Examining the Impact of Environmental Factors on the Risk of Cerebral Palsy

Amrin Ahmed

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

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

Preface

Amrin Ahmed was the primary author of all contents included in this thesis. Under the supervision of Dr. Éric Lavigne, Dr. Steven Hawken, and thesis advisory committee member, Dr. Anna Gunz, Amrin Ahmed was responsible for planning the study design and methodology, conducting the analyses, interpreting the findings, and drafting the manuscripts found within this thesis. The study cohort was assembled by Amrin Ahmed and Robert Talarico. All authors provided guidance and critical feedback in the analysis, writing, and revisions of the manuscripts.

This thesis project was approved by the Health Canada Research Ethics Board.

Acknowledgements

First and foremost, I give thanks to Allah (SWT), whose guidance and mercy have been the foundation of this journey. It is through His grace and support that I have been able to complete this degree, and I am deeply grateful for His continuous blessings.

I am profoundly grateful to my supervisors, Dr. Éric Lavigne and Dr. Steven Hawken. Your expertise, patience, and unwavering support have been instrumental in the development of this thesis. I am privileged to have learned from you both. I also extend my sincere thanks to my thesis advisory committee member, Dr. Anna Gunz, for her invaluable insights and continued encouragement, and my thesis examiners, Dr. Yanfang Guo, and Dr. Melissa Brouwers.

I would like to thank my colleagues and friends, especially Sarah, Deena, Michala, and Maisha, whose support made this experience all the more memorable. I am deeply grateful for the moments we shared throughout this journey.

To my brothers, thank you for your constant support and for always being there when I needed you.

To my twin sister, you have been my constant companion through every challenge and triumph. Your love, support, and understanding have been invaluable, and I am so grateful to have you by my side.

Lastly, to my parents, who crossed oceans to provide me and my siblings with better opportunities—thank you for your boundless love, sacrifices, and unwavering belief in me. Your strength and dedication have been my greatest inspiration, and I will forever be indebted to you.

Table of Contents

List of tables

List of figures

Abbreviations

ADHD	Attention Deficit-Hyperactivity Disorder
ALE	Active Living Environment
AOD	Aerosol Optical Depth
AQAS	Air Quality Assessment Section
AQHI	Air Quality Health Index
AQS	Air Quality System
ASD	Autism Spectrum Disorder
ASHAS	Air Sectors Health Assessment Section
BC	Black Carbon
BMI	Body Mass Index
BoNT-A	Botulinum Toxin Type A
BORN	Better Outcomes and Registry Network
CAAQS	Canadian Ambient Air Quality Standards
Can-ALE	Canadian Active Living Environments
CANUE	Canadian Urban Environmental Health Research Consortium
CCI	Canadian Classification of Health Interventions
CI	Confidence Interval
CIHI	Canadian Institute for Health Information
CNV	Copy Number Variant
CO	Carbon Monoxide
COPD	Chronic Obstructive Pulmonary Disease
CP	Cerebral Palsy
DAD	Discharge Abstract Database
DAG	Directed Acyclic Graph
DBP	Diastolic Blood Pressure
DLNM	Distributed Lag Non-Linear Model
DM	Diabetes Mellitus
DUST	Mineral Dust
EC	Elemental Carbon
GA	Gestational Age
GDM	Gestational Diabetes Mellitus
GSV	Google Street View
GVI	Green View Index
HICs	High-Income Countries
HR	Hazard Ratio
HYPER	Ontario Hypertension Dataset
IBD	Inflammatory Bowel Disease
ICD	International Classification of Diseases
ICES	Institute of Clinical and Evaluative Sciences

ID	Intellectual Disability
IDW	Inverse Distance Weighting
IKN	ICES Key Number
IQR	Interquartile Range
IUGR	Intrauterine Growth Restriction
LMICs	Low and Middle-Income Countries
LUR	Land-Use Regression
MAPK	Mitogen-Activated Protein Kinase
NACRS	National Ambulatory Care Reporting System
NAPS	National Air Pollution Surveillance
NDVI	Normalized Difference Vegetation Index
NH_3	Ammonia
NH_4	Ammonium
NO_2	Nitrogen Dioxide
NO_3	Nitrate
NOx	Nitrogen Oxide
O_3	Ozone
OC	Organic Carbon
ODD	Ontario Diabetes Database
OHIP	Ontario Health Insurance Program
OM	Organic Matter
ON-Marg	Ontario Marginalization Index
OR	Odds Ratio
PGDM	Pregestational Diabetes Mellitus
PIVH	Peri-Intraventricular Hemorrhaging
PM	Particulate Matter
$PM_{2.5}$	Particulate Matter with Diameter ≤ 2.5 μm
PSD	Project Specific Data
ROS	Reactive Oxygen Species
RPDB	Registered Persons Database
RR	Relative Risk
SBP	Systolic Blood Pressure
SES	Socioeconomic Status
SGA	Small for Gestational Age
SO	Sulfur
SO_4	Sulfate
SOx	Sulfur Oxide
SS	Sea Salt
TAC	Thesis Advisory Committee
VOC	Volatile Organic Compound

Abstract

Background: Cerebral palsy (CP) is a neurodevelopmental disorder that may be influenced by prenatal environmental exposures, such as air pollution ($PM_{2.5}$), greenspaces, and active living environments (ALE).

Methods: Cohort data from health administrative databases in Ontario, Canada were linked to air pollution ($PM_{2.5}$ components, $PM_{2.5}$ mass, O_3, and NO_2), greenspace (normalized difference vegetation index and green view index), and active living environment data (park proximity and Can-ALE) based on six-digit residential postal codes.

Results: Exposure to $PM_{2.5}$ component of sulfate (SO_4) during early gestation was associated with an increased risk of CP, while closer residential proximity to parks was linked to a decreased risk. No significant associations were observed for other pollutants or greenspace metrics.

Conclusions: Adverse and protective environmental influences were identified in relation to CP risk in this thesis. These findings highlight the need for further investigation on how specific environmental exposures during pregnancy may contribute to CP risk.

Chapter 1. Introduction

1.1 Background

Cerebral palsy (CP) is a broad term that is used to describe neurological conditions characterized by developmental delays, and limitations in motor or locomotive activities.[1] Affecting approximately 2 to 3 per 1000 live births in Canada,[2] CP is considered the most diagnosed motor disability in children.[3] Globally, there are currently more than 17 million individuals living with CP, highlighting the widespread impact of this neurological condition on communities worldwide.[4] Efforts to raise awareness, promote accessibility, and advocate for the rights of those with CP play a crucial role in fostering a more inclusive society that recognizes and accommodates the diverse needs of individuals affected by this condition. Overall, CP is an umbrella term that is used to describe the symptoms of CP. This means that there can be varying levels and severities of the disorder.

There are four main classifications of CP, which are characterized by their clinical signs and symptoms: spastic, dyskinetic, ataxic, and mixed CP.[5,6] Spastic CP makes up approximately 80% of total CP cases,[7] and can be further categorized into subtypes of spastic hemiplegia, spastic diplegia, and spastic quadriplegia.[2] Overall, individuals with spastic CP experience muscle stiffness, spasms, and pain,[8] and the further classifications of hemiplegia, diplegia, and quadriplegia describe the limbs that are affected by the symptoms. Children with spastic hemiplegia often develop symptoms that affect only one side of the body, while diplegia affects mostly the lower limbs, and quadriplegia affects all limbs.[9] Dyskinetic CP, also known as athetoid CP, is often characterized by involuntary muscle movement such as twitching and abnormal posture.[10] Ataxic CP, also known as hypotonic CP, affects approximately 5% of CP cases,[11] and can be characterized by loss of balance and coordination.[12] Lastly, cases of CP in which the individual has a combination of these clinical symptoms can be classified as having mixed CP.[2]

Overall, the manifestation of CP for individuals can range in severity from slight tremors and trouble walking to severe cognitive impairments,[13] and is often diagnosed within the first two years after birth.[14] Following diagnosis, CP becomes a lifelong condition that remains nonprogressive over time.[15]

While there is no cure for CP, there exist many treatments and therapies that help with the management of symptoms, and improvement of function and participation. Treatments include rehabilitative and pharmacological interventions, such as physical therapy, treadmill training, the use of adaptive equipment, and oral intake of medication such as baclofen, clonazepam, clonidine, and dantrolene.[2]

More invasive procedures, such as orthopedic surgery and the use of botulinum toxin type A (BoNT-A) injections have also been explored in the management of CP.[16,17] Overall, treating CP requires an interdisciplinary approach involving various health professionals, such as pediatricians, audiologists, nutritionists, and speech-language therapists.[2] As a result of this increased health care resource utilization, CP poses a financial and economic burden for parents and caregivers of children with CP. In 2010, it was estimated that the direct health care costs for families of Canadian children with CP was approximately $11,700 which was significantly higher than the $600 cost for Canadian children without CP.[18] A systematic review done on the economic impact of CP globally also found that governments bear significant costs through various support programs, including pensions, allowances, and equipment assistance.[19] In addition, a Canadian modelled projection study that was done for 2011 to 2031 found that the total health sector costs associated with CP will continue to rise steadily over the next few years.[18]

Overall, CP has multifactorial origins, with a range of prenatal, perinatal, and postnatal factors contributing to its development.[18,20] Prenatal causes can include genetic mutations, brain

malformations, and infections affecting the developing fetus.[21] Complications during labor and delivery, such as oxygen deprivation, trauma, or premature birth, are common perinatal factors linked to CP.[22] Additionally, postnatal causes may involve infections or injuries that affect the developing brain in the early years of life.[23] While the exact cause may not always be identified, a combination of genetic susceptibility and environmental factors often plays a role.

