ratios (HRs) for overall CHD per 1 μg/m^3 increase in prenatal WFS $PM_{2.5}$ concentration across different lag-response functions modelled using natural splines.

Note: The model was adjusted for weekly non-WFS $PM_{2.5}$ concentrations (cross-basis), weekly mean ambient temperature (cross-basis), maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability with random intercepts at FSA level.

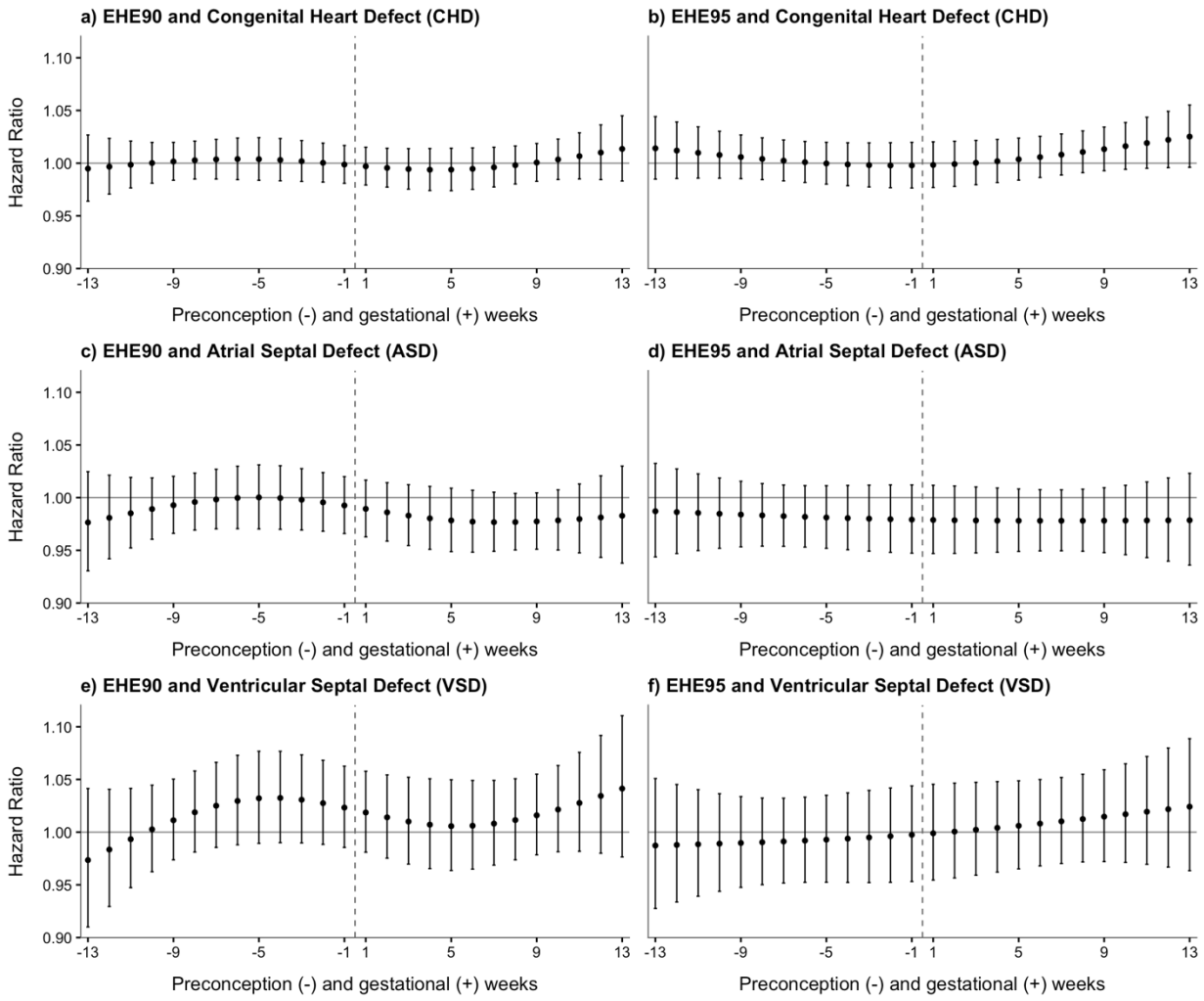
Abbrev. CHD, Congenital Heart Defect; FSA, Forward Sortation Areas; WFS, Wildfire Smoke.



Supplementary Figure S6. Exposure-response curve of the association between WFS $PM_{2.5}$ and CHD during cardiogenesis.

Note: The model was adjusted for mean non-WFS $PM_{2.5}$ concentrations, mean ambient temperature, maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability with random intercepts at FSA level. The curve was plotted up to the 99.9^{th} percentile of WFS $PM_{2.5}$ concentration distribution.

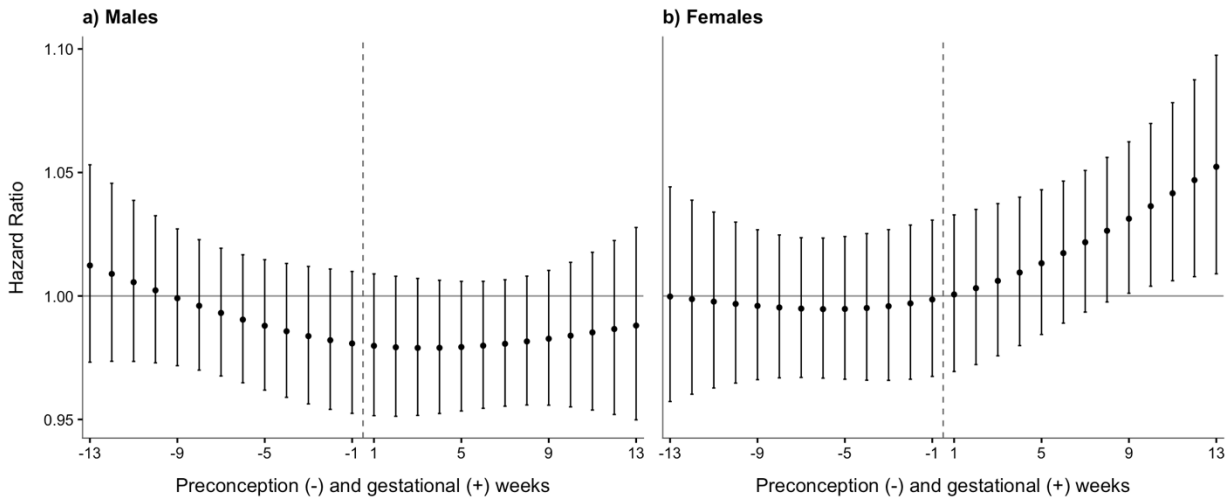
Abbrev. CHD, Congenital Heart Defect; FSA, Forward Sortation Areas; WFS, Wildfire Smoke.



Supplementary Figure S7. Association between presence of EHEs and overall CHD with its subtypes during periconception further adjusting for maternal comorbidities.

Note: EHEs were defined as daily maximum temperature exceeding threshold percentiles of regional temperature distribution for number of consecutive days (EHE90 – 90th percentile for at least 3 consecutive days, EHE95 – 95th percentile for at least 2 consecutive days). All models were adjusted for maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, maternal comorbidities, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability with random intercepts at FSA level.

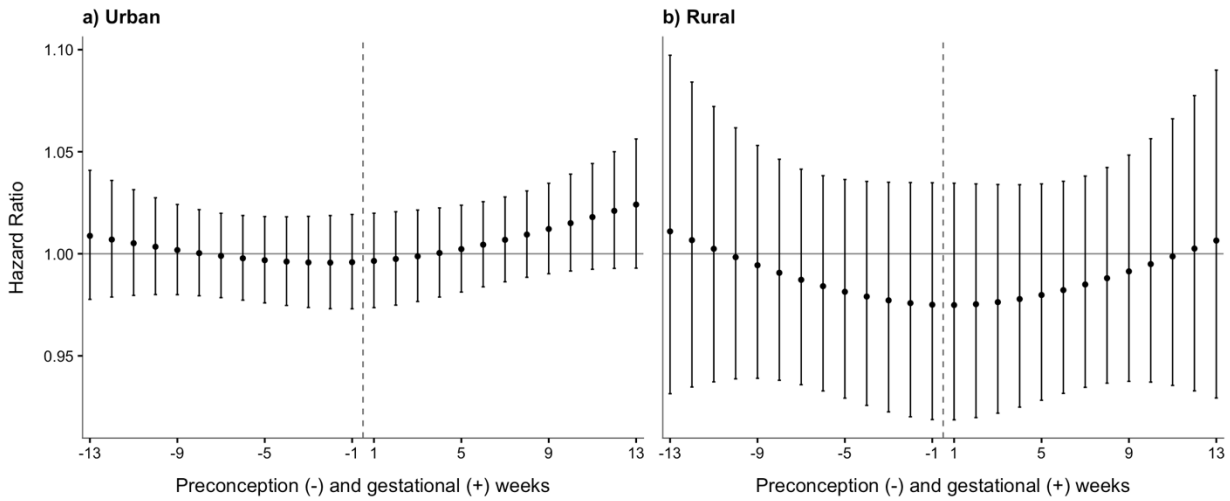
Abbrev. CHD, Congenital Heart Defect; EHE, Extreme Heat Event; FSA, Forward Sortation Areas.



Supplementary Figure S8. Association between presence of EHE95 and overall CHD during periconception stratified by infant sex.

Note: EHE95 was defined as daily maximum temperature exceeding the 95th percentile of regional temperature distribution for at least 2 consecutive days. All models were adjusted for maternal age at delivery, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability with random intercepts at FSA level.

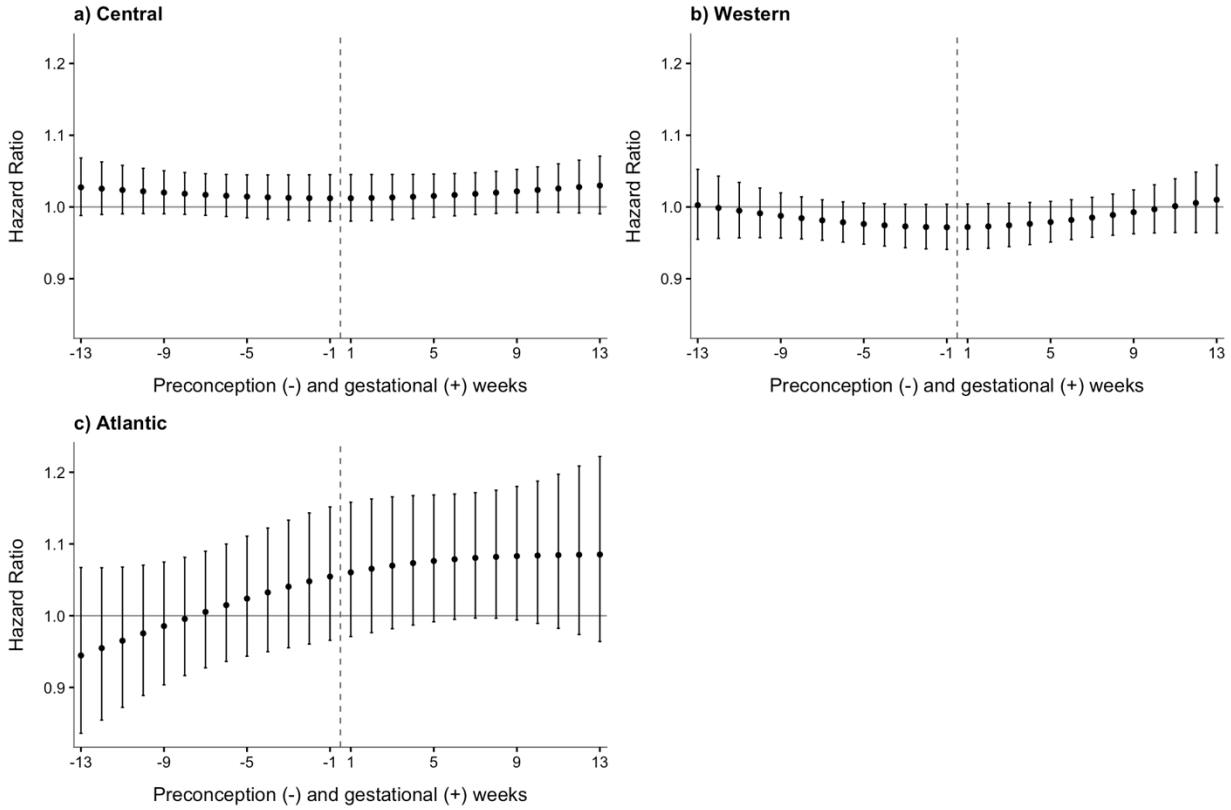
Abbrev. CHD, Congenital Heart Defect; EHE, Extreme Heat Event; FSA, Forward Sortation Areas.



Supplementary Figure S9. Association between presence of EHE95 and overall CHD during periconception stratified by rurality of maternal residence at birth.

Note: EHE95 was defined as daily maximum temperature exceeding the 95th percentile of regional temperature distribution for at least 2 consecutive days. All models were adjusted for maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, quintiles of instability, ethno-cultural composition, dependency and vulnerability with random intercepts at FSA level.