In recent years, environmental factors, including exposure to air pollution and lack of greenspace, have been implicated as potential contributors to the development of CP and other neurological conditions.[24,25] Prenatally, exposure to air pollutants, such as fine particulate matter ($PM_{2.5}$) and environmental toxins, may adversely affect fetal brain development.[26] Conversely, access to greenspace has shown positive correlations with cognitive development in children.[27] Limited greenspaces and factors contributing to active living in urban environments, where air pollution tends to be higher, may deprive individuals of the cognitive and neuroprotective benefits associated with natural surroundings.[28] Overall, advances in medical research continue to enhance our understanding of the intricate interplay of these factors, paving the way for improved preventive measures and interventions to mitigate the risk and impact of CP.

1.2 Rationale

The complex nature of CP poses a challenge when trying to determine risk factors and exposures that should be avoided during prenatal, perinatal, and postnatal periods. To build on current findings and better understand the etiological reasoning for this disorder, further research in this area needs to be done. Firstly, while the association between CP and $PM_{2.5}$ has been explored, there still exists a gap in knowledge in identifying which specific components of $PM_{2.5}$ are attributable to this risk. The major components of $PM_{2.5}$ include black carbon (BC); sulfate

(SO_4^{2-}); ammonium (NH_4^+); nitrate (NO_3^-); organic matter (OM); sea salt (SS); and mineral dust (dust).[29] Each of these pollutants, when considered separately, have been identified to exert adverse effects on human health to some extent.[30] In addition, critical windows of exposure during pregnancy that correspond to specific stages of fetal brain development need to be precisely identified, as this knowledge is essential for developing targeted interventions aimed at minimizing the potential adverse effects of environmental factors on the developing brain and reducing the risk of CP. Furthermore, while the protective effects of greenspace have been studied on neurological conditions such as asthma and attention deficit-hyperactivity disorder (ADHD),[31,32] associations with CP risk and development have not yet been explored in the literature.

By identifying the specific components of $PM_{2.5}$ and critical windows of exposure during gestation that are associated with CP risk, this study may help make a significant contribution to public health efforts aimed at reducing the burden of CP. This can include developing strategies to improve air quality regulations, reduce traffic emissions, and promote cleaner transportation options. Additionally, understanding the protective effect of greenspaces and active living environments (ALEs) on CP development can help guide urban planning and design, highlighting the importance of incorporating green spaces into urban environments to promote healthy development.

1.3 Thesis objectives

The overall aim of this thesis was to examine the association between environmental factors, specifically exposure to $PM_{2.5}$ composition, greenspaces, and ALEs with CP using a cohort in Ontario, Canada. Specific objectives include:

1) To assess the individual components of $PM_{2.5}$ and critical windows of exposure during

pregnancy that are associated with CP risk.

2) To assess the association between gestational exposure to residential greenspaces, ALEs and CP risk.

1.4 Overview of chapters

This thesis is comprised of six chapters. Following the introductory chapter, the objectives of this thesis will be addressed in the following manner:

- Chapter 2 provides a thorough review of the literature available on the epidemiology of CP, including prenatal, perinatal, and postnatal environmental risk factors with a particular focus on $PM_{2.5,}$ greenspace, and ALE exposures.
- Chapter 3 includes an overview of the data sources used for this thesis. This includes the methods of data linkage and a brief overview of the source cohort.
- Chapter 4 addresses objective 1 and includes a manuscript titled "*Prenatal exposure to fine particulate matter composition and risk of cerebral palsy: A population-based retrospective cohort study in Ontario, Canada*". This study evaluates the association between the individual components of $PM_{2.5}$ and CP using survival analysis techniques such as cox proportional hazards models and distributed non-linear lag models (DLNM).
- Chapter 5 addresses objective 2 and includes a manuscript titled "*Associations of prenatal exposure to residential greenspace and active living environments with cerebral palsy: A population-based cohort study in Ontario, Canada*". This study evaluates the association between different greenspace exposure measures, such as normalized difference vegetation index (NDVI) and Green View Index (GVI), ALE indicators, and the risk of CP.

- Chapter 6 is a discussion chapter, which summarizes key findings and conclusions from chapters 4 and 5, while also identifying steps for future research.

1.5 References

1. Appleton RE, Gupta R. Cerebral palsy: not always what it seems. *Arch Dis Child*. 2019;104(8):809-814. doi:10.1136/archdischild-2018-315633

2. Patel DR, Neelakantan M, Pandher K, Merrick J. Cerebral palsy in children: a clinical overview. *Transl Pediatr*. 2020;9(Suppl 1):S125-S12S135. doi:10.21037/tp.2020.01.01

3. Van Naarden Braun K, Doernberg N, Schieve L, Christensen D, Goodman A, Yeargin-Allsopp M. Birth Prevalence of Cerebral Palsy: A Population-Based Study. *Pediatrics*. 2016;137(1):e20152872. doi:10.1542/peds.2015-2872

4. Graham HK, Rosenbaum P, Paneth N, et al. Cerebral palsy. *Nat Rev Dis Primer*. 2016;2(15082). doi:10.1038/nrdp.2015.82

5. Sadowska M, Sarecka-Hujar B, Kopyta I. Cerebral Palsy: Current Opinions on Definition, Epidemiology, Risk Factors, Classification and Treatment Options. *Neuropsychiatr Dis Treat*. 2020;16:1505-1518. doi:10.2147/NDT.S235165

6. Paulson A, Vargus-Adams J. Overview of Four Functional Classification Systems Commonly Used in Cerebral Palsy. Accessed August 23, 2023. https://www.mdpi.com/2227-9067/4/4/30

7. Skoutelis VC, Kanellopoulos AD, Kontogeorgakos VA, Dinopoulos A, Papagelopoulos PJ. The orthopaedic aspect of spastic cerebral palsy. *J Orthop*. 2020;22:553-558. doi:10.1016/j.jor.2020.11.002

8. Ghai A, Garg N, Hooda S, Gupta T. Spasticity – Pathogenesis, prevention and treatment strategies. *Saudi J Anaesth*. 2013;7(4):453. doi:10.4103/1658-354X.121087

9. Gulati S, Sondhi V. Cerebral Palsy: An Overview. *Indian J Pediatr*. 2018;85(11):1006-1016. doi:10.1007/s12098-017-2475-1

10. Li X, Arya K. Athetoid Cerebral Palsy. In: *StatPearls*. StatPearls Publishing; 2023. Accessed August 23, 2023. http://www.ncbi.nlm.nih.gov/books/NBK563160/

11. Levy JP, Oskoui M, Ng P, et al. Ataxic-hypotonic cerebral palsy in a cerebral palsy registry: Insights into a distinct subtype. *Neurol Clin Pract*. 2020;10(2):131-139. doi:10.1212/CPJ.0000000000000713

12. Yoo M, Ahn JH, Park ES. The Effects of Over-Ground Robot-Assisted Gait Training for Children with Ataxic Cerebral Palsy: A Case Report. *Sensors*. 2021;21(23):7875. doi:10.3390/s21237875

13. Pearson TS, Pons R, Ghaoui R, Sue CM. Genetic mimics of cerebral palsy. *Mov Disord*. 2019;34(5):625-636. doi:10.1002/mds.27655

14. te Velde A, Tantsis E, Novak I, et al. Age of Diagnosis, Fidelity and Acceptability of an Early Diagnosis Clinic for Cerebral Palsy: A Single Site Implementation Study. *Brain Sci*. 2021;11(8):1074. doi:10.3390/brainsci11081074

15. Mezaal MA, Nouri KA, Abdool S, Safar KA, Nadeem ASM. Cerebral Palsy In Adults Consequences of Non Progressive Pathology. *Open Neurol J*. 2009;3:24-26. doi:10.2174/1874205X00903010024