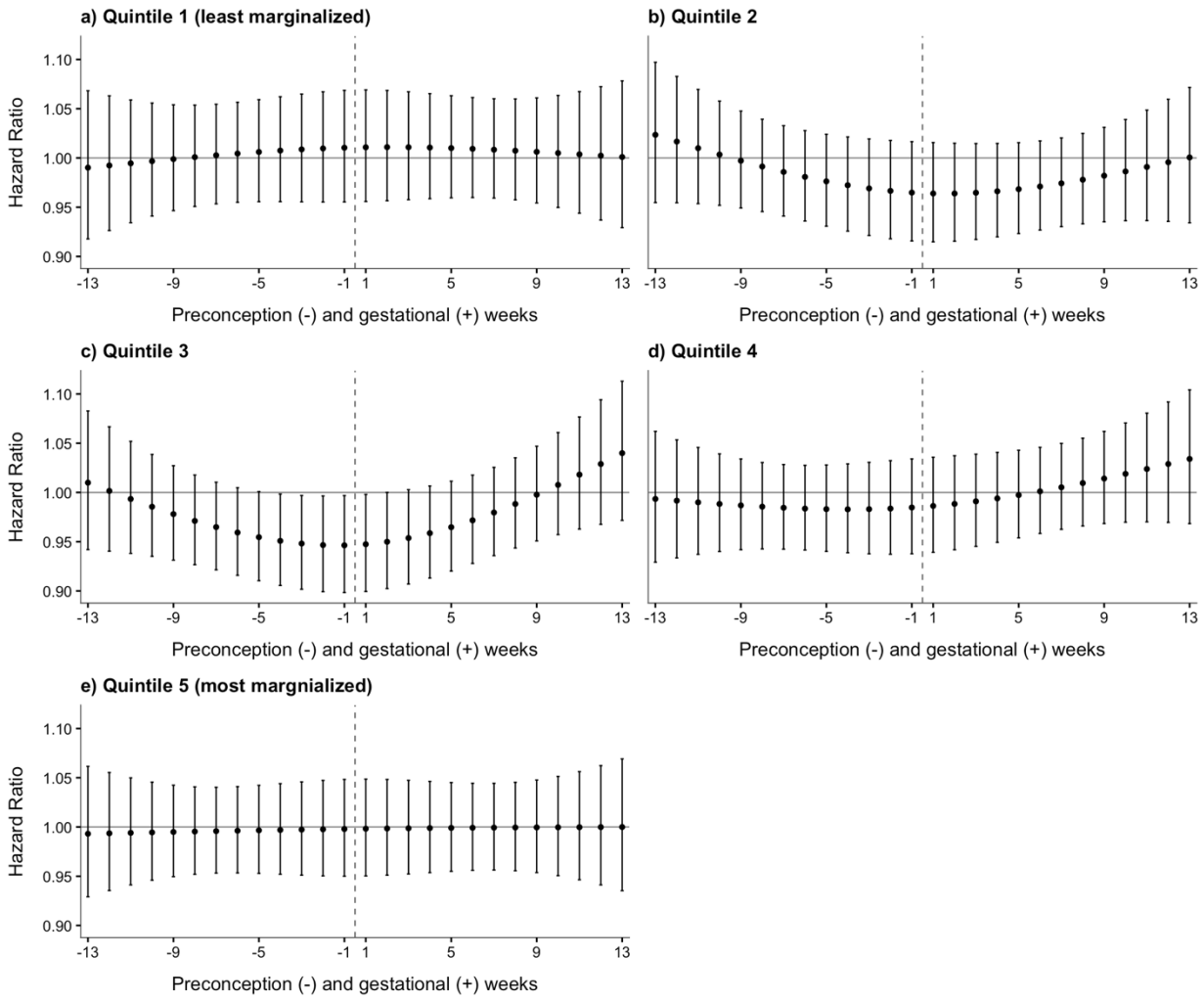
Abbrev. CHD, Congenital Heart Defect; EHE, Extreme Heat Event; FSA, Forward Sortation Areas.



Supplementary Figure S10. Association between presence of EHE95 and overall CHD during periconception stratified by geographical regions.

Note: EHE95 was defined as daily maximum temperature exceeding the 95th percentile of regional temperature distribution for at least 2 consecutive days. All models were adjusted for maternal age at delivery, infant sex, parity, season of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability with random intercepts at FSA level.

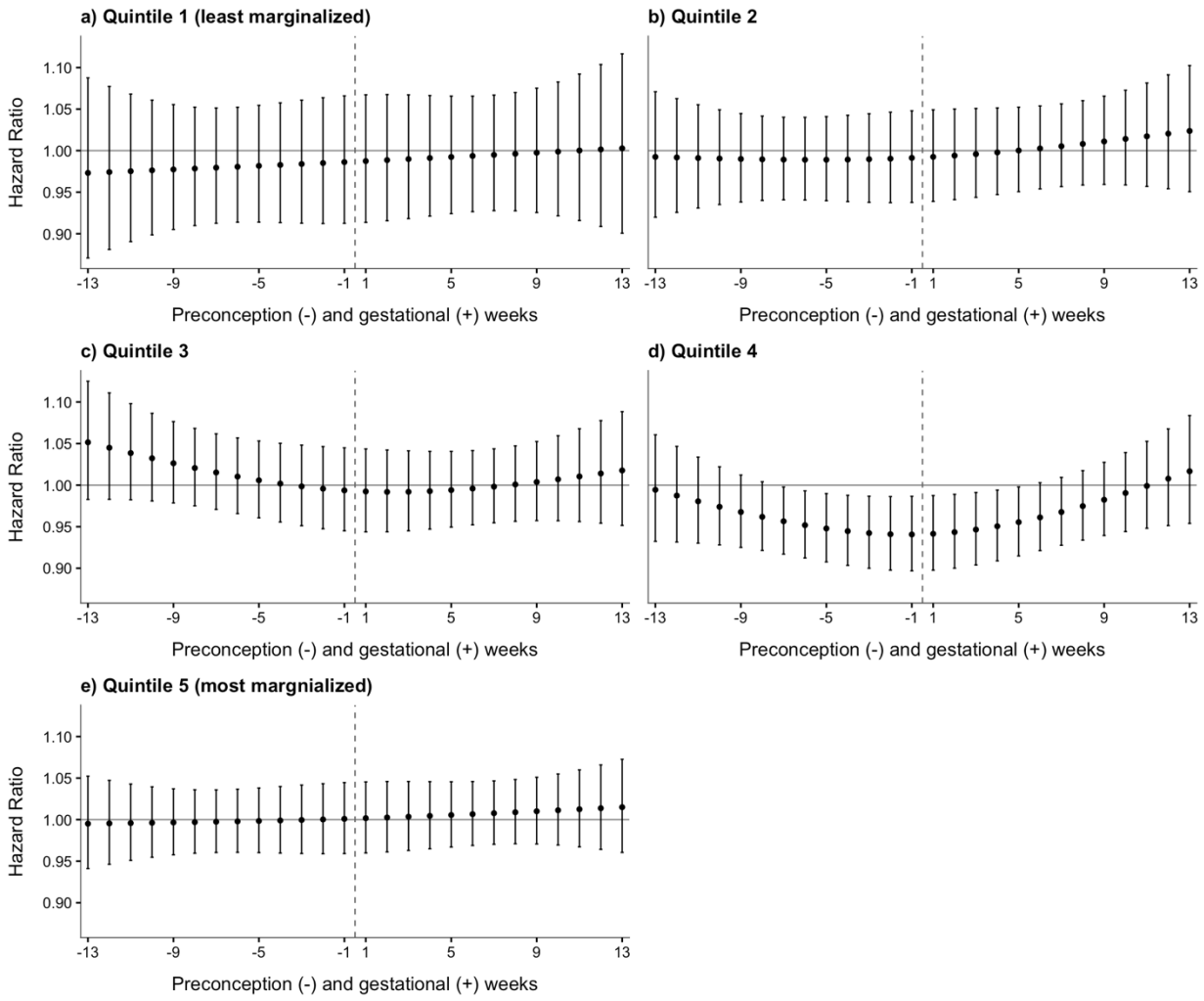
Abbrev. CHD, Congenital Heart Defect; EHE, Extreme Heat Event; FSA, Forward Sortation Areas.



Supplementary Figure S11. Association between presence of EHE95 and overall CHD during periconception stratified by residential instability quintiles.

Note: EHE95 was defined as daily maximum temperature exceeding the 95th percentile of regional temperature distribution for at least 2 consecutive days. All models were adjusted for maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of ethno-cultural composition, dependency and vulnerability with random intercepts at FSA level.

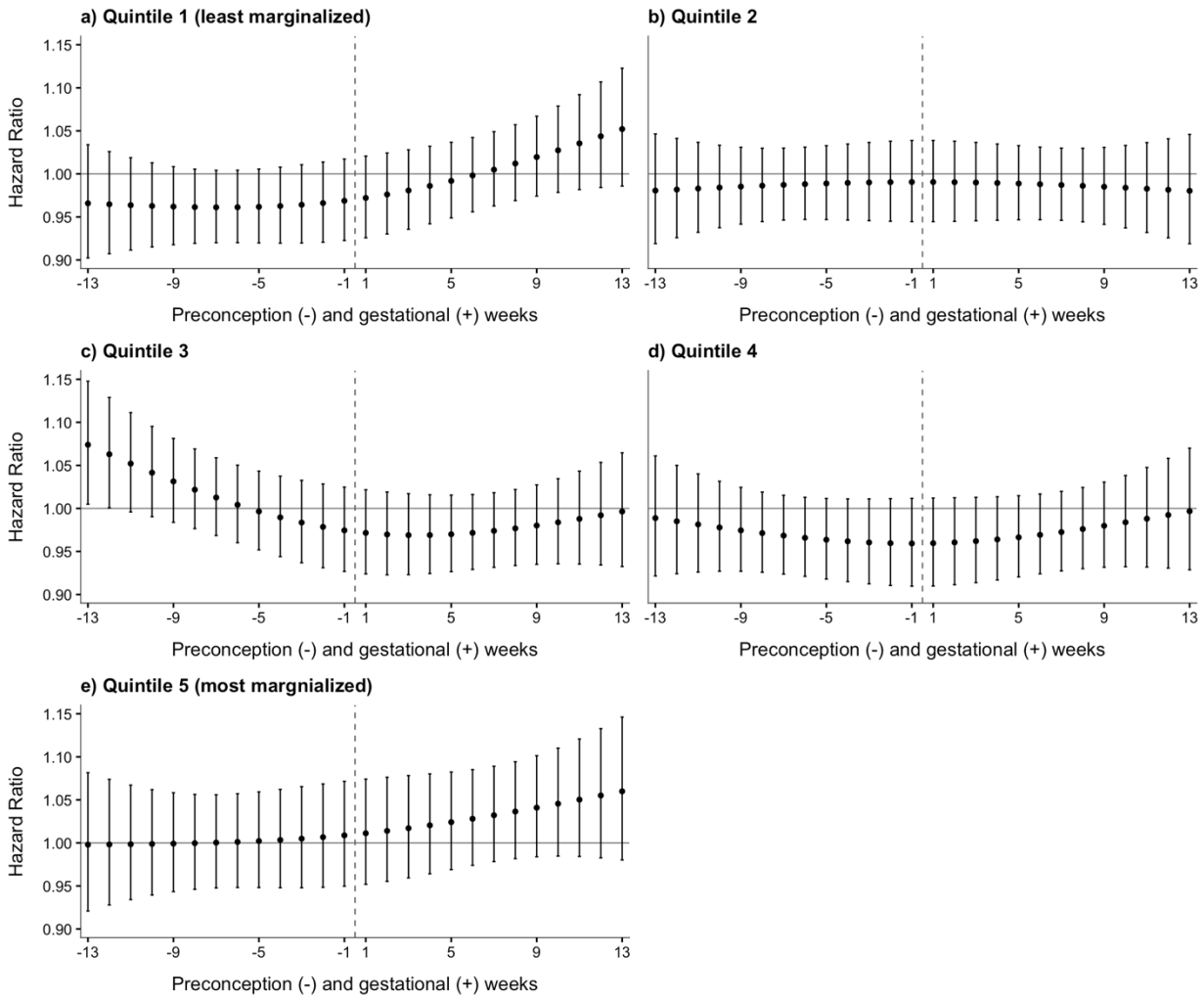
Abbrev. CHD, Congenital Heart Defect; EHE, Extreme Heat Event; FSA, Forward Sortation Areas.



Supplementary Figure S12. Association between presence of EHE95 and overall CHD during periconception stratified by ethno-cultural composition quintiles.

Note: EHE95 was defined as daily maximum temperature exceeding the 95th percentile of regional temperature distribution for at least 2 consecutive days. All models were adjusted for maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, dependency and vulnerability with random intercepts at FSA level.