16. Berker AN, Yalçın MS. Cerebral Palsy: Orthopedic Aspects and Rehabilitation. *Pediatr Clin North Am*. 2008;55(5):1209-1225. doi:10.1016/j.pcl.2008.07.011

17. Flyckt N, Wong C, Michelsen JS. Non-pharmacological and non-surgical treatment of pain in children and adolescents with cerebral palsy: A scoping review. *J Pediatr Rehabil Med*. 2022;15(1):49-67. doi:10.3233/PRM-210046

18. Amankwah N, Oskoui M, Garner R, et al. Cerebral palsy in Canada, 2011-2031: results of a microsimulation modelling study of epidemiological and cost impacts. *Health Promot Chronic Dis Prev Can Res Policy Pract*. 2020;40(2):25-37. doi:10.24095/hpcdp.40.2.01

19. Tonmukayakul U, Shih STF, Bourke-Taylor H, et al. Systematic review of the economic impact of cerebral palsy. *Res Dev Disabil*. 2018;80:93-101. doi:10.1016/j.ridd.2018.06.012

20. Reddihough DS, Collins KJ. The epidemiology and causes of cerebral palsy. *Aust J Physiother*. 2003;49(1):7-12. doi:10.1016/S0004-9514(14)60183-5

21. Pascual JM, Koenigsberger MR. [Cerebral palsy: prenatal risk factors]. *Rev Neurol*. 2003;37(3):275-280.

22. Badawi N, Mcintyre S, Hunt RW. Perinatal care with a view to preventing cerebral palsy. *Dev Med Child Neurol*. 2021;63(2):156-161. doi:10.1111/dmcn.14754

23. Owens L, Shieh E, Case A. Postnatal Causes of Cerebral Palsy. In: Miller F, Bachrach S, Lennon N, O'Neil ME, eds. *Cerebral Palsy*. Springer International Publishing; 2020:77-83. doi:10.1007/978-3-319-74558-9_7

24. Hu Y, Zhang Y, Talarico R, et al. Prenatal Exposure to Ambient Air Pollution and Offspring Cerebral Palsy in Ontario, Canada: A Population-Based Cohort Study. *ISEE Conf Abstr*. Published online September 18, 2022. doi:10.1289/isee.2022.P-0481

25. Klompmaker JO, Laden F, Browning MHEM, et al. Associations of Greenness, Parks, and Blue Space With Neurodegenerative Disease Hospitalizations Among Older US Adults. *JAMA Netw Open*. 2022;5(12):e2247664. doi:10.1001/jamanetworkopen.2022.47664

26. Cserbik D, Chen JC, McConnell R, et al. Fine particulate matter exposure during childhood relates to hemispheric-specific differences in brain structure. *Environ Int*. 2020;143:105933. doi:10.1016/j.envint.2020.105933

27. Dadvand P, Nieuwenhuijsen MJ, Esnaola M, et al. Green spaces and cognitive development in primary schoolchildren. *Proc Natl Acad Sci*. 2015;112(26):7937-7942. doi:10.1073/pnas.1503402112

28. Bikis A. Urban Air Pollution and Greenness in Relation to Public Health. *J Environ Public Health*. 2023;2023:8516622. doi:10.1155/2023/8516622

29. Dominici F, Wang Y, Correia AW, Ezzati M, Pope CAI, Dockery DW. Chemical Composition of Fine Particulate Matter and Life Expectancy: In 95 US Counties Between 2002 and 2007. *Epidemiology*. 2015;26(4):556. doi:10.1097/EDE.0000000000000297

30. Wang Y, Xiao S, Zhang Y, et al. Long-term exposure to PM2.5 major components and mortality in the southeastern United States. *Environ Int*. 2022;158:106969. doi:10.1016/j.envint.2021.106969

31. Dong Y, Liu H, Zheng T. Association between Green Space Structure and the Prevalence of Asthma: A Case Study of Toronto. *Int J Environ Res Public Health*. 2021;18(11):5852. doi:10.3390/ijerph18115852

32. Amoly E, Dadvand P, Forns J, et al. Green and blue spaces and behavioral development in Barcelona schoolchildren: the BREATHE project. *Environ Health Perspect*. 2014;122(12):1351-1358. doi:10.1289/ehp.1408215

Chapter 2. Literature Review

2.1 Epidemiology of CP

CP is currently the most commonly diagnosed motor disability in childhood worldwide.[33] Following the work of Dr. William John Little, an early pioneer involved in the recognition and description of CP in the early 19th century, the study of CP and its associated risks have been an area of increased interest and investigation.[34] While prevalence rates can vary across different populations and regions, it is estimated that CP affects approximately 2 to 3 per 1000 live births, in Canada.[2] A systematic analysis done in 2022 by McIntyre et al. found that when looking at 27 countries, the global birth prevalence of CP in low- and middle-income countries (LMICs) was significantly higher than in high-income countries (HICs).[35] This was confirmed by another study that found prevalence estimates to be severely underrepresented in LMICs, noting that in regions such as Bangladesh and Moldova, the prevalence estimates for CP are almost double that of the higher income countries.[36] This can be attributed to many factors, such as lack of access to healthcare services and education.[37]

Nonetheless, HICs continue to experience a steady increase in cases of CP, despite having access to leading treatments and interventions.[38] A study done by Amankwah et al. found that while in 2011 there was approximately 75,000 Canadians who were living with CP, this number is expected to reach 94,000 by 2031.[18] From the same time interval, the study also found that the number of newly diagnosed cases of CP is expected to increase from 1800 to 2200, highlighting the steadily growing rate of incidence and prevalence in Canada.[18] Overall, with a slight increasing trend for cases and costs related to CP, understanding the etiology of this condition is imperative in developing preventative measures needed to reduce the incidence of CP.

In recent decades, CP can be diagnosed within the first two years of life using clinical signs and standardized assessments, and is thus considered a childhood disorder.[2] However, the age for

early diagnosis can reach up to 5 years in LMICs where diagnostic tools may not be available.[39] Early diagnosis of CP remains an important factor in CP treatment as it facilitates the implementation of timely and targeted interventions, significantly influencing the long-term outcomes for affected individuals.[40] Identifying signs of CP in infancy allows healthcare professionals to initiate early therapeutic and rehabilitative measures, addressing motor and developmental challenges during the critical periods of neuroplasticity.[41] While uncommon, the diagnosis and onset of CP can also manifest in later years of life, stemming from brain injuries or infection.[42] Among children, a 2016 European study also found the incidence of CP diagnosis per 1000 births was higher in males (2.2, 99% CI (confidence interval): 2.0-2.3) compared with females (1.7, 99% CI: 1.5-1.8), indicating a difference of approximately 30%.[43] However, these sex differences were not found to be significant when assessing different types and severities of CP.[44]

Overall, CP is a complex disorder that necessitates a multifaceted understanding, encompassing genetic, environmental, prenatal, and postnatal factors, to inform comprehensive approaches to diagnosis, treatment, and support for individuals affected by this condition. The various mechanisms by which CP can manifest are illustrated in Figure 1.

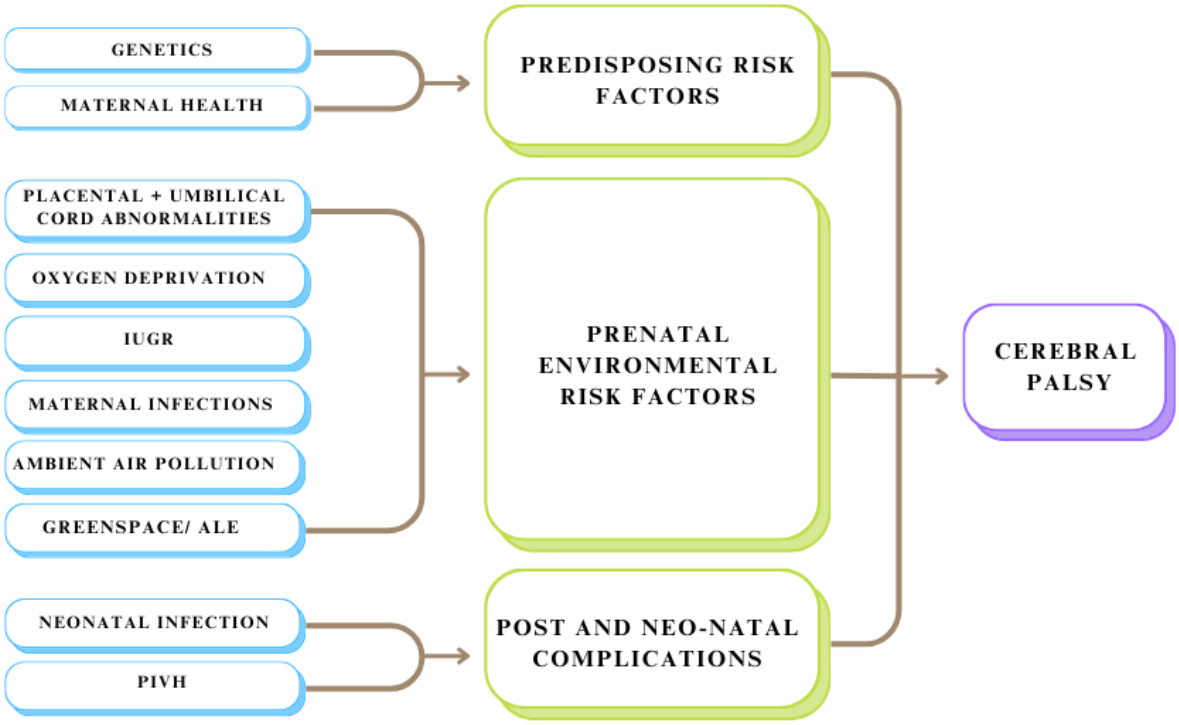


Figure 1. Overview of factors related to CP etiology

2.2 Overview of CP etiology

In general, CP is caused by infection or injury to the brain during its developmental stages.[2] Approximately 85% of cases of CP are categorized as congenital, indicating that the condition is present at or shortly after birth.[45] However, the mechanisms by which these injuries or infections occur can vary and may be attributed to predisposing risk factors, as well as perinatal and postnatal exposures.[46,47]

2.2.1 Predisposing risk factors

2.2.1.1 Genetics and inheritance

In recent years, the use of exome and whole genome sequencing techniques have been able to identify associations between various genes and the development of CP.[48–50] A review of genetic studies in 2021 found at least 18 genes and 5 copy number variants (CNVs) to be associated with

CP risk.[51] Of these, notable genes included BXO31 and RHOB, two genes that when mutated were found to have significant associations with the development of CP.[52] Many of these identified genes were also noted to have associations with other neurodevelopmental conditions, explaining the co-occurrence of these disorders with CP.[51] A 2018 study done by Reid et al. found intellectual disability (ID) to be prevalent in about 45% of the CP cohort.[53] Similarly, another study investigating the presence of epilepsy and autism spectrum disorders (ASD) in children with CP, found prevalence rates of approximately 40% and 7%, respectively, indicating similar pathological mechanisms.[54] Furthermore, although genetics contribute significantly to the progression of CP, this condition is not directly inherited. It is also important to note that while the potential genetic basis of CP has been investigated, the interplay of various genetic modifications and additional environmental factors are what is responsible for the true etiology of CP, contributing to its complex nature.

2.2.1.2 Maternal health

Various factors related to maternal health have also been identified as risk factors for health outcomes and neurodevelopmental disorders.

Maternal smoking has been identified as a significant risk factor for CP development in offspring. In 2019, a population-based study investigating the effects of maternal smoking found significantly increased risk of hospitalizations related to neurological conditions for offspring with smoking mothers (adjusted HR (hazard ratio): 1.58, 95% CI: 1.33-1.89).[55] Another research study conducted in China explored the impact of second hand tobacco smoke exposure on pregnant women and its association with the occurrence of CP in their offspring. The findings revealed a significant increase in the likelihood of CP among pregnancies where mothers were exposed to secondhand smoke (adjusted OR (odds ratio): 1.44, 95% CI: 1.02-2.04).[56] The harmful effects of

tobacco smoke on fetal development are well-documented, as smoking exposes the developing fetus to various toxins and compounds that can adversely impact the developing brain.[57]

Maternal obesity is another significant factor associated with increased risk of CP in offspring. In a meta-analysis of five cohort studies, the risk of CP was found to increase with each grade of maternal obesity. Overall, the pooled adjusted OR for CP in offspring of overweight mothers, compared to normal weight mothers was 1.51 (95% CI: 1.24-1.84).[58] Along with maternal weight, diet is another risk factor that has been studied in the literature. A well balanced and sufficient diet during pregnancy is crucial for appropriate brain development.[59] A study in 2016 aimed to examine how early undernutrition influenced locomotor activity and the expression of the myofibrillar protein (MuRF-1) in an experimental rat model of CP. This study found that undernutrition during the perinatal period further intensified the symptoms of locomotion and muscle atrophy that are associated with CP.[60]

In recent years, socioeconomic status (SES) has been identified as an influencer of CP cases, as disparities in SES can impact access to healthcare, quality of prenatal and perinatal care, and the availability of supportive resources, all of which may contribute to the prevalence and outcomes of CP.[61,62] A systematic review done by Solaski et al. included twelve studies, of which eight highlighted low SES as a risk factor linked to an increased prevalence of CP. In three of these studies, associations remained statistically significant even after adjusting for variables such as birthweight and gestational age (GA). Moreover, two of the studies considered additional confounding factors such as multiple births and the timing of CP acquisition, and still found notable effects of SES. Additionally, three of these studies revealed linear negative correlations between the prevalence of CP and SES.[63] A more recent Taiwanese study also found a higher prevalence of CP to be linked with low family income, with adjusted relative risk (RR) ranging

from 5.1 (95% CI: 4.2-6.2) to 6.4 (95% CI: 5.4-7.6).[64] Parity and multiple births are additional maternal factors that have been found to correlate with CP outcomes in literature. One study found an OR of 4.86 (95% CI: 1.02-23.03) when investigating history of multiple births and CP between cases and controls, reporting significant associations between multiple births and CP ($P < 0.05$).[65]

Existing maternal chronic conditions, such as hypertension and diabetes mellitus (DM), have also been found to influence birth outcomes. A meta-analysis investigating the risk factors of CP found that out of the 12 articles incorporated in the analysis, six explored the association between maternal pregnancy-induced hypertension and CP. These six studies exhibited no heterogeneity ($\chi^2=7.69$, $P=0.17$, $I^2=35\%$), and found a pooled OR value of 1.93 (95% CI: 1.48-2.52).[66] Similarly, a population-based cohort study discovered offspring of mothers with pregestational diabetes mellitus (PGDM) demonstrated an elevated risk of CP (HR: 1.84, 95% CI: 1.59-2.14), even when accounting for maternal sociodemographic and clinical factors. Conversely, no associations were observed between gestational diabetes mellitus (GDM) and CP (HR: 0.91, 95% CI: 0.77-1.06).[67] Nonetheless, offspring of mothers with DM have been found to have clear links with increased risk of various neurodevelopmental disorders including ASD,[68–70] ADHD,[68,71,72] and cognitive dysfunction.[68,73]

Overall, pre-existing maternal health factors and conditions have significant influence on the risk and manifestation of CP in offspring, emphasizing the importance of comprehensive maternal care strategies.

2.2.2 Prenatal environmental risk factors

2.2.2.1 Placental and umbilical cord abnormalities

The prenatal environment in which the fetus develops plays a pivotal role in the occurrence of CP. The literature describes in-depth how changes in the placental environment can alter risk of CP. One national cohort study done in Norway found that the presence of placental abnormalities, including placenta previa (RR: 3.03, 95% CI: 2.00-4.61), placental abruption (RR: 10.63, 95% CI: 8.57-13.18), and a retained placenta (RR: 1.71, 95% CI: 1.32-2.22), was associated with an elevated risk of CP. In addition, velamentous umbilical insertion (RR: 2.11, 95% CI: 1.65-2.60), and umbilical cord knots (RR: 1.53, 95% CI: 1.15-2.04) were also found to increase risk of CP.[74] These prenatal placental and umbilical complications have been found to lead to oxygen deprivation, which can lead to further developmental anomalies.