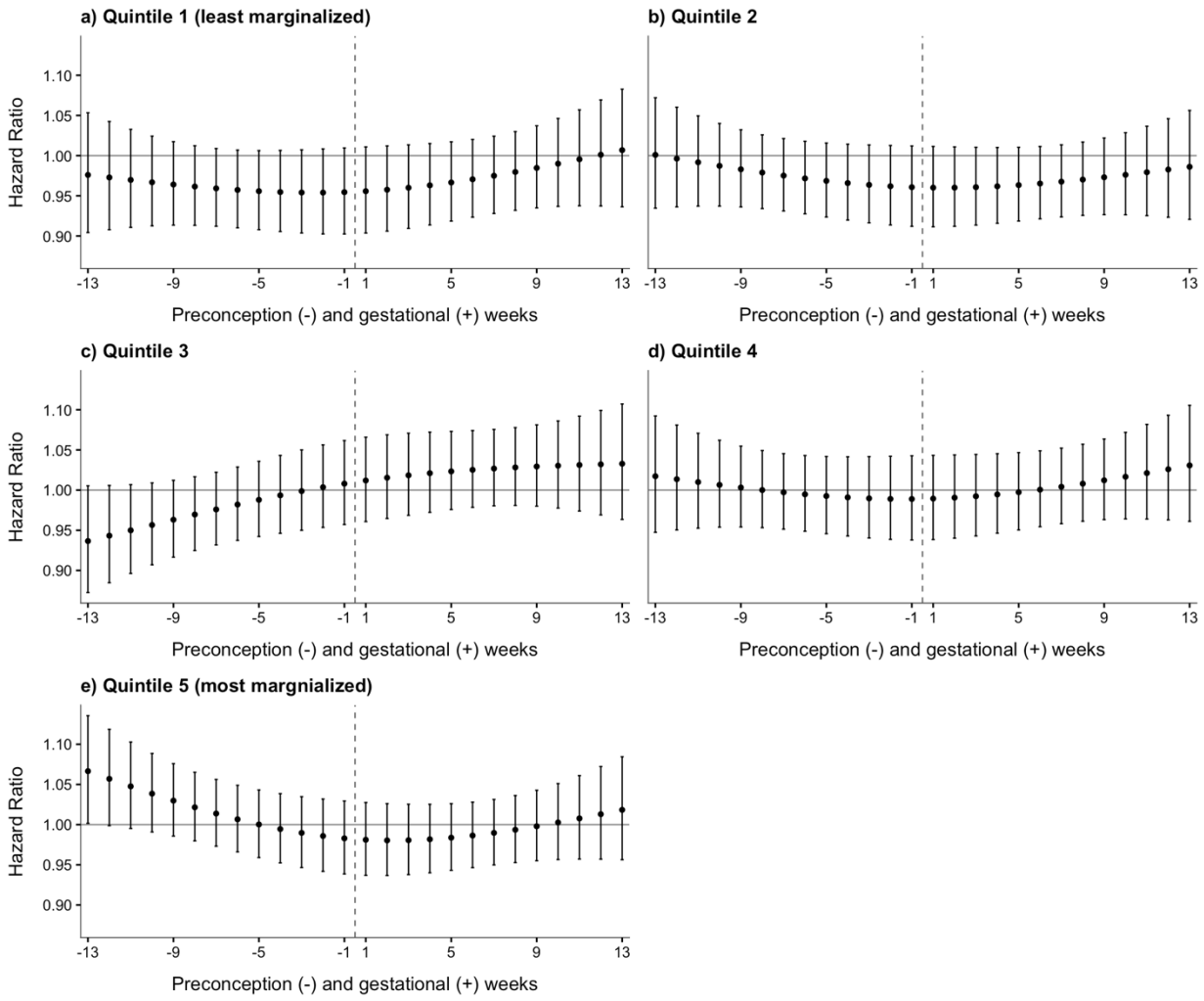
Abbrev. CHD, Congenital Heart Defect; EHE, Extreme Heat Event; FSA, Forward Sortation Areas.



Supplementary Figure S13. Association between presence of EHE95 and overall CHD during periconception stratified by economic dependency quintiles.

Note: EHE95 was defined as daily maximum temperature exceeding the 95th percentile of regional temperature distribution for at least 2 consecutive days. All models were adjusted for maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, and vulnerability with random intercepts at FSA level.

Abbrev. CHD, Congenital Heart Defect; EHE, Extreme Heat Event; FSA, Forward Sortation Areas.



Supplementary Figure S14. Association between presence of EHE95 and overall CHD during periconception stratified by situational vulnerability quintiles.

Note: EHE95 was defined as daily maximum temperature exceeding the 95th percentile of regional temperature distribution for at least 2 consecutive days. All models were adjusted for maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition and dependency with random intercepts at FSA level.

Abbrev. CHD, Congenital Heart Defect; EHE, Extreme Heat Event; FSA, Forward Sortation Areas.

Supplementary Table S1. Pearson correlation coefficients of $PM_{2.5}$ pollutants and ambient temperature.

Meteorological variable	Exposure window	Mean (SD)	Pearson correlation coefficients											
			WFS $PM_{2.5}$			Non-WFS $PM_{2.5}$			All-source $PM_{2.5}$			Ambient temperature		
			Preconception	First trimester	Periconception	Preconception	First trimester	Periconception	Preconception	First trimester	Periconception	Preconception	First trimester	Periconception
WFS $PM_{2.5}$	Preconception	0.58 (1.53)	1.00											
	First trimester	0.56 (1.49)	0.02	1.00										
	Periconception	0.57 (1.08)	0.72	0.71	1.00									
Non-WFS $PM_{2.5}$	Preconception	6.52 (0.62)	-0.01	-0.12	-0.09	1.00								
	First trimester	6.52 (0.62)	0.09	-0.01	0.06	0.30	1.00							
	Periconception	6.52 (0.50)	0.05	-0.08	-0.02	0.81	0.81	1.00						
All-source $PM_{2.5}$	Preconception	7.10 (1.64)	0.93	-0.02	0.64	0.37	0.20	0.35	1.00					
	First trimester	7.08 (1.62)	0.06	0.92	0.68	0.01	0.38	0.24	0.05	1.00				
	Periconception	7.09 (1.18)	0.68	0.61	0.91	0.26	0.39	0.41	0.73	0.72	1.00			
Ambient temperature	Preconception	7.01 (9.13)	0.33	0.03	0.25	0.01	0.15	0.10	0.31	0.09	0.27	1.00		
	First trimester	6.79 (9.10)	-0.09	0.33	0.16	0.03	0.02	0.03	-0.07	0.31	0.16	0.10	1.00	
	Periconception	6.89 (6.75)	0.16	0.24	0.28	0.03	0.11	0.09	0.16	0.27	0.29	0.74	0.74	1.00

Supplementary Table S2. Cumulative Hazard Ratios (95% Confidence Intervals) associated with 1 μg/m^3 increase in $PM_{2.5}$ or presence of EHE during periconception on overall CHD and their corresponding Akaike Information Criterion (AIC) estimates.

Cross-basis	Metric	Lag-response model			
		Ns (df = 2)	Ns (df = 3)	Ns (df = 4)	Ns (df = 5)
WFS $PM_{2.5}$	HR (95% CI)	1.007 (0.993, 1.022)	1.007 (0.993, 1.022)	1.007 (0.993, 1.022)	1.007 (0.992, 1.021)
	AIC	661173.7	**661173.1**	661174.4	661175.3
Non-WFS $PM_{2.5}$	HR (95% CI)	0.989 (0.952, 1.028)	0.988 (0.951, 1.027)	0.988 (0.951, 1.027)	0.989 (0.951, 1.028)
	AIC	661173.3	**661173.1**	661173.5	661174.6
All-source $PM_{2.5}$	HR (95% CI)	1.004 (0.991, 1.016)	1.004 (0.992, 1.017)	1.004 (0.992, 1.017)	1.004 (0.991, 1.017)
	AIC	661168.1	**661167.8**	661169.5	661170.9
EHE90	HR (95% CI)	0.998 (0.711, 1.402)	0.989 (0.703, 1.392)	0.988 (0.702, 1.390)	0.985 (0.699, 1.386)
	AIC	661238.1	661238.9	**661237.9**	661240.0
EHE95	HR (95% CI)	1.227 (0.810, 1.858)	1.167 (0.766, 1.777)	1.166 (0.766, 1.777)	1.159 (0.761, 1.767)
	AIC	661234.2	**661233.3**	661234.6	661236.1

Note: WFS and non-WFS $PM_{2.5}$ were examined in a two-pollutant model adjusting for the cross-basis of both exposures. All models were adjusted for maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability with random intercepts at FSA level. $PM_{2.5}$ pollutant models were further adjusted for cross-basis of ambient temperature.

Abbrev. CHD, Congenital Heart Defect; EHE, Extreme Heat Event; FSA, Forward Sortation Areas; WFS, Wildfire Smoke.

Supplementary Table S3. Association between overall CHD and its subtypes per 1 μg/m^3 increase in all-source, WFS and non-WFS $PM_{2.5}$.

CHD subtype	Exposure window	WFS $PM_{2.5}$ HR (95% CI)	All-source $PM_{2.5}$ HR (95% CI)	Non-WFS $PM_{2.5}$ HR (95% CI)
CHD	Preconception	1.001 (0.991, 1.010)	1.001 (0.992, 1.009)	1.003 (0.976, 1.031)
	First trimester	1.007 (0.997, 1.016)	1.004 (0.996, 1.012)	0.985 (0.958, 1.012)
	Periconception	1.007 (0.993, 1.022)	1.004 (0.992, 1.017)	0.988 (0.951, 1.027)
	Cardiogenesis	1.003 (0.999, 1.008)	1.002 (0.998, 1.006)	0.993 (0.980, 1.006)
ASD	Preconception	0.979 (0.963, 0.995)	0.980 (0.966, 0.994)	0.994 (0.952, 1.037)
	First trimester	1.007 (0.993, 1.022)	1.002 (0.988, 1.015)	0.967 (0.927, 1.010)
	Periconception	0.986 (0.963, 1.010)	0.982 (0.962, 1.002)	0.961 (0.905, 1.021)
	Cardiogenesis	1.004 (0.997, 1.011)	1.001 (0.995, 1.008)	0.985 (0.965, 1.005)
	Sensitive window[a]	0.983 (0.969, 0.996)	0.984 (0.972, 0.996)	-
VSD	Preconception	0.990 (0.970, 1.011)	0.997 (0.980, 1.015)	1.038 (0.982, 1.097)
	First trimester	1.008 (0.990, 1.027)	1.005 (0.988, 1.022)	0.979 (0.925, 1.035)
	Periconception	0.999 (0.969, 1.029)	1.002 (0.977, 1.028)	1.015 (0.941, 1.096)
	Cardiogenesis	1.004 (0.995, 1.013)	1.003 (0.995, 1.015)	0.989 (0.963, 1.016)

Note: All-source $PM_{2.5}$ was examined in a single pollutant model, while WFS and non-WFS $PM_{2.5}$ were examined in a two-pollutant model adjusting for the cross-basis of both exposures. All models were adjusted for weekly mean ambient temperature (cross-basis), maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability with random intercepts at FSA level.

Abbrev. ASD, Atrial Septal Defect; CHD, Congenital Heart Defect; VSD, Ventricular Septal Defect; FSA, Forward Sortation Areas; WFS, Wildfire Smoke.
*Sensitive window[a] corresponds to 6-13 weeks prior to conception.

Supplementary Table S4. Association between overall CHD and its subtypes per 1 μg/m^3 increase in all-source, WFS and non-WFS $PM_{2.5}$ further adjusting for maternal comorbidities.

CHD subtype	Exposure window	WFS $PM_{2.5}$ HR (95% CI)	All-source $PM_{2.5}$ HR (95% CI)	Non-WFS $PM_{2.5}$ HR (95% CI)
CHD	Preconception	1.001 (0.992, 1.011)	1.000 (0.992, 1.009)	1.002 (0.975, 1.030)
	First trimester	1.007 (0.998, 1.017)	1.004 (0.996, 1.013)	0.985 (0.958, 1.012)
	Periconception	1.008 (0.994, 1.023)	1.005 (0.992, 1.017)	0.986 (0.949, 1.025)
	Cardiogenesis	1.003 (0.999, 1.008)	1.002 (0.998, 1.006)	0.993 (0.980, 1.006)
ASD	Preconception	0.979 (0.963, 0.996)	0.980 (0.966, 0.994)	0.993 (0.951, 1.036)
	First trimester	1.008 (0.993, 1.023)	1.002 (0.989, 1.016)	0.968 (0.927, 1.010)
	Periconception	0.987 (0.963, 1.011)	0.982 (0.962, 1.003)	0.961 (0.905, 1.020)
	Cardiogenesis	1.004 (0.997, 1.011)	1.002 (0.995, 1.008)	0.985 (0.965, 1.005)
	Sensitive window[a]	0.983 (0.970, 0.996)	0.984 (0.972, 0.996)	-
VSD	Preconception	0.990 (0.970, 1.010)	0.998 (0.981, 1.015)	1.043 (0.987, 1.102)
	First trimester	1.007 (0.988, 1.026)	1.004 (0.988, 1.021)	0.982 (0.928, 1.038)
	Periconception	0.997 (0.967, 1.027)	1.002 (0.977, 1.028)	1.024 (0.949, 1.105)
	Cardiogenesis	1.004 (0.995, 1.013)	1.002 (0.994, 1.010)	0.991 (0.965, 1.018)

Note: All-source $PM_{2.5}$ was examined in a single pollutant model, while WFS and non-WFS $PM_{2.5}$ were examined in a two-pollutant model adjusting for the cross-basis of both exposures. All models were adjusted for weekly mean ambient temperature (cross-basis), maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, maternal comorbidities, quintiles of instability, ethno-cultural composition, dependency and vulnerability with random intercepts at FSA level.

Abbrev. ASD, Atrial Septal Defect; CHD, Congenital Heart Defect; VSD, Ventricular Septal Defect; FSA, Forward Sortation Areas; WFS, Wildfire Smoke.
*Sensitive window[a] corresponds to 6-13 weeks prior to conception.

Supplementary Table S5. Association between overall CHD and its subtypes per 1 μg/m^3 increase in all-source, WFS and non-WFS $PM_{2.5}$ using mixed-effects log-binomial models.