2.2.2.2 Birth asphyxia

Also known as birth asphyxia, oxygen deprivation in utero or during birth can lead to neurological harm and an increased risk of CP.[75] While only approximately 10% of CP cases are attributed to birth asphyxia, proper oxygenation is crucial for cerebral development.[76] One study looking at the effects of chronic fetal hypoxia in sheep found increased vascularity in the white matter, reduced neuronal density, and impaired myelination—changes that adversely affect neurodevelopment.[77] Furthermore, various prenatal models involving oxygen deprivation were investigated in a systematic review done by Visco et al., which found multiple neurogenetic changes to be reported, including hippocampal functional deficits.[78]

2.2.2.3 Intrauterine Growth Restriction (IUGR) and Birth weight

Knots in the umbilical cord, as previously mentioned, and intrauterine growth restriction (IUGR) have also been linked to prenatal hypoxia.[79–81] IUGR is essentially the inability of the fetus to reach its genetic growth potential, primarily caused by an adverse prenatal environment.[82]

In the literature, a systematic review and meta-analysis encompassing 89 samples extracted from 60 studies found that those born with IUGR and classified as small for gestational age (SGA) exhibited notably lower cognitive scores, compared to children born at an appropriate GA.[83] Additionally, a 2022 matched case-control study investigating the associations between birthweight and CP found that the risk of CP showed a gradual increase as birth weight percentiles dropped below the 50th centile, with those who identified as SGA having an OR of 2.43 (95% CI: 1.57-3.73).[84]

2.2.2.4 Maternal infections

During the prenatal period, maternal infections can also effect fetal and cerebral development.[85–87] Maternal intrauterine infections can be bacterial or viral in nature and can lead to an inflammatory response in the fetus.[88] This inflammatory response can then cause developmental delays and damage to brain cells, increasing the risk of CP.[89] A 2020 systematic review done by Ayubi et al. found that the pooled RR from 37 studies presented a CP risk of 2.50 for mothers who had an infection of any type during pregnancy, and a pooled RR of 2.85 for mothers who experienced chorioamnionitis, which is an infection of the placenta and amniotic fluid, during pregnancy.[90] The maternal microbiome's influence on the fetal microbiome has been proven to have great importance during development, and has shown to cause pregnancy complications such as preterm birth, which is an additional risk factor for CP.[91,92] Preterm birth poses an additional risk for CP as it can disrupt crucial periods of development and growth, potentially leading to delays that coincide with the manifestation of CP.[93] In addition, one retrospective cohort study found that while CP was associated with chorioamnionitis (OR: 3.1, 95% CI: 2.9-3.4), CP was also linked with other maternal infections such as genitourinary infection (OR: 1.4, 95% CI: 1.3-1.6) and respiratory infection (OR: 1.9, 95% CI: 1.5-2.2).[85]

2.2.2.5 Ambient air pollution

Ambient air pollution has emerged as a concerning environmental factor linked to the risk of CP. Studies investigating the association between air quality and CP suggest that exposure to certain air pollutants during pregnancy may contribute to adverse neurological outcomes in the offspring.[94] One recent study by Zhang et al. found a clear association between prenatal exposure to $PM_{2.5}$ and CP (cumulative HR: 1.11, 95% CI: 1.03-1.12). Additionally, this study found a higher risk of CP development in males compared to females, confirming previous findings.[24]

Critical windows of exposure during pregnancy have also been identified as increasing the risk of certain disorders. A retrospective study done in pregnant Ontarian women found that exposure to $PM_{2.5}$ during early pregnancy, and ozone (O_3) exposure during the end of the first trimester and through the second trimester, were linked to gestational diabetes.[95] Exposure to $PM_{2.5}$ and nitrogen dioxide (NO_2) during the mid-to-late pregnancy window was also found to increase the risk of low birth weight and childhood blood pressure.[96,97] In addition to the mentioned risks associated with air pollutants during pregnancy, it is worth noting that assessing critical windows of exposure has been a valuable approach in studies investigating birth outcomes. By identifying specific time frames during pregnancy when the developing fetus may be more susceptible to the effects of environmental factors, researchers can gain insights into the biological plausibility of these associations. Overall, the literature has proven the existence of critical windows of exposure during pregnancy that may increase susceptibility to negative health outcomes.

2.2.2.6 Greenspace exposure

While no current literature exists on the association between greenspace exposure and CP, the influence of greenspace has gained attention in recent research due to its protective effects, warranting further investigation into its potential impact on neurodevelopmental outcomes.

Greenspace exposure has been linked to improved mental wellbeing and general health.[98] One twin study published in 2015 found that increased availability of green spaces correlated directly with lower levels of depression.[99] In addition, a systematic review including 12 articles on the topic of greenspace and mental wellbeing of children found that greenspace exposure was correlated with enhanced mental well-being, overall health, and cognitive development in children. Additionally, the review found greenspace exposure to help with attention restoration, memory, competence, supportive social connections, self-discipline, stress moderation, improved behaviors, and improved symptoms of ADHD.[100] One study done in 2022 was also able to identify the protective effect of prenatal greenspace exposure on the development of ASD. This study found a slight reduction in the odds of ASD for children exposed to greenspace-rich areas during the prenatal period.[101] A similar study assessing greenspace and paediatric inflammatory bowel disease (IBD) also found a reduced risk of disease in children who were exposed to higher levels of greenspace during childhood.[102]

In addition to greenspaces, it is important to further investigate indicators of healthy and active living environments in communities. This includes assessing the availability and accessibility of recreational facilities, walkability of neighborhoods, quality of public transportation, and safety of these physical environments. A 2022 study done by Mah et al. found ALEs to be associated with lowered levels of all-cause hospitalization in Canada (OR: 0.66, 95% CI: 0.54-0.81; as compared to the reference/lowest quintile), stating that ALEs may help promote

physical activity.[103] Understanding these factors can provide a more comprehensive view of how community design influences residents' physical activity levels, mental well-being, and overall health outcomes.

Overall, the study of the association between greenspace exposure, ALEs, and CP will provide novel insights for the field of environmental epidemiology, offering a comprehensive understanding of how natural environments may contribute to the prevention or mitigation of CP.

2.2.3 Postnatal and neonatal risk factors

2.2.3.1 Peri-intraventricular hemorrhage (PIVH)

In the literature, post and neo-natal complications are also recognized to be significant contributors to CP risk. Peri-intraventricular hemorrhaging (PIVH), a condition in which blood accumulates in the cerebral ventricles and harms white matter at birth, has been found to be associated with CP.[104] A systematic review and meta-analysis found that premature infants with any level of PIVH faced an elevated risk of CP, compared to infants without PIVH (3.4, 95% CI 1.60-7.22, 9 studies).[105] Overall, PIVH has been linked heavily with other neurodevelopmental disorders as well.[106–109]

2.2.3.2 Neonatal infections

Additionally, infections during the neonatal period, such as sepsis or meningitis, can further compound the risk of CP. A study by Glass et al. found a clear relationship between recurrent postnatal infections and white matter injury,[110] while a meta-analysis of 14 studies revealed that extremely preterm infants who experienced neonatal sepsis faced an elevated risk of impairments, including CP and neurosensory deficits, in comparison to infants without sepsis (OR: 3.18, 95%

CI: 2.29-4.41).[111] Overall, the neonatal period holds profound significance in the developmental trajectory of CP, particularly in terms of brain development. While the prenatal fetal period is crucial for laying the foundation, the neonatal period remains a critical phase as the intricate processes of neural maturation, synaptogenesis, and myelination continue.[112] As such, recognizing the importance of the neonatal period in CP risk is important, as it represents a critical window for interventions, support, and care that can profoundly impact the lifelong trajectory of brain development and function.

2.2.4 Directed Acyclic Graph (DAG)

Exploring the link between etiological risk factors and CP poses a challenge due to the complex nature of CP and the possibility of covariation. To better understand the interrelationships among these factors and facilitate the development of a robust statistical model capable of controlling potential confounding variables, a directed acyclic graph (DAG) was constructed (see Figure 2).

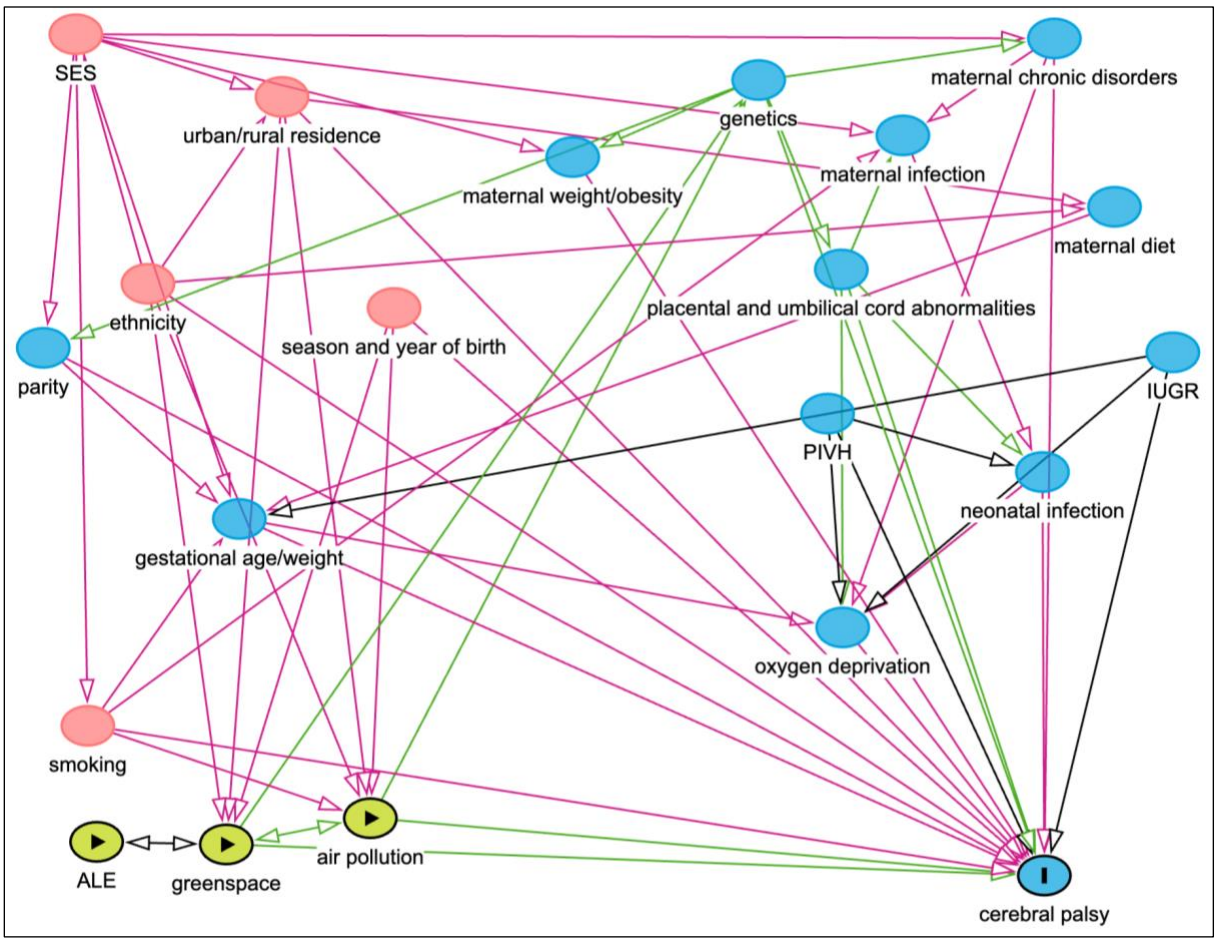


Figure 2. Overall directed acyclic graph (DAG) for CP

Of these risk factors, ambient air pollution, greenspace, and ALE exposures remain scarce in the literature in the context of CP. Since these are the main exposures in this thesis, the next two sections will delve deeper into their available literature.

2.3 Ambient Air Pollution and CP

Ambient air pollution refers to substances in the outdoor atmosphere that lead to poor air quality and negative health effects.[113] There are various common air pollutants, also known as criteria pollutants, which are used to assess air quality standards by governments. This includes

carbon monoxide (CO), nitrogen oxide (NOx), sulfur oxide (SOx), lead, volatile organic compounds (VOCs), ground-level ozone, ammonia (NH_3), and particulate matter (PM).[114–116]

PM is a mixture of solid particles and liquid droplets suspended in the air, originating from sources like vehicle emissions, industrial processes, construction activities, agricultural practices, and natural sources such as dust and wildfires.[117] PM can differ in size, solubility, and composition.[118] Fine particulate matter, also known as $PM_{2.5}$, has a diameter of less than 2.5 μm.[117] Exposure to $PM_{2.5}$ can be harmful due to its ability to penetrate deep into lungs, carrying in harmful toxins.[47] Overall, the specific sources and contributions of these pollutants can vary geographically and depend on local emission regulations and industrial activities.

The Harvard Six Cities study done in the early 1990s first discovered that exposure to fine particulate matter increased mortality rates.[119] Since then, a large body of evidence has been found to support the arguments of $PM_{2.5}$'s harmful effects.[120–122] One study done by Liu et al. in 2016 found that when rats were exposed to a low dose of $PM_{2.5}$, there were adverse perinatal outcomes, including increased blood mononuclear cells, platelets, and interleukin-6 levels, as well as placental pathological changes such as thrombus and chorioamnionitis, suggesting pathological changes that occurred during placental and fetal development. Similarly, a meta-analysis by Ghosh et al. looking at ambient and household $PM_{2.5}$ pollution and adverse perinatal outcomes found that exposure to increased ambient $PM_{2.5}$ levels were linked to increased risk of low birth weight and preterm birth.[124] Additionally, it was estimated that globally, $PM_{2.5}$ exposure in 2019 contributed to a population-weighted mean reduction of 89 grams in birth weight and a decrease of 3.4 weeks in GA.[124] The results emphasize the significance of tackling $PM_{2.5}$ exposure as a means to mitigate negative birth outcomes, especially in LMICs. Numerous studies have been done exploring the association between air pollution and neurodevelopmental disorders, including conditions like

ASD and ADHD.[125] A 2022 study found that higher exposures to $PM_{2.5}$ during the initial two trimesters of pregnancy were linked to an elevated risk of ASD in children, particularly in boys.[126] Additionally, a meta-analysis investigating the association between air pollutants and ADHD found that children exposed to elevated levels of heavy metals and lead had a significantly increased risk of developing ADHD, with a RR of 2.41 (95% CI: 1.49-3.90), compared to those exposed to lower levels.[127] While various other studies also exist that detail the effect of $PM_{2.5}$ on respiratory outcomes or cancer,[128–130] there are very few studies that have been done assessing the relationship between CP and $PM_{2.5}$.

Overall, while suggested links between $PM_{2.5}$ and CP are present in animal studies,[123,131] the specific components of $PM_{2.5}$ that are responsible for this increased risk have not yet been identified. $PM_{2.5}$ is composed of a complex mixture of pollutants, including black carbon (BC); sulfate (SO_4^{2-}); ammonium (NH_4^+); nitrate (NO_3^-); organic matter (OM); sea salt (SS); and mineral dust (dust).[129] The most common sources of BC is from the combustion of fossil fuels, such as diesel and coal, open biomass burning (e.g., residential wood burning and forest fires), such as deforestation and crop residue burning, and the use of biofuels in cooking.[132] SO_4 has similar anthropogenic origins, which is the combustion of gasoline and diesel fuel.[133] NH_4 emissions mainly arise from agricultural practices, such as livestock waste and fertilizer application.[134] NO_3 has been found to be emitted from transportation sources, such as motor vehicles and engines, fossil fuels, and the oil and gas industry.[135] OM and VOCs emanate from vehicle emissions, industrial processes, solvents, fuel evaporation, and various household products.[136] SS is usually found in higher concentrations in coastal areas, as it is sourced from ocean spray.[137] Finally, dust is found to have natural sources, such as the desert, as well as anthropogenic sources, such as agricultural soil and roads.[138] In addition to the air pollutants from $PM_{2.5}$ composition, NO_2 and O_3

have also been key air pollutants which affect health outcomes. Sources of NO_2 are mainly linked to traffic, as well as tobacco smoke and burning appliances,[139] while O_3 is a secondary pollutant that forms from sources such as vehicle exhaust, industrial activities, power plants, and chemical solvents.[140]

From this list, specific components such as sulfur (SO)[141] and ammonia (NH_3),[142] have been proven to have harmful effects in separate studies. For example, a study done in 2013 found early exposure to SO_2 and O_3 to be associated with an increased risk of ASD.[143] Moreso, NH_3 has been identified as a contributor to adverse respiratory health effects such as shortness of breath, stress, drowsiness, mood changes, and other detrimental impacts.[134] Identifying the specific components of $PM_{2.5}$ that are most harmful is crucial for regulatory purposes and public health interventions. By understanding which specific pollutants or components within air pollution pose the greatest risks, policymakers and regulators can implement targeted measures to mitigate exposure and reduce adverse health outcomes. This knowledge enables the development of more effective air quality standards, emission controls, and pollution reduction strategies, leading to improved air quality and better protection of public health. By targeting individual exposure sources, the etiology of CP and other neurological disorders may also become clearer.

2.4 Greenspace Exposure, ALEs, and CP

Exposure to greenspaces during prenatal periods have also been proven to influence birth outcomes. A systematic review and meta-analysis assessing the influence of residential greenness on adverse pregnancy outcomes found higher levels of birth weight (β: 20.22, 95% CI:13.50-26.93, compared to the lowest group), lower odds of low birth weight (OR: 0.86, 95% CI:0.75-0.99), lowered odds of SGA (OR: 0.93, 95% CI:0.88-1.00), and increased head circumference measures

in higher exposure levels of greenness.[144] Overall, greenspace is described as the presence of ecological agents, such as vegetation and nature in surrounding settings.[145] This can be measured using metrics such as the Normalized Difference Vegetation Index (NDVI) or the Green View Index (GVI).[146]

NDVI, derived from satellite imagery, measures the difference between near-infrared and red-light reflectance, providing insights into the presence and vigor of vegetation. A higher NDVI typically indicates denser and healthier vegetation.[147] GVI, on the other hand, specifically focuses on the greenness of vegetation, offering a complementary perspective on plant health and vitality.[148] Overall, these are two important greenspace metrics widely used in the literature to assess and quantify the health, density, and extent of vegetation in a given area.