CHD subtype	Exposure window	WFS $PM_{2.5}$ RR (95% CI)	All-source $PM_{2.5}$ RR (95% CI)	Non-WFS $PM_{2.5}$ RR (95% CI)
CHD	Preconception	1.000 (0.991, 1.010)	1.000 (0.992, 1.009)	1.004 (0.978, 1.032)
	First trimester	1.006 (0.997, 1.016)	1.004 (0.996, 1.012)	0.986 (0.960, 1.014)
	Periconception	1.007 (0.992, 1.023)	1.004 (0.992, 1.017)	0.991 (0.953, 1.029)
	Cardiogenesis	1.003 (0.999, 1.007)	1.002 (0.998, 1.006)	0.993 (0.981, 1.006)
ASD	Preconception	0.978 (0.962, 0.994)	0.980 (0.966, 0.994)	0.998 (0.956, 1.041)
	First trimester	1.007 (0.993, 1.022)	1.002 (0.989, 1.015)	0.970 (0.929, 1.012)
	Periconception	0.985 (0.962, 1.009)	0.982 (0.962, 1.002)	0.968 (0.911, 1.027)
	Cardiogenesis	1.004 (0.997, 1.011)	1.001 (0.995, 1.008)	0.986 (0.966, 1.006)
	Sensitive window[a]	0.982 (0.969, 0.995)	0.984 (0.972, 0.995)	-
VSD	Preconception	0.990 (0.970, 1.011)	0.997 (0.980, 1.014)	1.037 (0.981, 1.096)
	First trimester	1.008 (0.990, 1.027)	1.005 (0.988, 1.022)	0.979 (0.926, 1.035)
	Periconception	0.998 (0.969, 1.029)	1.002 (0.977, 1.027)	1.015 (0.941, 1.095)
	Cardiogenesis	1.004 (0.995, 1.013)	1.002 (0.994, 1.010)	0.989 (0.963, 1.016)

Note: All-source $PM_{2.5}$ was examined in a single pollutant model, while WFS and non-WFS $PM_{2.5}$ were examined in a two-pollutant model adjusting for the cross-basis of both exposures. All models were adjusted for weekly mean ambient temperature (cross-basis), maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability with random intercepts at FSA level.

Abbrev. ASD, Atrial Septal Defect; CHD, Congenital Heart Defect; VSD, Ventricular Septal Defect; FSA, Forward Sortation Areas; WFS, Wildfire Smoke.
*Sensitive window[a] corresponds to 6-13 weeks prior to conception.

Supplementary Table S6. Association between overall CHD and its subtypes per 1 μg/m^3 increase in all-source, WFS and non-WFS $PM_{2.5}$ during first trimester.

CHD subtype	Exposure window	WFS $PM_{2.5}$ HR (95% CI)	All-source $PM_{2.5}$ HR (95% CI)	Non-WFS $PM_{2.5}$ HR (95% CI)
CHD	First trimester	1.006 (0.996, 1.016)	1.004 (0.996, 1.013)	0.997 (0.968, 1.026)
	Cardiogenesis	1.004 (0.998, 1.009)	1.003 (0.997, 1.009)	0.983 (0.964, 1.002)
ASD	First trimester	1.005 (0.990, 1.021)	1.000 (0.986, 1.014)	0.971 (0.928, 1.016)
	Cardiogenesis	1.003 (0.995, 1.012)	1.002 (0.993, 1.011)	0.987 (0.958, 1.017)
VSD	First trimester	1.012 (0.992, 1.032)	1.009 (0.991, 1.027)	0.994 (0.937, 1.054)
	Cardiogenesis	1.004 (0.993, 1.016)	1.002 (0.990, 1.014)	0.975 (0.947, 1.016)

Note: All-source $PM_{2.5}$ was examined in a single pollutant model, while WFS and non-WFS $PM_{2.5}$ were examined in a two-pollutant model adjusting for the cross-basis of both exposures. All models were adjusted for weekly mean ambient temperature (cross-basis), maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability with random intercepts at FSA level.

Abbrev. ASD, Atrial Septal Defect; CHD, Congenital Heart Defect; VSD, Ventricular Septal Defect; FSA, Forward Sortation Areas; WFS, Wildfire Smoke.

Supplementary Table S7. Association between overall CHD per 1 μg/m^3 increase in all-source, WFS and non-WFS $PM_{2.5}$ in the subset of cohort with complete NO_2 data.

Statistical model	Exposure window	WFS $PM_{2.5}$ HR (95% CI)	All-source $PM_{2.5}$ HR (95% CI)	Non-WFS $PM_{2.5}$ HR (95% CI)
Primary	Preconception	0.995 (0.983, 1.007)	0.996 (0.985, 1.006)	0.996 (0.964, 1.028)
	First trimester	1.004 (0.993, 1.015)	1.003 (0.993, 1.013)	0.989 (0.957, 1.022)
	Periconception	0.999 (0.982, 1.017)	0.998 (0.983, 1.014)	0.985 (0.941, 1.031)
	Cardiogenesis	1.003 (0.997, 1.007)	1.001 (0.997, 1.006)	0.995 (0.979, 1.011)
Primary + NO_2 adjusted	Preconception	0.995 (0.983, 1.007)	0.995 (0.984, 1.005)	0.995 (0.964, 1.028)
	First trimester	1.004 (0.993, 1.015)	1.002 (0.992, 1.012)	0.988 (0.956, 1.021)
	Periconception	0.999 (0.982, 1.017)	0.996 (0.981, 1.012)	0.983 (0.940, 1.029)
	Cardiogenesis	1.002 (0.997, 1.007)	1.001 (0.996, 1.006)	0.994 (0.979, 1.010)

Note: All-source $PM_{2.5}$ was examined in a single pollutant model, while WFS and non-WFS $PM_{2.5}$ were examined in a two-pollutant model adjusting for the cross-basis of both exposures. The primary model was adjusted for weekly mean ambient temperature (cross-basis), maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability with random intercepts at FSA level.

Abbrev. CHD, Congenital Heart Defect; FSA, Forward Sortation Areas; NO_2, Nitrogen Dioxide; WFS, Wildfire Smoke.

Supplementary Table S8. Association between overall CHD per 1 μg/m^3 increase in WFS $PM_{2.5}$ during periconception, adjusting for alternative specifications of seasonality.

Statistical Model	Seasonal covariate	HR (95% CI)	SE	AIC
Model 1 (Primary model)	Day-of-year of conception	1.007 (0.993, 1.022)	0.0074	661173.1
Model 2	Season of conception (categorical)	1.014 (1.000, 1.029)	0.0071	661176.1
Model 3	Month of conception (categorical)	1.011 (0.996, 1.025)	0.0073	661185.3
Model 4	Epiweek[a] in a year of conception	1.010 (0.996, 1.025)	0.0073	661175.9
Model 5	Season of conception (categorical), Epiweek[a] in a year of conception	1.010 (0.996, 1.025)	0.0073	661181.0

Note: All models were adjusted for weekly non-WFS $PM_{2.5}$ (cross-basis), weekly mean ambient temperature (cross-basis), maternal age at delivery, infant sex, parity, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability with random intercepts at FSA level.

Abbrev. Akaike Information Criterion, AIC; CHD, Congenital Heart Defect; FSA, Forward Sortation Areas; SE, Standard Error; WFS, Wildfire Smoke.
*Season of conception categorized into Spring (April – June), Summer (July – September), Fall (October – December) and Winter (January – March).
*Epidemiologic week[a] in a year modeled using natural cubic splines with 3 dfs.

Supplementary Table S9. Stratified analysis of associations between 1 μg/m^3 increase in WFS $PM_{2.5}$ concentration on CHD during periconception.

Characteristic	Cohort size (cases)	HR (95% CI)	p-value
Infant sex			
Male	945,370 (12,545)	1.007 (0.988, 1.027)	Ref.
Female	892,265 (10,460)	1.005 (0.983, 1.026)	0.87
Rurality			
Urban	1,587,130 (19,900)	1.006 (0.990, 1.022)	Ref.
Rural	247,870 (3,060)	1.014 (0.979, 1.050)	0.96
Geographical region			
Central	944,885 (11,880)	0.939 (0.868, 1.015)	Ref.
Western	791,265 (9,645)	1.023 (1.007, 1.040)	0.61
Atlantic	101,480 (1,475)	0.996 (0.795, 1.248)	0.36
Residential instability quintile			
Quintile 1 (least marginalized)	302,850 (3,450)	0.980 (0.939, 1.022)	Ref.
Quintile 2	333,810 (3,975)	1.013 (0.979, 1.049)	0.26
Quintile 3	319,000 (4,000)	0.981 (0.947, 1.016)	0.22
Quintile 4	341,950 (4,400)	1.004 (0.973, 1.036)	0.73
Quintile 5 (most marginalized)	325,535 (4,325)	1.009 (0.973, 1.045)	0.43
Ethno-cultural composition quintile			
Quintile 1 (least marginalized)	138,060 (1,705)	1.006 (0.958, 1.056)	Ref.
Quintile 2	258,950 (3,315)	0.970 (0.935, 1.006)	0.34
Quintile 3	318,930 (4,150)	0.994 (0.962, 1.027)	0.55
Quintile 4	376,780 (4,665)	1.001 (0.967, 1.035)	0.24
Quintile 5 (most marginalized)	530,425 (6,355)	1.028 (0.993, 1.065)	0.66
Economic dependency quintile			
Quintile 1 (least marginalized)	379,325 (4,425)	0.990 (0.958, 1.021)	Ref.
Quintile 2	374,235 (4,665)	0.996 (0.964, 1.029)	0.14
Quintile 3	338,320 (4,330)	0.989 (0.955, 1.025)	0.49
Quintile 4	302,165 (3,810)	0.990 (0.952, 1.029)	0.25
Quintile 5 (most marginalized)	229,100 (2,965)	1.038 (0.997, 1.080)	0.42
Situational vulnerability quintile			
Quintile 1 (least marginalized)	322,310 (3,410)	0.965 (0.925, 1.008)	Ref.
Quintile 2	342,205 (4,035)	0.970 (0.934, 1.008)	0.57
Quintile 3	315,935 (3,980)	1.018 (0.983, 1.054)	0.38
Quintile 4	304,615 (3,870)	1.023 (0.989, 1.058)	0.06
Quintile 5 (most marginalized)	338,085 (4,900)	0.999 (0.970, 1.030)	0.07

Note: All models were adjusted for weekly non-WFS $PM_{2.5}$ (cross-basis), weekly mean ambient temperature (cross-basis), maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability, with random intercepts at FSA level. The stratifying variable was excluded from its corresponding model.
In accordance with Statistics Canada disclosure rules, all frequencies were randomly rounded to base five. As a result, there may be discrepancies between column totals and totals by infant/maternal characteristic. Statistical analyses employed unrounded data.
Abbrev. CHD, Congenital Heart Defect; FSA, Forward Sortation Areas; WFS, Wildfire Smoke.

Supplementary Table S10. P-value of effect modification from stratified analyses of association between presence of EHE95 on CHD during periconception.

Characteristic	Cohort size (cases)	p-value of effect modification
Infant sex		
Male	945,370 (12,545)	Ref.
Female	892,265 (10,460)	0.04
Rurality		
Urban	1,587,130 (19,900)	Ref.
Rural	247,870 (3,060)	0.34
Geographical region		
Central	944,885 (11,880)	Ref.
Western	791,265 (9,645)	0.30
Atlantic	101,480 (1,475)	0.44
Residential instability quintile		
Quintile 1 (least marginalized)	302,850 (3,450)	Ref.
Quintile 2	333,810 (3,975)	0.27
Quintile 3	319,000 (4,000)	0.10
Quintile 4	341,950 (4,400)	0.37
Quintile 5 (most marginalized)	325,535 (4,325)	0.43
Ethno-cultural composition quintile		
Quintile 1 (least marginalized)	138,060 (1,705)	Ref.
Quintile 2	258,950 (3,315)	0.97
Quintile 3	318,930 (4,150)	0.76
Quintile 4	376,780 (4,665)	0.61
Quintile 5 (most marginalized)	530,425 (6,355)	0.56
Economic dependency quintile		
Quintile 1 (least marginalized)	379,325 (4,425)	Ref.
Quintile 2	374,235 (4,665)	0.25
Quintile 3	338,320 (4,330)	0.21
Quintile 4	302,165 (3,810)	0.34
Quintile 5 (most marginalized)	229,100 (2,965)	0.95
Situational vulnerability quintile		
Quintile 1 (least marginalized)	322,310 (3,410)	Ref.
Quintile 2	342,205 (4,035)	0.28
Quintile 3	315,935 (3,980)	0.38
Quintile 4	304,615 (3,870)	0.18
Quintile 5 (most marginalized)	338,085 (4,900)	0.06

Note: EHE95 was defined as daily maximum temperature exceeding the 95th percentile of regional temperature distribution for at least 2 consecutive days. All models were adjusted for maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability, with random intercepts at FSA level. The stratifying variable was excluded from its corresponding model. In accordance with Statistics Canada disclosure rules, all frequencies were randomly rounded to base five. As a result, there may be discrepancies between column totals and totals by infant/maternal characteristic. Statistical analyses employed unrounded data.
Abbrev. CHD, Congenital Heart Defect; EHE, Extreme Heat Event; FSA, Forward Sortation Areas.

Supplementary Table S11. Hazard Ratios, Relative Excess Risk due to Interaction, Attributable Proportions and their 95% Confidence Intervals for the joint association of EHEs and WFS events on overall CHD during cardiogenesis.