Generally, greenspaces help improve air quality through processes such as deposition and dispersion.[149] Deposition involves the accumulation of air pollutants on the surface of vegetal elements, such as tree leaves. Through adsorption or absorption by the vegetation, these air pollutants can be removed from the environment, reducing their atmospheric concentrations and exposure to individuals.[152] Similarly, dispersion refers to the process in which air pollutants are prevented from freely circulating in the air by serving as an environmental filter. This changes the trajectory of the air pollutants and ultimately the risk of exposure for individuals. Several studies examining the presence of greenspace in urban settings have identified a reduced risk of mortality.[124] In urban environments, the presence of forestry and other greenspaces was also found to be associated with lower concentrations of PM and other air pollutants.[125,126]

NDVI is most commonly used in environmental epidemiological studies assessing health outcomes.[127] One systematic review found higher NDVI levels to be associated with lower levels

of systolic (SBP = −0.77 mmHg, 95% CI: −1.23 to −0.32) and diastolic (DBP = −0.32 mmHg, 95% CI: −0.57 to −0.07) blood pressure.[128] As mentioned earlier, maternal hypertension is a risk factor for CP, thus decreased blood pressure due to NDVI exposure during gestation may potentially influence birth outcomes and CP risk. In addition, a meta-analysis including 5 studies found a 0.1 unit increase in NDVI to be linked with lowered odds of obesity and overweightness in children (OR: 0.91, 95% CI: 0.84-0.98, I^2 = 7%)

However, while many studies have found beneficial effects for NDVI exposure, adverse effects for this greenspace metric have also been found in some studies. One study done looking at an Ontarian cohort of children found increased risk of childhood asthma for exposure to NDVI (HR: 1.029, 95% CI: 1.008-1.035, per IQR=0.08-unit increase).[129] Similar results were found in another study, which attributed findings to sensitivity to allergens.[130]

GVI is another commonly used greenspace metric which assesses eye-level greenery and has been found to be positively correlated with participation in recreational and physical activities.[131] One study found increased levels of GVI to be associated with improved lung function, but this became non-significant when air pollution exposure measures were considered, highlighting the importance of carefully controlling for other environmental factors, such as air quality, when evaluating the health benefits of greenspaces.[132]

In addition to greenspace metrics, indicators of active and healthy living environments should be considered as well. While associations between NDVI, GVI and beneficial health outcomes have been found in various studies, these metrics do not often consider the additional factors of usability and accessibility of greenspaces. This means that even if an area has high vegetation or green street views, it may not necessarily translate into health benefits if the spaces

are not easily accessible or suitable for physical activity. Factors such as the quality of maintenance, safety, availability of amenities, and connectivity to residential areas are crucial in determining whether greenspaces are effectively utilized by the community. To assess these additional environmental factors, indicators such as park proximity and ALE indexes were used.

Park proximity refers to the distance between an individual's residence and the nearest park or greenspace, and it is a key factor in determining how likely people are to use these areas for recreation and physical activity.[133] Proximity to parks has been consistently linked with positive health outcomes, such as increased physical activity, lower stress levels, and improved mental health.[133–135] The closer individuals live to a park, the more likely they are to visit it regularly, which can lead to higher levels of exercise and social interaction, both of which are beneficial for overall well-being. However, simply having a park nearby does not guarantee its use; factors such as the quality, safety, and accessibility of the park, as well as personal motivation, also play significant roles in determining its usability.

Similarly, ALE indexes are comprehensive tools that are used to measure and assess the quality of environments that promote physical activity and healthy lifestyles in communities.[136] These indexes often consider multiple factors that determine how conducive the built environment in a community is to physical activity. One study assessing ALEs and cardiometabolic mortality found a 22% reduction in older women living in higher ALE neighborhoods (HR 0.78, 95% CI 0.63-0.97).[137] However, similar to greenspace measures, it is important to recognize that ALE indexes, while valuable, may not fully capture all aspects of active living, such as cultural and social factors.

Overall, while increased urbanization can lead to poor air quality and increased air pollution, the implementation of greenspaces and environments that promote active living can help offset these effects. Greenspaces not only improve air quality by filtering pollutants, but also provide areas for physical activity, which can reduce the risk of various health conditions. While the protective effect of greenspace is studied in varying disorders and conditions, the association between greenspace and CP has not yet been studied. Investigating this relationship in this thesis will provide valuable and novel insights into this area of research, which may potentially help guide future public health strategies for urban planning and the promotion of green environments.

2.5 References

1. Metz C, Jaster M, Walch E, Sarpong-Bengelsdorf A, Kaindl AM, Schneider J. Clinical Phenotype of Cerebral Palsy Depends on the Cause: Is It Really Cerebral Palsy? A Retrospective Study. *J Child Neurol*. 2022;37(2):112-118. doi:10.1177/08830738211059686

2. Panteliadis C, Panteliadis P, Vassilyadi F. Hallmarks in the history of cerebral palsy: from antiquity to mid-20th century. *Brain Dev*. 2013;35(4):285-292. doi:10.1016/j.braindev.2012.05.003

3. Patel DR, Neelakantan M, Pandher K, Merrick J. Cerebral palsy in children: a clinical overview. *Transl Pediatr*. 2020;9(Suppl 1):S125-S12S135. doi:10.21037/tp.2020.01.01

4. McIntyre S, Goldsmith S, Webb A, et al. Global prevalence of cerebral palsy: A systematic analysis. *Dev Med Child Neurol*. 2022;64(12):1494-1506. doi:10.1111/dmcn.15346

5. McIntyre S, Goldsmith S, Webb A, et al. Global prevalence of cerebral palsy: A systematic analysis. *Dev Med Child Neurol*. 2022;64(12):1494-1506. doi:10.1111/dmcn.15346

6. Jahan I, Muhit M, Hardianto D, et al. Epidemiology of cerebral palsy in low- and middle-income countries: preliminary findings from an international multi-centre cerebral palsy register. *Dev Med Child Neurol*. 2021;63(11):1327-1336. doi:10.1111/dmcn.14926

7. Cans C, De-la-Cruz J, Mermet MA. Epidemiology of cerebral palsy. *Paediatr Child Health*. 2008;18(9):393-398. doi:10.1016/j.paed.2008.05.015

8. Amankwah N, Oskoui M, Garner R, et al. Cerebral palsy in Canada, 2011-2031: results of a microsimulation modelling study of epidemiological and cost impacts. *Health Promot Chronic Dis Prev Can Res Policy Pract*. 2020;40(2):25-37. doi:10.24095/hpcdp.40.2.01

9. Khandaker G, Muhit M, Karim T, et al. Epidemiology of cerebral palsy in Bangladesh: a population-based surveillance study. *Dev Med Child Neurol*. 2019;61(5):601-609. doi:10.1111/dmcn.14013

10. te Velde A, Morgan C, Novak I, Tantsis E, Badawi N. Early Diagnosis and Classification of Cerebral Palsy: An Historical Perspective and Barriers to an Early Diagnosis. *J Clin Med*. 2019;8(10):1599. doi:10.3390/jcm8101599

11. Hadders-Algra M. Early Diagnosis and Early Intervention in Cerebral Palsy. *Front Neurol*. 2014;5:185. doi:10.3389/fneur.2014.00185

12. Vitrikas K, Dalton H, Breish D. Cerebral Palsy: An Overview. *Am Fam Physician*. 2020;101(4):213-220.

13. Jarvis S, Glinianaia SV, Arnaud C, et al. Case gender and severity in cerebral palsy varies with intrauterine growth. *Arch Dis Child*. 2005;90(5):474-479. doi:10.1136/adc.2004.052670

14. Romeo DM, Sini F, Brogna C, Albamonte E, Ricci D, Mercuri E. Sex differences in cerebral palsy on neuromotor outcome: a critical review. *Dev Med Child Neurol*. 2016;58(8):809-813. doi:10.1111/dmcn.13137

15. Jensen A. Cerebral palsy – brain repair with stem cells. *J Perinat Med*. 2023;51(6):737-751. doi:10.1515/jpm-2022-0505

16. Stavsky M, Mor O, Mastrolia SA, Greenbaum S, Than NG, Erez O. Cerebral Palsy—Trends in Epidemiology and Recent Development in Prenatal Mechanisms of Disease, Treatment, and Prevention. *Front Pediatr*. 2017;5:21. doi:10.3389/fped.2017.00021