EHE category	WFS impacted	HR/RERI/AP (95% CI)
EHE90	WFS $PM_{2.5}$ > 0 μg/m^3	
No	No	Ref.
Yes	No	0.977 (0.923, 1.034)
No	Yes	1.000 (0.953, 1.049)
Yes	Yes	1.011 (0.960, 1.065)
RERI		0.034 (-0.039, 0.107)
AP		0.034 (-0.038, 0.106)
EHE95	WFS $PM_{2.5}$ > 0 μg/m^3	
No	No	Ref.
Yes	No	0.966 (0.914, 1.021)
No	Yes	0.998 (0.951, 1.047)
Yes	Yes	1.004 (0.953, 1.057)
RERI		0.040 (-0.032, 0.112)
AP		0.040 (-0.032, 0.111)
EHE90	WFS $PM_{2.5}$ > 5 μg/m^3	
No	No	Ref.
Yes	No	1.011 (0.965, 1.059)
No	Yes	1.033 (0.976, 1.094)
Yes	Yes	0.991 (0.933, 1.053)
RERI		-0.053 (-0.138, 0.031)
AP		-0.054 (-0.140, 0.034)
EHE95	WFS $PM_{2.5}$ > 5 μg/m^3	
No	No	Ref.
Yes	No	0.996 (0.952, 1.044)
No	Yes	1.023 (0.967, 1.083)
Yes	Yes	0.989 (0.931, 1.051)
RERI		-0.031 (-0.114, 0.053)
AP		-0.031 (-0.116, 0.054)

Note: EHEs were defined as daily maximum temperature exceeding threshold percentiles of regional temperature distribution for number of consecutive days (90^{th} percentile for at least 3 consecutive days, 95^{th} percentile for at least 2 consecutive days). All models were adjusted for maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability.

Abbrev. CHD, Congenital Heart Defect; EHE, Extreme Heat Event; WFS, Wildfire Smoke.

Supplementary Table S12. Hazard Ratios, Relative Excess Risk due to Interaction, Attributable Proportions and their 95% Confidence Intervals for the joint association of EHEs and WFS events on overall CHD during cardiogenesis further adjusting for maternal comorbidities.

EHE category	WFS impacted	HR/RERI/AP (95% CI)
EHE90	WFS $PM_{2.5}$ > 0 μg/m^3	
No	No	Ref.
Yes	No	0.981 (0.927, 1.039)
No	Yes	1.002 (0.956, 1.052)
Yes	Yes	1.013 (0.961, 1.067)
RERI		0.029 (-0.044, 0.102)
AP		0.029 (-0.044, 0.101)
EHE95	WFS $PM_{2.5}$ > 0 μg/m^3	
No	No	Ref.
Yes	No	0.969 (0.916, 1.025)
No	Yes	1.000 (0.953, 1.049)
Yes	Yes	1.005 (0.954, 1.058)
RERI		0.036 (-0.036, 0.108)
AP		0.036 (-0.036, 0.107)
EHE90	WFS $PM_{2.5}$ > 5 μg/m^3	
No	No	Ref.
Yes	No	1.010 (0.968, 1.062)
No	Yes	1.035 (0.977, 1.095)
Yes	Yes	0.992 (0.933, 1.054)
RERI		-0.056 (-0.141, 0.029)
AP		-0.057 (-0.144, 0.030)
EHE95	WFS $PM_{2.5}$ > 5 μg/m^3	
No	No	Ref.
Yes	No	0.998 (0.954, 1.044)
No	Yes	1.024 (0.968, 1.084)
Yes	Yes	0.989 (0.931, 1.051)
RERI		-0.033 (-0.118, 0.051)
AP		-0.033 (-0.118, 0.052)

Note: EHEs were defined as daily maximum temperature exceeding threshold percentiles of regional temperature distribution for number of consecutive days (90^{th} percentile for at least 3 consecutive days, 95^{th} percentile for at least 2 consecutive days). All models were adjusted for maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, maternal comorbidities, quintiles of instability, ethno-cultural composition, dependency and vulnerability.

Abbrev. CHD, Congenital Heart Defect; EHE, Extreme Heat Event; WFS, Wildfire Smoke.

Supplementary Table S13. Hazard Ratios, Relative Excess Risk due to Interaction, Attributable Proportions and their 95% Confidence Intervals for the joint association of EHEs and high $PM_{2.5}$ stratified by presence of WFS on overall CHD during cardiogenesis.

EHE category	High $PM_{2.5}$	WFS impacted HR/RERI/AP (95% CI)	Non-WFS impacted HR/RERI/AP (95% CI)	Overall HR/RERI/AP (95% CI)
EHE90	All-source $PM_{2.5} > 80^{th}$ percentile			
No	No	Ref.	Ref.	Ref.
Yes	No	1.049 (0.966, 1.140)	0.975 (0.919, 1.033)	0.988 (0.943, 1.034)
No	Yes	1.121 (1.039, 1.209)	0.934 (0.848, 1.028)	1.019 (0.970, 1.071)
Yes	Yes	1.093 (1.009, 1.183)	1.035 (0.770, 1.390)	1.029 (0.972, 1.090)
RERI		-0.075 (-0.191, 0.036)	0.127 (-0.192, 0.445)	0.022 (-0.055, 0.100)
AP		-0.071 (-0.175, 0.033)	0.123 (-0.152, 0.397)	0.022 (-0.053, 0.097)
EHE95	All-source $PM_{2.5} > 80^{th}$ percentile			
No	No	Ref.	Ref.	Ref.
Yes	No	1.046 (0.964, 1.134)	0.967 (0.919, 1.024)	0.983 (0.939, 1.029)
No	Yes	1.120 (1.039, 1.208)	0.952 (0.866, 1.046)	1.025 (0.975, 1.078)
Yes	Yes	1.089 (1.008, 1.177)	0.839 (0.599, 1.177)	1.018 (0.961, 1.077)
RERI		-0.077 (-0.189, 0.036)	-0.079 (-0.379, 0.220)	0.009 (-0.068, 0.087)
AP		-0.070 (-0.174, 0.033)	-0.095 (-0.482, 0.292)	0.009 (-0.067, 0.085)

Note: EHEs were defined as daily maximum temperature exceeding threshold percentiles of regional temperature distribution for number of consecutive days (90^{th} percentile for at least 3 consecutive days, 95^{th} percentile for at least 2 consecutive days). All models were adjusted for maternal age at delivery, infant sex, parity, day-of-year of conception, year of conception, rurality of residence, quintiles of instability, ethno-cultural composition, dependency and vulnerability.

Abbrev. CHD, Congenital Heart Defect; EHE, Extreme Heat Event; WFS, Wildfire Smoke.

4.13 References

1. Ebi, K. L., Vanos, J., Baldwin, J. W., Bell, J. E., Hondula, D. M., Errett, N. A., Hayes, K., Reid, C. E., Saha, S., Spector, J., & Berry, P. (2021). Extreme Weather and Climate Change: Population Health and Health System Implications. *Annual Review of Public Health*, *42*, 293–315. https://doi.org/10.1146/annurev-publhealth-012420-105026

2. Xu, R., Yu, P., Abramson, M. J., Johnston, F. H., Samet, J. M., Bell, M. L., Haines, A., Ebi, K. L., Li, S., & Guo, Y. (2020). Wildfires, Global Climate Change, and Human Health. *New England Journal of Medicine*, *383*(22), 2173–2181. https://doi.org/10.1056/NEJMsr2028985

3. Wegesser, T. C., Pinkerton, K. E., & Last, J. A. (2009). California Wildfires of 2008: Coarse and Fine Particulate Matter Toxicity. *Environmental Health Perspectives*, *117*(6), 893–897. https://doi.org/10.1289/ehp.0800166

4. Ramirez, J. D., Maldonado, I., Mach, K. J., Potter, J., Balise, R. R., & Santos, H. (2024). Evaluating the Impact of Heat Stress on Placental Function: A Systematic Review. *International Journal of Environmental Research and Public Health*, *21*(8), 1111. https://doi.org/10.3390/ijerph21081111

5. Gangwar, R. S., Bevan, G. H., Palanivel, R., Das, L., & Rajagopalan, S. (2020). Oxidative stress pathways of air pollution mediated toxicity: Recent insights. *Redox Biology*, *34*, 101545. https://doi.org/10.1016/j.redox.2020.101545

6. Liu, Y., Chen, S., Zühlke, L., Black, G. C., Choy, M., Li, N., & Keavney, B. D. (2019). Global birth prevalence of congenital heart defects 1970–2017: Updated systematic review and meta-analysis of 260 studies. *International Journal of Epidemiology*, *48*(2), 455–463. https://doi.org/10.1093/ije/dyz009

7. Van Der Bom, T., Zomer, A. C., Zwinderman, A. H., Meijboom, F. J., Bouma, B. J., & Mulder, B. J. M. (2011). The changing epidemiology of congenital heart disease. *Nature Reviews Cardiology*, *8*(1), 50–60. https://doi.org/10.1038/nrcardio.2010.166

8. Choudhury, T., Gilbert, B., & Garg, V. (2025). Genetic and Environmental Contributors To Congenital Heart Disease. *Current Treatment Options in Cardiovascular Medicine*, *27*. https://doi.org/10.1007/s11936-025-01091-5

9. Hu, C.-Y., Huang, K., Fang, Y., Yang, X.-J., Ding, K., Jiang, W., Hua, X.-G., Huang, D.-Y., Jiang, Z.-X., & Zhang, X.-J. (2020). Maternal air pollution exposure and congenital heart defects in offspring: A systematic review and meta-analysis. *Chemosphere*, *253*, 126668. https://doi.org/10.1016/j.chemosphere.2020.126668

10. Krishnakumar, M., Hari, A., Gutjahr, G., Bendapudi, P., Ahamed, H., Prabhakaran, P., Kumar, R. K., & Raj, M. (2024). Impact of exposure to extreme heat events during pregnancy on the incidence of congenital heart disease in offspring: A meta-analysis. *BMJ Paediatrics Open*, *8*(1), e002848. https://doi.org/10.1136/bmjpo-2024-002848

11. Hu, J. K., Trišović, A., Bakshi, A., Braun, D., Dominici, F., & Casey, J. A. (2025). Coexposure to extreme heat, wildfire burn zones, and wildfire smoke in the Western US from 2006 to 2020. *Science Advances*, *11*(18), eadq6453. https://doi.org/10.1126/sciadv.adq6453

12. Cleland, S. E., Paul, N., Coker, E. S., & Henderson, S. B. (2025). The Co-occurrence of Wildfire Smoke and Extreme Heat Events in British Columbia, 2010–2022: Evaluating Spatiotemporal Trends and Inequities in Exposure Burden. *ACS ES&T Air*, *2*(3), 319–330. https://doi.org/10.1021/acsestair.4c00219

13. Grandjean, P., Barouki, R., Bellinger, D. C., Casteleyn, L., Chadwick, L. H., Cordier, S., Etzel, R. A., Gray, K. A., Ha, E.-H., Junien, C., Karagas, M., Kawamoto, T., Lawrence, B. P., Perera, F. P., Prins, G. S., Puga, A., Rosenfeld, C. S., Sherr, D. H., Sly, P. D., … Heindel, J. J. (2015). Life-Long Implications of Developmental Exposure to Environmental Stressors: New Perspectives. *Endocrinology*, *156*(10), 3408–3415. https://doi.org/10.1210/en.2015-1350

14. Statistics Canada. (2024, September 10). *Statistics Canada, Canadian Vital Statistics—Birth database (CVSB)*. https://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&Id=1544655

15. Statistics Canada. (2021, November 17). *Dictionary, Census of Population, 2021—Figure 1.1 Hierarchy of standard geographic areas for dissemination, 2021 Census*. Government of Canada. https://www12.statcan.gc.ca/census-recensement/2021/ref/dict/fig/index-eng.cfm?ID=F1_1

16. Houyel, L., & Meilhac, S. M. (2021). Heart Development and Congenital Structural Heart Defects. *Annual Review of Genomics and Human Genetics*, *22*(1), 257–284. https://doi.org/10.1146/annurev-genom-083118-015012

17. Zubrzycki, M., Schramm, R., Costard-Jäckle, A., Grohmann, J., Gummert, J. F., & Zubrzycka, M. (2024). Cardiac Development and Factors Influencing the Development of Congenital Heart Defects (CHDs): Part I. *International Journal of Molecular Sciences*, *25*(13), 7117. https://doi.org/10.3390/ijms25137117

18. Paul, N., Yao, J., McLean, K. E., Stieb, D. M., & Henderson, S. B. (2022). The Canadian Optimized Statistical Smoke Exposure Model (CanOSSEM): A machine learning approach to estimate national daily fine particulate matter (PM2.5) exposure. *Science of The Total Environment*, *850*, 157956. https://doi.org/10.1016/j.scitotenv.2022.157956

19. Cleland, S. E., Hamilton, O. P. X.-Q., Brauer, M., & Henderson, S. B. (2026). Multiyear wildfire smoke exposure (MultiWiSE) metrics: A data-driven approach to characterizing episodic PM2.5 exposures for epidemiologic research. *Journal of Exposure Science & Environmental Epidemiology*. https://doi.org/10.1038/s41370-026-00876-5

20. Gelaro, R., McCarty, W., Suárez, M. J., Todling, R., Molod, A., Takacs, L., Randles, C. A., Darmenov, A., Bosilovich, M. G., Reichle, R., Wargan, K., Coy, L., Cullather, R., Draper, C., Akella, S., Buchard, V., Conaty, A., Silva, A. M. da, Gu, W., … Zhao, B. (2017). The Modern-Era Retrospective Analysis for Research and Applications, Version 2 (MERRA-2). *Journal of Climate*, *30*(14), 5419–5454. https://doi.org/10.1175/JCLI-D-16-0758.1

21. Lin, S., Lin, Z., Ou, Y., Soim, A., Shrestha, S., Lu, Y., Sheridan, S., Luben, T. J., Fitzgerald, E., Bell, E., Shaw, G. M., Reefhuis, J., Langlois, P. H., Romitti, P., Feldkamp, M. L., Malik, S., Pantea, C., Nayak, S., Hwang, S.-A., & Browne, M. (2018). Maternal ambient heat exposure during early pregnancy in summer and spring and congenital heart defects – A large US population-based, case-control study. *Environment International*, *118*, 211–221. https://doi.org/10.1016/j.envint.2018.04.043

22. Canadian Institute for Health Information. (2025, May 5). *Discharge Abstract Database (DAD) metadata | CIHI*. Canadian Institute for Health Information. https://www.cihi.ca/en/discharge-abstract-database-dad-metadata

23. Public Health Agency of Canada. (2024, May 15). *Provincial and Territorial Congenital Anomalies Surveillance: A summary of surveillance programs across Canada*. Government of Canada. https://www.canada.ca/en/public-health/services/reports-publications/health-promotion-chronic-disease-prevention-canada-research-policy-practice/vol-44-no-5-2024/provincial-territorial-congenital-anomalies-surveillance-summary-surveillance-programs.html

24. Picciotto, S., Huang, S., Lurmann, F., Pavlovic, N., Ying Chang, S., Mukherjee, A., Goin, D. E., Sklar, R., Noth, E., Morello-Frosch, R., & Padula, A. M. (2024). Pregnancy exposure to PM2.5 from wildland fire smoke and preterm birth in California. *Environment International*, *186*, 108583. https://doi.org/10.1016/j.envint.2024.108583

25. Stolwijk, A. M., Straatman, H., & Zielhuis, G. A. (1999). Studying seasonality by using sine and cosine functions in regression analysis. *Journal of Epidemiology and Community Health*, *53*(4), 235–238. https://doi.org/10.1136/jech.53.4.235

26. Government of Canada, S. C. (2024, November 28). *The Canadian Index of Multiple Deprivation (CIMD)*. Government of Canada. https://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=5274

27. Buckley, J. P., Samet, J. M., & Richardson, D. B. (2014). Commentary: Does Air Pollution Confound Studies of Temperature? *Epidemiology*, *25*(2), 242–245. https://doi.org/10.1097/EDE.0000000000000051

28. Chen, X., Chen, S., Zhu, Z., Luo, J., Wang, H., Wulayin, M., Huang, C., Zhao, W., & Wang, Q. (2023). Identifying the critical windows and joint effects of temperature and PM2.5 exposure on small for gestational age. *Environment International*, *173*, 107832. https://doi.org/10.1016/j.envint.2023.107832

29. Wong, J., Kohari, K., Bahtiyar, M. O., & Copel, J. (2022). Impact of prenatally diagnosed congenital heart defects on outcomes and management. *Journal of Clinical Ultrasound*, *50*(5), 646–654. https://doi.org/10.1002/jcu.23219

30. Gasparrini, A., Armstrong, B., & Kenward, M. G. (2010). Distributed lag non-linear models. *Statistics in Medicine*, *29*(21), 2224–2234. https://doi.org/10.1002/sim.3940

31. Knol, M. J., & VanderWeele, T. J. (2012). Recommendations for presenting analyses of effect modification and interaction. *International Journal of Epidemiology*, *41*(2), 514–520. https://doi.org/10.1093/ije/dyr218

32. Hosmer, D. W., & Lemeshow, S. (1992). Confidence Interval Estimation of Interaction: *Epidemiology*, *3*(5), 452–456. https://doi.org/10.1097/00001648-199209000-00012

33. Stingone, J. A., Luben, T. J., Sheridan, S. C., Langlois, P. H., Shaw, G. M., Reefhuis, J., Romitti, P. A., Feldkamp, M. L., Nembhard, W. N., Browne, M. L., & Lin, S. (2019). Associations between fine particulate matter, extreme heat events, and congenital heart defects. *Environmental Epidemiology*, *3*(6), e071. https://doi.org/10.1097/EE9.0000000000000071

34. Park, B. Y., Vedhanayagam, K., Ortiz-Luis, J., Basu, R., Gheorghe, C. P., Govindappagari, S., Abinader, R., & Yao, R. (2025). Living Near Wildfires and the Risk of Fetal Congenital Heart Defects: Evaluating Critical Windows of Vulnerability. *AJP Reports*, *15*(1), e18–e24. https://doi.org/10.1055/a-2528-3588

35. Padula, A. M., Mayo, J. A., Lurmann, F. W., Pavlovic, N. R., & Shaw, G. M. (2026). Wildland fire smoke and birth defects in California. *Journal of Exposure Science & Environmental Epidemiology*. https://doi.org/10.1038/s41370-026-00885-4

36. Requia, W. J., Kill, E., Papatheodorou, S., Koutrakis, P., & Schwartz, J. D. (2022). Prenatal exposure to wildfire-related air pollution and birth defects in Brazil. *Journal of Exposure Science & Environmental Epidemiology*, *32*(4), 596–603. https://doi.org/10.1038/s41370-021-00380-y

37. Sherris, A. R., Dearborn, L. C., Goin, D. E., Loftus, C. T., Szpiro, A. A., Casey, J. A., Ilango, S. D., Angal, J., Bennett, D. H., Buxton, M. A., Camargo, C. A., Carroll, K. N.,

Childs, M. L., Cioffi, C., Croen, L. A., Dabelea, D., Eick, S. M., Farzan, S. F., Ferrara, A., … Padula, A. M. (2025). Wildfire-specific fine particulate matter and preterm birth: A US ECHO Cohort analysis. *The Lancet Planetary Health*, 101324. https://doi.org/10.1016/j.lanplh.2025.101324

38. Stingone, J. A., Luben, T. J., Daniels, J. L., Fuentes, M., Richardson, D. B., Aylsworth, A. S., Herring, A. H., Anderka, M., Botto, L., Correa, A., Gilboa, S. M., Langlois, P. H., Mosley, B., Shaw, G. M., Siffel, C., Olshan, A. F., & the National Birth Defects Prevention Study. (2014). Maternal Exposure to Criteria Air Pollutants and Congenital Heart Defects in Offspring: Results from the National Birth Defects Prevention Study. *Environmental Health Perspectives*, *122*(8), 863–872. https://doi.org/10.1289/ehp.1307289

39. Yang, B.-Y., Qu, Y., Guo, Y., Markevych, I., Heinrich, J., Bloom, M. S., Bai, Z., Knibbs, L. C., Li, S., Chen, G., Jalaludin, B., Morawska, L., Gao, M., Han, B., Yu, Y., Liu, X.-X., Ou, Y., Mai, J., Gao, X., … Dong, G.-H. (2021). Maternal exposure to ambient air pollution and congenital heart defects in China. *Environment International*, *153*, 106548. https://doi.org/10.1016/j.envint.2021.106548

40. Liew, Z., Olsen, J., Cui, X., Ritz, B., & Arah, O. A. (2015). Bias from conditioning on live birth in pregnancy cohorts: An illustration based on neurodevelopment in children after prenatal exposure to organic pollutants. *International Journal of Epidemiology*, *44*(1), 345–354. https://doi.org/10.1093/ije/dyu249

41. Leung, M., Kioumourtzoglou, M.-A., Raz, R., & Weisskopf, M. G. (2021). Bias due to Selection on Live Births in Studies of Environmental Exposures during Pregnancy: A Simulation Study. *Environmental Health Perspectives*, *129*(4), 047001. https://doi.org/10.1289/EHP7961

42. Deegan, D. F., Nigam, P., & Engel, N. (2021). Sexual Dimorphism of the Heart: Genetics, Epigenetics, and Development. *Frontiers in Cardiovascular Medicine*, *8*, 668252. https://doi.org/10.3389/fcvm.2021.668252

43. Chiarello, D. I., Ustáriz, J., Marín, R., Carrasco-Wong, I., Farías, M., Giordano, A., Gallardo, F. S., Illanes, S. E., & Gutiérrez, J. (2023). Cellular mechanisms linking to outdoor and indoor air pollution damage during pregnancy. *Frontiers in Endocrinology*, *14*. https://doi.org/10.3389/fendo.2023.1084986

44. Meng, Q., Liu, J., Shen, J., Del Rosario, I., Janzen, C., Devaskar, S. U., Lakey, P. S. J., Shiraiwa, M., Weichenthal, S., Zhu, Y., Oroumiyeh, F., Banerjee, S., Paulson, S. E., Jerrett, M., Paul, K. C., & Ritz, B. (2024). Ambient exposure to fine particulate matter with oxidative potential affects oxidative stress biomarkers in pregnancy. *American Journal of Epidemiology*, *194*(1), 27–34. https://doi.org/10.1093/aje/kwae152

45. Konkel, L. (2019). Taking the Heat: Potential Fetal Health Effects of Hot Temperatures. *Environmental Health Perspectives*, *127*(10), 102002. https://doi.org/10.1289/EHP6221

46. Hussain, T., Murtaza, G., Metwally, E., Kalhoro, D. H., Kalhoro, M. S., Rahu, B. A., Sahito, R. G. A., Yin, Y., Yang, H., Chughtai, M. I., & Tan, B. (2021). The Role of Oxidative Stress and Antioxidant Balance in Pregnancy. *Mediators of Inflammation*, *2021*(1), 9962860. https://doi.org/10.1155/2021/9962860

47. Impellizzeri, P., Nascimben, F., Di Fabrizio, D., Antonuccio, P., Antonelli, E., Peri, F. M., Calabrese, U., Arena, S., & Romeo, C. (2022). Pathogenesis of Congenital Malformations: Possible Role of Oxidative Stress. *American Journal of Perinatology*, *39*(08), 816–823. https://doi.org/10.1055/s-0040-1721081

48. Krasovich Southworth, E., Qiu, M., Gould, C. F., Kawano, A., Wen, J., Heft-Neal, S., Kilpatrick Voss, K., Lopez, A., Fendorf, S., Burney, J. A., & Burke, M. (2025). The Influence of Wildfire Smoke on Ambient PM2.5 Chemical Species Concentrations in the Contiguous US. *Environmental Science & Technology*, *59*(6), 2961–2973. https://doi.org/10.1021/acs.est.4c09011

49. Sparks, T. L., & Wagner, J. (2021). Composition of particulate matter during a wildfire smoke episode in an urban area. *Aerosol Science and Technology*, *55*(6), 734–747. https://doi.org/10.1080/02786826.2021.1895429

50. Grigorieva, E., & Lukyanets, A. (2021). Combined Effect of Hot Weather and Outdoor Air Pollution on Respiratory Health: Literature Review. *Atmosphere*, *12*(6), 790. https://doi.org/10.3390/atmos12060790

51. Jepson, B. M., Metz, T. D., Miller, T. A., Son, S. L., Ou, Z., Presson, A. P., Nance, A., & Pinto, N. M. (2023). Pregnancy loss in major fetal congenital heart disease: Incidence, risk factors and timing. *Ultrasound in Obstetrics & Gynecology*, *62*(1), 75–87. https://doi.org/10.1002/uog.26231

52. Hystad, P., Setton, E., Cervantes, A., Poplawski, K., Deschenes, S., Brauer, M., Van Donkelaar, A., Lamsal, L., Martin, R., Jerrett, M., & Demers, P. (2011). Creating National Air Pollution Models for Population Exposure Assessment in Canada. *Environmental Health Perspectives*, *119*(8), 1123–1129. https://doi.org/10.1289/ehp.1002976

Chapter 5. Discussion

5.1 Summary of Findings

5.1.1 Summary of thesis objectives

Climate change has contributed to increasing temperature anomalies and amplified wildfire seasons over the recent years. Although numerous research has examined the implications of wildfires on the relationship between environmental exposures and birth outcomes, specifically preterm birth and low birth weight, a limited number of studies have explored its effects on congenital anomalies, including CHD. This thesis aimed to address these knowledge gaps through an investigation of the association between prenatal environmental exposures of EHE, $PM_{2.5}$ arising from different sources (all-source, WFS, non-WFS) along with their potential synergistic effects on CHD. Through the identification of CHD risk imposed by wildfires, the findings of this thesis contribute to the expanding body of literature on the implications of wildfires on the relationship between environmental factors and birth outcomes.

5.1.2 Summary of thesis findings

The independent effects of EHEs and $PM_{2.5}$ rising from different sources (all-source, WFS, and non-WFS) on CHD were examined in Chapter 4. In the study, no clear evidence of association between periconception exposure to WFS $PM_{2.5}$ and CHD risk was found. Similarly, no consistent association was observed between EHEs and CHD, although an effect modification with infant sex was identified with elevated risk observed for female infants. Moreover, potential synergistic effects between WFS and EHEs were explored in Chapter 4, and no significant additive interaction was identified.

5.2 Integration of Findings

There is currently very limited number of published studies that have investigated the association between wildfire-related air pollutants and CHD. As highlighted previously in Chapter 4, the overall findings have been inconsistent, with positive associations observed only within certain subgroups or for specific subtypes. Furthermore, variation in exposure assessment of wildfire smoke across these studies warrants greater caution in comparison of results. For instance, a case-control study in California, United States used quartiles of $PM_{2.5}$ density attributable to fire sources to estimate the effects of wildfire,[1] while two retrospective cohort studies in Brazil and California used presence of wildfire events.[2,3]

Moreover, the mixed findings across studies may also be attributable to differences in $PM_{2.5}$ concentration distribution between countries and variation in covariates adjusted for in statistical models. This was also evident in Chapter 4, where the association between WFS $PM_{2.5}$ and overall CHD reached statistical significance only when seasonality was modelled as a categorical season-of-conception term in sensitivity analysis. This may highlight the importance of seasonality adjustment, particularly considering the highly temporal trend of environmental exposures. Although previous studies have commonly modelled seasonality as a categorical variable, this approach may have been insufficient to capture residual seasonal variation. Therefore, assessing alternative specification of seasonality, that allow for more flexible adjustment of temporal variation in WFS, may be a meaningful sensitivity analysis in future studies to further test the robustness of associations. In addition, the all-source $PM_{2.5}$ concentrations were relatively low across Canada compared to other countries, with minimal variation in $PM_{2.5}$ levels observed outside of major wildfire events. Consequently, limited exposure heterogeneity combined with lower levels of absolute $PM_{2.5}$ concentrations across

Canada may have also attributed to the overall null association found within the full cohort in Chapter 4. Notably, a small positive association was identified only in the Western region in stratified analysis, where majority of severe WFS events have occurred. Additional studies covering more recent and severe wildfire seasons are recommended in the future to further examine the underlying relationship between WFS $PM_{2.5}$ and the risk of CHD.

While cautious interpretation is warranted given our findings in Chapter 4 were not robust in sensitivity analyses, higher point estimates between WFS $PM_{2.5}$ and CHD were consistently observed compared to non-WFS $PM_{2.5}$. Previous toxicological literature has also highlighted the distinct chemical composition of WFS $PM_{2.5}$ which may exhibit more detrimental health effects than $PM_{2.5}$ from urban background sources.[4] Notably, $PM_{2.5}$ arising from wildfires or biomass burning are composed of higher concentrations of organic carbon (OC), elemental carbon (EC) and polycyclic aromatic hydrocarbons (PAHs) compared to $PM_{2.5}$ arising from other sources.[5–8] Evidence from cellular and animal studies revealed these particular constituents of WFS $PM_{2.5}$ are also associated with increased oxidative and pro-inflammatory potentials, which is the underlying biological mechanism recognized to influence fetal growth including cardiac development.[9–12] Furthermore, a greater proportion of smaller particles in WFS $PM_{2.5}$ allows the pollutant to penetrate more deeply into the lungs, with evidence indicating increased pulmonary toxicity in humans.[13–15] The stronger association observed between WFS $PM_{2.5}$ and CHD risk compared to all-source $PM_{2.5}$ may also be attributable to the episodic nature of wildfire events. Wildfire events are characterized by highly temporal smoke episodes, which often result in high-intensity and short-duration spikes in $PM_{2.5}$ concentrations.[16,17] Given that WFS $PM_{2.5}$ exposure in this thesis was obtained by isolating the non-wildfire estimates from all-source $PM_{2.5}$

concentration during smoke-impacted weeks, these episodic characteristics of wildfire events may have been attenuated when analyzing the effects of all-source $PM_{2.5}$.

No consistent association between EHEs and CHD risk was observed in this thesis, although stratified analysis in Chapter 4 identified potential effect modification by infant sex with elevated risk observed among females. Overall, the relationship between prenatal heat exposure and CHD has been mixed as indicated by a recent meta-analysis conducted by Krishnakumar and colleagues.[18] In particular, high heterogeneity in the association has been observed depending on the climate zone of each study region with mostly null effects observed across North America, which is consistent with the findings of this thesis. This is likely attributable to difference in baseline temperature distribution between countries, as EHEs were defined based on relative thresholds. While an observational study conducted in China also observed elevated CHD risk among females per 1°C increase at the 95th percentile of local temperature distribution, no significant effect modification was reported.[19] Even though previous literature has highlighted the sex difference in the prevalence of varying CHD subtypes, there is currently limited biological evidence underlying this potential interaction.[20,21] A possible biological mechanism includes potential sex differences in the post-transcriptional regulation of specific exons and splicing factors, which may influence the expression of cardiac proteins as evident by previous animal studies.[22]

Despite some positive point estimates of RERI observed for the combined effects of any WFS events and EHEs, no significant additive interaction has been identified in this thesis. There is currently limited evidence on this potential synergistic effect, and only a few studies have explored the broader interaction with all-source $PM_{2.5}$ and heat. A case-control study conducted in the United States by Stingone and colleagues has examined the additive interaction between

high all-source $PM_{2.5}$ and EHEs, where positive significant RERI was only observed for the CHD subtype of septal defects during the cardiogenesis window (RERI: 0.35, 95% CI: 0.04, 0.67).[23] Given the growing co-occurrence of wildfire events and temperature anomalies,[24] along with the biological plausibility of increased ventilation and deposition of air pollutants in humans when exposed to heat,[25] further research examining this potential synergistic effect is recommended.

5.3 Strengths

A major strength of this thesis includes the large sample size of the study cohort, with over 1.8 million mother-infant pairs, covering most regions in Canada excluding the province of Quebec. This has allowed robust statistical power to examine the outcome of CHD, despite it being a rare disease. In addition, it has enabled the assessment of potential effect modification of varying characteristics including infant sex, rurality of residence and multiple SES indicators.

Another strength includes the methodology of exposure assessment of $PM_{2.5}$, which estimated the isolated $PM_{2.5}$ concentration arising from wildfires. This method further enabled incorporation of a two-pollutant model, which simultaneously adjusted for both WFS and non-WFS $PM_{2.5}$ concentrations. Through this approach, the background $PM_{2.5}$ concentrations were accounted for when estimating the effects of either WFS or non-WFS $PM_{2.5}$ exposures. Collectively, this allowed us to capture the implication of wildfires on the association between ambient $PM_{2.5}$ and CHD through comparison of risks associated with $PM_{2.5}$ arising from all-source, wildfires and non-wildfires. Given the difference in the chemical composition of WFS $PM_{2.5}$ pollutants compared to $PM_{2.5}$ arising from other sources, as highlighted before, the results provided an informative comparison of CHD risk.

Furthermore, the employment of DLMs in this study allowed examination of potential sensitive windows of susceptibility through analysis of weekly effects of environmental exposures. This approach was especially crucial when examining the effects of WFS $PM_{2.5}$. Previous research has often used either the presence or the number of wildfire events throughout a relatively wide exposure window ranging from each pregnancy month to trimesters. Therefore, the incorporation of cumulative effects of weekly WFS $PM_{2.5}$ allowed us to account for the temporal dynamics and intensity of wildfire events throughout each gestational week during the periconception period.

5.4 Limitations

Although the usage of health administrative data for the construction of the cohort enabled the study to capture large sample sizes across Canada, there also exists inherent limitations. Since the collection of such administrative data is not originally intended for research purposes, it is important to acknowledge potential variability in coding practices, data quality standards and neonatal screening protocols across different hospitals. These postnatal factors may also influence the clinical diagnosis of CHD across different regions throughout the study years. In addition, due to limited data, we were unable to collect information on several confounders including maternal obesity and substance usage such as maternal smoking or alcohol consumption.

Another limitation includes the methodology used for the exposure assessment of WFS $PM_{2.5}$. Although the incorporation of the MultiWiSE approach allowed us to isolate the concentration of all-source $PM_{2.5}$ into WFS and non-WFS components, there are limitations associated with this method.[26] The isolation of WFS $PM_{2.5}$ was computed based on the concentration distribution of all-source $PM_{2.5}$ during pre-specified wildfire season period,

without the employment of satellite-derived detection of smoke presence. This may lead to potential exposure misclassification of smoke-impacted weeks when the concentration of all-source $PM_{2.5}$ is low, or during the presence of wildfire events outside the pre-defined wildfire season.

It is also important to note that environmental exposures were assigned using outdoor ambient air pollutants and temperature metrics, based on the geographic residence of mother-infant pairs. Therefore, the estimates of these environmental stressors may not truly reflect the exposures experienced by individuals, depending on their daily mobility patterns.[27] Furthermore, the study period also partially coincides with the COVID-19 pandemic. Variabilities in mobility patterns, healthcare access and individual behavioural changes, as consequences of the pandemic and frequent lockdowns may have potentially influenced the underlying relationship.

5.5 Recommendations for future wildfire seasons

Although no clear evidence of association between WFS $PM_{2.5}$ and CHD risk was found in this thesis, consistent positive direction of estimates was observed. This finding contribute to the growing evidence of potential adverse health implications associated with wildfires, and further highlights the importance of strengthening prenatal care protocols and maternal health guidelines. Given the increasing intensity and extension of wildfire seasons in Canada over the recent years[28] with projected escalation of global wildfire events,[29] promotion of active air quality and heat event monitoring tools along with targeted educational programs for pregnant individuals is imperative to mitigate health risks posed by environmental stressors.

Notably, systematic monitoring of ambient pollutant concentrations and their potential health risks is communicated through the Air Quality Health Index (AQHI) in Canada.[30] The AQHI incorporates a numeric index system ranging from 1 to 10+ with each value indicating its

associated air quality level and estimated health risk. Moreover, the Regional Air Quality Deterministic Prediction System (RAQDPS) incorporates satellite-based detection of smoke plume to estimate the dispersion of $PM_{2.5}$ arising from wildfires across Canada and issues public health warnings in the presence of wildfire events.[31] In particular, the public can effectively monitor air quality and heat events through usage of WeatherCAN, a mobile app which employs AQHI and enables custom notifications for specific air quality levels and absolute temperature thresholds.[32] Incorporation of these tools into prenatal care protocols and enhancing risk communications will allow pregnant individuals to stay informed and take protective measures. These can include avoidance of outdoor activity during wildfire events or EHEs, and usage of portable air purifiers certified by the Association of Home Appliance Manufacturers (AHAM) with high-efficiency particulate air (HEPA) filters.[33] Overall, strengthened precautionary approach to educate and protect the health of pregnant mothers and their infants is especially crucial for future wildfire seasons.

5.6 Implications for future research

This thesis examined the implications of wildfires in the relationship between environmental exposures with CHD in infants. While the methodology of exposure assessment in our study allowed analysis of potential variation in CHD risk posed by $PM_{2.5}$ arising from different sources, a key limitation included the reliance on concentration distribution thresholds to derive the WFS $PM_{2.5}$ estimates. Future studies should consider integrating a satellite-based smoke plume method for more accurate detection of smoke-impacted weeks, which may reduce exposure misclassification and improve the precision of source-specific $PM_{2.5}$ isolation.

Moreover, future studies should also consider examining the independent effects of relevant characteristics of wildfire events including frequency, duration and intensity of smoke

episodes as highlighted by Cleland and colleagues.[26] In particular, potential non-linear relationship between WFS and CHD risk could be further investigated based on previous literature suggesting possible behavioural changes of individuals during intense smoke events.[34] For instance, visible smoke and smell during intense wildfire events may prompt protective behaviours, which may be less common during wildfire events with lower smoke exposures. Understanding the distinct health implications of smoke episode patterns would strengthen evidence for more targeted and actionable public health guidelines during wildfire seasons.

5.7 Conclusion

This thesis examined the implication of wildfires on the association between prenatal exposure to environmental stressors and CHD in infants. Overall, no clear evidence of association between WFS $PM_{2.5}$ and EHE on CHD risk was observed. Nonetheless, the findings of this thesis underscore the importance of further research on the health risks of environmental exposures in the context of intensifying wildfire seasons.

5.8 References

1. Padula, A. M., Mayo, J. A., Lurmann, F. W., Pavlovic, N. R., & Shaw, G. M. (2026). Wildland fire smoke and birth defects in California. *Journal of Exposure Science & Environmental Epidemiology*. https://doi.org/10.1038/s41370-026-00885-4

2. Requia, W. J., Kill, E., Papatheodorou, S., Koutrakis, P., & Schwartz, J. D. (2022). Prenatal exposure to wildfire-related air pollution and birth defects in Brazil. *Journal of Exposure Science & Environmental Epidemiology*, *32*(4), 596–603. https://doi.org/10.1038/s41370-021-00380-y

3. Park, B. Y., Vedhanayagam, K., Ortiz-Luis, J., Basu, R., Gheorghe, C. P., Govindappagari, S., Abinader, R., & Yao, R. (2025). Living Near Wildfires and the Risk of Fetal Congenital Heart Defects: Evaluating Critical Windows of Vulnerability. *AJP Reports*, *15*(1), e18–e24. https://doi.org/10.1055/a-2528-3588

4. Zhang, Y., Tingting, Y., Huang, W., Yu, P., Chen, G., Xu, R., Song, J., Guo, Y., & Li, S. (2024). Health Impacts of Wildfire Smoke on Children and Adolescents: A Systematic Review and Meta-analysis. *Current Environmental Health Reports*, *11*(1), 46–60. https://doi.org/10.1007/s40572-023-00420-9

5. Krasovich Southworth, E., Qiu, M., Gould, C. F., Kawano, A., Wen, J., Heft-Neal, S., Kilpatrick Voss, K., Lopez, A., Fendorf, S., Burney, J. A., & Burke, M. (2025). The Influence of Wildfire Smoke on Ambient PM2.5 Chemical Species Concentrations in the Contiguous US. *Environmental Science & Technology*, *59*(6), 2961–2973. https://doi.org/10.1021/acs.est.4c09011

6. Spracklen, D. V., Logan, J. A., Mickley, L. J., Park, R. J., Yevich, R., Westerling, A. L., & Jaffe, D. A. (2007). Wildfires drive interannual variability of organic carbon aerosol in the western U.S. in summer. *Geophysical Research Letters*, *34*(16). https://doi.org/10.1029/2007GL030037

7. Elzein, A., Stewart, G. J., Swift, S. J., Nelson, B. S., Crilley, L. R., Alam, M. S., Reyes-Villegas, E., Gadi, R., Harrison, R. M., Hamilton, J. F., & Lewis, A. C. (2020). A comparison of $PM_{2.5}$ -bound polycyclic aromatic hydrocarbons in summer Beijing (China) and Delhi (India). *Atmospheric Chemistry and Physics*, *20*(22), 14303–14319. https://doi.org/10.5194/acp-20-14303-2020

8. Kocbach, A., Li, Y., Yttri, K. E., Cassee, F. R., Schwarze, P. E., & Namork, E. (2006). Physicochemical characterisation of combustion particles from vehicle exhaust and residential wood smoke. *Particle and Fibre Toxicology*, *3*(1), 1. https://doi.org/10.1186/1743-8977-3-1

9. Gangwar, R. S., Bevan, G. H., Palanivel, R., Das, L., & Rajagopalan, S. (2020). Oxidative stress pathways of air pollution mediated toxicity: Recent insights. *Redox Biology*, *34*, 101545. https://doi.org/10.1016/j.redox.2020.101545

10. Vilas-Boas, V., Chatterjee, N., Carvalho, A., & Alfaro-Moreno, E. (2024). Particulate matter-induced oxidative stress – Mechanistic insights and antioxidant approaches reported in in vitro studies. *Environmental Toxicology and Pharmacology*, *110*, 104529. https://doi.org/10.1016/j.etap.2024.104529

11. Jiao, A., Zhu, S., Chen, X., He, Q., Benmarhnia, T., & Wu, J. (2026). Associations of PM2.5 and PAHs from wildland fires with pregnancy outcomes: Evidence based on high-resolution exposure assessment. *Environmental Research*, *298*, 124195. https://doi.org/10.1016/j.envres.2026.124195

12. Zhang, Y., Dong, S., Wang, H., Tao, S., & Kiyama, R. (2016). Biological impact of environmental polycyclic aromatic hydrocarbons (ePAHs) as endocrine disruptors. *Environmental Pollution*, *213*, 809–824. https://doi.org/10.1016/j.envpol.2016.03.050

13. Kim, Y. H., Warren, S. H., Krantz, Q. T., King, C., Jaskot, R., Preston, W. T., George, B. J., Hays, M. D., Landis, M. S., Higuchi, M., DeMarini, D. M., & Gilmour, M. I. (2018). Mutagenicity and Lung Toxicity of Smoldering vs. Flaming Emissions from Various Biomass Fuels: Implications for Health Effects from Wildland Fires. *Environmental Health Perspectives*, *126*(1), 017011. https://doi.org/10.1289/EHP2200

14. Wegesser, T. C., Pinkerton, K. E., & Last, J. A. (2009). California Wildfires of 2008: Coarse and Fine Particulate Matter Toxicity. *Environmental Health Perspectives*, *117*(6), 893–897. https://doi.org/10.1289/ehp.0800166

15. Black, C., Tesfaigzi, Y., Bassein, J. A., & Miller, L. A. (2017). Wildfire smoke exposure and human health: Significant gaps in research for a growing public health issue. *Environmental Toxicology and Pharmacology*, *55*, 186–195. https://doi.org/10.1016/j.etap.2017.08.022

16. Hadley, M. B., Henderson, S. B., Brauer, M., & Vedanthan, R. (2022). Protecting Cardiovascular Health From Wildfire Smoke. *Circulation*, *146*(10), 788–801. https://doi.org/10.1161/CIRCULATIONAHA.121.058058

17. Makkonen, U., Hellén, H., Anttila, P., & Ferm, M. (2010). Size distribution and chemical composition of airborne particles in south-eastern Finland during different seasons and wildfire episodes in 2006. *Science of The Total Environment*, *408*(3), 644–651. https://doi.org/10.1016/j.scitotenv.2009.10.050

18. Krishnakumar, M., Hari, A., Gutjahr, G., Bendapudi, P., Ahamed, H., Prabhakaran, P., Kumar, R. K., & Raj, M. (2024). Impact of exposure to extreme heat events during

pregnancy on the incidence of congenital heart disease in offspring: A meta-analysis. *BMJ Paediatrics Open*, *8*(1), e002848. https://doi.org/10.1136/bmjpo-2024-002848

19. Xu, W., Li, D., Shao, Z., You, Y., Pan, F., Lou, H., Li, J., Jin, Y., Wu, T., Pan, L., An, J., Xu, J., Cheng, W., Tao, L., Lei, Y., Huang, C., & Shu, Q. (2023). The prenatal weekly temperature exposure and neonatal congenital heart disease: A large population-based observational study in China. *Environmental Science and Pollution Research International*, *30*(13), 38282–38291. https://doi.org/10.1007/s11356-022-24396-5

20. Lastivka, I. V., Pishak, V. P., Ryznychuk, M. O., & Khmara, T. V. (2020). Risk factor analysis for congenital heart defects in children. *Regulatory Mechanisms in Biosystems*, *11*(4), 524–530. https://doi.org/10.15421/022080

21. Pugnaloni, F., Felici, A., Corno, A.-F., Marino, B., Versacci, P., & Putotto, C. (2023). Gender differences in congenital heart defects: A narrative review. *Translational Pediatrics*, *12*(9), 1753–1764. https://doi.org/10.21037/tp-23-260

22. Conlon, F. L., & Arnold, A. P. (2023). Sex-chromosome mechanisms in cardiac development and disease. *Nature Cardiovascular Research*, *2*(4), 340–350. https://doi.org/10.1038/s44161-023-00256-4

23. Stingone, J. A., Luben, T. J., Sheridan, S. C., Langlois, P. H., Shaw, G. M., Reefhuis, J., Romitti, P. A., Feldkamp, M. L., Nembhard, W. N., Browne, M. L., & Lin, S. (2019). Associations between fine particulate matter, extreme heat events, and congenital heart defects. *Environmental Epidemiology*, *3*(6), e071. https://doi.org/10.1097/EE9.0000000000000071

24. Cleland, S. E., Paul, N., Coker, E. S., & Henderson, S. B. (2025). The Co-occurrence of Wildfire Smoke and Extreme Heat Events in British Columbia, 2010–2022: Evaluating Spatiotemporal Trends and Inequities in Exposure Burden. *ACS ES&T Air*, *2*(3), 319–330. https://doi.org/10.1021/acsestair.4c00219

25. Grigorieva, E., & Lukyanets, A. (2021). Combined Effect of Hot Weather and Outdoor Air Pollution on Respiratory Health: Literature Review. *Atmosphere*, *12*(6), 790. https://doi.org/10.3390/atmos12060790

26. Cleland, S. E., Hamilton, O. P. X.-Q., Brauer, M., & Henderson, S. B. (2026). Multiyear wildfire smoke exposure (MultiWiSE) metrics: A data-driven approach to characterizing episodic PM2.5 exposures for epidemiologic research. *Journal of Exposure Science & Environmental Epidemiology*. https://doi.org/10.1038/s41370-026-00876-5

27. Yu, X., Ivey, C., Huang, Z., Gurram, S., Sivaraman, V., Shen, H., Eluru, N., Hasan, S., Henneman, L., Shi, G., Zhang, H., Yu, H., & Zheng, J. (2020). Quantifying the impact of daily mobility on errors in air pollution exposure estimation using mobile phone location

data. *Environment International*, *141*, 105772. https://doi.org/10.1016/j.envint.2020.105772

28. Wang, W., Wang, X., Flannigan, M. D., Guindon, L., Swystun, T., Castellanos-Acuna, D., Wu, W., & Wang, G. (2025). Canadian forests are more conducive to high-severity fires in recent decades. *Science*, *387*(6729), 91–97. https://doi.org/10.1126/science.ado1006

29. Popescu, A., Paulson, A., Christianson, A., Sullivan, A., Tulloch, A., Bilbao, B., Mathison, C., Robinson, C., Ganz, D., Nangoma, D., Saah, D., Armenteras, D., Driscoll, D., Hankins, D., Kelley, D., Langer, E., Baker, E., Reisen, F., Robinne, F.-N., … Charlton, V. (2022). *Spreading like wildfire: The rising threat of extraordinary landscape fires—A rapid response assessment* (A. Sullivan, E. Baker, & T. Kurvits, Eds.). United Nations Environment Program (UNEP). USGS Publications Warehouse. https://pubs.usgs.gov/publication/70243263

30. Environment and Climate Change Canada. (2021, April 28). *About the Air Quality Health Index*. Government of Canada. https://www.canada.ca/en/environment-climate-change/services/air-quality-health-index/about.html

31. Environment and Climate Change Canada. (2026, March 2). *Air quality and weather*. Government of Canada. https://www.canada.ca/en/environment-climate-change/services/air-quality-health-index/weather.html

32. Environment and Climate Change Canada. (2025, September 8). *WeatherCAN*. Government of Canada. https://www.canada.ca/en/environment-climate-change/services/weather-general-tools-resources/weathercan.html#toc3

33. Health Canada. (2021, December 24). *Using a portable air cleaner to improve indoor air*. Government of Canada. https://www.canada.ca/en/health-canada/services/air-quality/indoor-air-contaminants/choosing-portable-purifier.html

34. Lei, Y., Lei, T.-H., Lu, C., Zhang, X., & Wang, F. (2024). Wildfire Smoke: Health Effects, Mechanisms, and Mitigation. *Environmental Science & Technology*, *58*(48), 21097–21119. https://doi.org/10.1021/acs.est.4c06653

Appendix A – STROBE Statement Checklist for the Manuscript

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3	Abstract: "We conducted a population-based cohort study..."
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3	Abstract: Methods and Results sections
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	Introduction: "Prenatal exposure to environmental stressors…"
Objectives	3	State specific objectives, including any prespecified hypotheses	5	Introduction: "The independent associations between periconception exposure to EHEs, $PM_{2.5}$ from wildfire smoke…"
Methods				
Study design	4	Present key elements of study design early in the paper	5	Methods: "This retrospective cohort study included…"
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5, 10	Methods (pg.5): "all singleton live births from January 1st, 2013 to December 31st, 2021 in Canada…" Methods (pg.10): "where the follow-up period was limited from birth until…"

Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6	Methods (pg.5): "Linked mother-infant data was obtained from the Canadian Vital Statistics Birth Database…" Methods (pg.6): "Mother-infant pairs with missing or invalid information…" Supplementary Figure S1
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-10, 12	Methods (pg.6): All-source, WFS and Non-WFS $PM_{2.5}$ Exposure Assessment section Methods (pg.8): Ambient Temperature and EHE Exposure Assessment section Methods (pg.8): Congenital Heart Defects Outcome section Methods (pg.9): Covariates section Methods (pg.12): "Stratified analyses were also performed to assess…"
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-10	Methods (pg.6): All-source, WFS and Non-WFS $PM_{2.5}$ Exposure Assessment section

				Methods (pg.8): Ambient Temperature and EHE Exposure Assessment section Methods (pg.8): Congenital Heart Defects Outcome section Methods (pg.9): Covariates section
Bias	9	Describe any efforts to address potential sources of bias	9-10	Methods (pg.9): Covariates section
Study size	10	Explain how the study size was arrived at	6	Methods (pg.6): "There were a total of 3,389,335 recorded live births…" Supplementary Figure S1

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10	Methods (pg.9): "These included: maternal age at delivery…"
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10	Methods (pg.10): "Cox proportional hazards models were…"
		(*b*) Describe any methods used to examine subgroups and interactions	12-13	Methods (pg.12): "Stratified analyses were also performed…" Methods (pg.12): "The interactive effects of WFS and EHE…"
		(*c*) Explain how missing data were addressed	6, 9	Methods (pg.6): "Mother-infant pairs with missing or invalid…" Methods (pg.9): "parity (none, 1, ≥2, missing), seasonality…"
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10	Methods (pg.10): "where the follow-up period was limited from…"
		(*e*) Describe any sensitivity analyses	11-12	Methods (pg.11): "Sensitivity analyses were conducted to assess…"
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, 13	Methods (pg.6): "There were a total of 3,389,335 recorded live births…" Results (pg.13): "Our study included a total of 1,837,635 singleton…" Supplementary Figure S1

		(b) Give reasons for non-participation at each stage	Supplementary File	Supplementary Figure S1
		(c) Consider use of a flow diagram	Supplementary File	Supplementary Figure S1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	29-30	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	29-30	Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9	Methods (pg.9): "providing at least one complete year of records…"
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	13	Results (pg.13): "Among the cohort, 23,005 (1.3%) infants were diagnosed with CHD…"
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	31-34	Figures 1-4 Supplementary Tables S3 and S11 included in the Supplementary File
		(*b*) Report category boundaries when continuous variables were categorized	34	Figure 4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	Not relevant

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplementary File	Supplementary Figures S5-S14 and Tables S4-S10, S12-S13
Discussion				
Key results	18	Summarise key results with reference to study objectives	16	Discussion (pg.16): "Positive point estimates were observed between…"
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20-21	Discussion (pg.20): "There are also a few limitations in this study…"
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-19	Discussion (pg.17): "Moreover, lower levels of absolute $PM_{2.5}$…"
Generalisability	21	Discuss the generalisability (external validity) of the study results	17, 20	Discussion (pg.17): "Overall, these mixed findings are likely…" Discussion (pg.20): "Although our study cohort included…"
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22	Declarations (pg.22): Funding section

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.