17. Marret S, Vanhulle C, Laquerriere A. Chapter 16 - Pathophysiology of cerebral palsy. In: Dulac O, Lassonde M, Sarnat HB, eds. *Handbook of Clinical Neurology*. Vol 111. Pediatric Neurology Part I. Elsevier; 2013:169-176. doi:10.1016/B978-0-444-52891-9.00016-6

18. May HJ, Fasheun JA, Bain JM, et al. Genetic testing in individuals with cerebral palsy. *Dev Med Child Neurol*. 2021;63(12):1448-1455. doi:10.1111/dmcn.14948

19. Freedman M, Jon Matthew Farber MD. Exome sequencing should be used for diagnosing cerebral palsy. 2023;40. Accessed November 16, 2023. https://www.contemporarypediatrics.com/view/exome-sequencing-should-be-used-for-diagnosing-cerebral-palsy

20. Gonzalez-Mantilla PJ, Hu Y, Myers SM, et al. Diagnostic Yield of Exome Sequencing in Cerebral Palsy and Implications for Genetic Testing Guidelines: A Systematic Review and Meta-analysis. *JAMA Pediatr*. 2023;177(5):472-478. doi:10.1001/jamapediatrics.2023.0008

21. Lewis SA, Shetty S, Wilson BA, et al. Insights From Genetic Studies of Cerebral Palsy. *Front Neurol*. 2021;11. Accessed November 16, 2023. https://www.frontiersin.org/articles/10.3389/fneur.2020.625428

22. Jin SC, Lewis SA, Bakhtiari S, et al. Mutations disrupting neuritogenesis genes confer risk for cerebral palsy. *Nat Genet*. 2020;52(10):1046-1056. doi:10.1038/s41588-020-0695-1

23. Reid SM, Meehan EM, Arnup SJ, Reddihough DS. Intellectual disability in cerebral palsy: a population-based retrospective study. *Dev Med Child Neurol*. 2018;60(7):687-694. doi:10.1111/dmcn.13773

24. Christensen D, Van Naarden Braun K, Doernberg NS, et al. Prevalence of cerebral palsy, co-occurring autism spectrum disorders, and motor functioning – Autism and Developmental Disabilities Monitoring Network, USA, 2008. *Dev Med Child Neurol*. 2014;56(1):59-65. doi:10.1111/dmcn.12268

25. Gutvirtz G, Wainstock T, Landau D, Sheiner E. Maternal smoking during pregnancy and long-term neurological morbidity of the offspring. *Addict Behav*. 2019;88:86-91. doi:10.1016/j.addbeh.2018.08.013

26. Ren S, Xie S, Li X, et al. The association between maternal exposure to secondhand smoke during pregnancy and their children's cerebral palsy, Shandong, China. *Tob Induc Dis*. 2020;18:87. doi:10.18332/tid/127872

27. Wickström R. Effects of Nicotine During Pregnancy: Human and Experimental Evidence. *Curr Neuropharmacol*. 2007;5(3):213-222. doi:10.2174/157015907781695955

28. Zhang J, Peng L, Chang Q, et al. Maternal obesity and risk of cerebral palsy in children: a systematic review and meta-analysis. *Dev Med Child Neurol*. 2019;61(1):31-38. doi:10.1111/dmcn.13982

29. Shaw OEF, Yager JY. Preventing childhood and lifelong disability: Maternal dietary supplementation for perinatal brain injury. *Pharmacol Res*. 2019;139:228-242. doi:10.1016/j.phrs.2018.08.022

30. Silva KOG da, Pereira S da C, Portovedo M, et al. Effects of maternal low-protein diet on parameters of locomotor activity in a rat model of cerebral palsy. *Int J Dev Neurosci*. 2016;52:38-45. doi:10.1016/j.ijdevneu.2016.05.002

31. Benavente-Fernández I, Synnes A, Grunau RE, et al. Association of Socioeconomic Status and Brain Injury With Neurodevelopmental Outcomes of Very Preterm Children. *JAMA Netw Open*. 2019;2(5):e192914. doi:10.1001/jamanetworkopen.2019.2914

32. Benavente-Fernández I, Siddiqi A, Miller SP. Socioeconomic status and brain injury in children born preterm: modifying neurodevelopmental outcome. *Pediatr Res*. 2020;87(2):391-398. doi:10.1038/s41390-019-0646-7

33. Solaski M, Majnemer A, Oskoui M. Contribution of socio-economic status on the prevalence of cerebral palsy: a systematic search and review. *Dev Med Child Neurol*. 2014;56(11):1043-1051. doi:10.1111/dmcn.12456

34. Tseng SH, Lee JY, Chou YL, Sheu ML, Lee YW. Association between socioeconomic status and cerebral palsy. *PLOS ONE*. 2018;13(1):e0191724. doi:10.1371/journal.pone.0191724

35. Aqsa Ghazal, Sarfraz Ahmad, Syeda Rahat, Syeda Bushra. Association between Risk Factors & Cerebral Palsy and Prevalence of its Different Types. *Pak J Med Health Sci*. 2019;13(3). chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://pjmhsonline.com/2019/july_sep/pdf/786.pdf

36. Chen D, Huang M, Yin Y, et al. Risk factors of cerebral palsy in children: a systematic review and meta-analysis. *Transl Pediatr*. 2022;11(4):556-564. doi:10.21037/tp-22-78

37. Ahmed A, Rosella LC, Oskoui M, Watson T, Yang S. In utero Exposure to Maternal Diabetes and the Risk of Cerebral Palsy: A Population-based Cohort Study. *Epidemiology*. 2023;34(2):247. doi:10.1097/EDE.0000000000001574

38. Chen KR, Yu T, Lien YJ, Chou YY, Kuo PL. Childhood neurodevelopmental disorders and maternal diabetes: A population-based cohort study. *Dev Med Child Neurol*. 2023;65(7):933-941. doi:10.1111/dmcn.15488

39. Xiang AH, Wang X, Martinez MP, et al. Association of Maternal Diabetes With Autism in Offspring. *JAMA*. 2015;313(14):1425-1434. doi:10.1001/jama.2015.2707

40. Xu G, Jing J, Bowers K, Liu B, Bao W. Maternal Diabetes and the Risk of Autism Spectrum Disorders in the Offspring: A Systematic Review and Meta-Analysis. *J Autism Dev Disord*. 2014;44(4):766-775. doi:10.1007/s10803-013-1928-2

41. Ornoy A, Reece EA, Pavlinkova G, Kappen C, Miller RK. Effect of maternal diabetes on the embryo, fetus, and children: Congenital anomalies, genetic and epigenetic changes and developmental outcomes. *Birth Defects Res Part C Embryo Today Rev*. 2015;105(1):53-72. doi:10.1002/bdrc.21090

42. Guo D, Ju R, Zhou Q, et al. Association of maternal diabetes with attention deficit/hyperactivity disorder (ADHD) in offspring: A meta-analysis and review. *Diabetes Res Clin Pract*. 2020;165:108269. doi:10.1016/j.diabres.2020.108269

43. Sousa R a. LD, Torres YS, Figueiredo CP, Passos GF, Clarke JR. Consequences of gestational diabetes to the brain and behavior of the offspring. *An Acad Bras Ciênc*. 2017;90:2279-2291. doi:10.1590/0001-3765201720170264

44. Ebbing C, Rasmussen S, Kessler J, Moster D. Association of placental and umbilical cord characteristics with cerebral palsy: national cohort study. *Ultrasound Obstet Gynecol*. 2023;61(2):224-230. doi:10.1002/uog.26047

45. Zhang S, Li B, Zhang X, Zhu C, Wang X. Birth Asphyxia Is Associated With Increased Risk of Cerebral Palsy: A Meta-Analysis. *Front Neurol*. 2020;11. Accessed August 23, 2023. https://www.frontiersin.org/articles/10.3389/fneur.2020.00704

46. Nelson KB, Blair E. Prenatal Factors in Singletons with Cerebral Palsy Born at or near Term. *N Engl J Med*. 2015;373(10):946-953. doi:10.1056/NEJMra1505261

47. Lawrence KM, McGovern PE, Mejaddam A, et al. Chronic intrauterine hypoxia alters neurodevelopment in fetal sheep. *J Thorac Cardiovasc Surg*. 2019;157(5):1982-1991. doi:10.1016/j.jtcvs.2018.12.093

48. Visco DB, Toscano AE, Juárez PAR, et al. A systematic review of neurogenesis in animal models of early brain damage: Implications for cerebral palsy. *Exp Neurol*. 2021;340:113643. doi:10.1016/j.expneurol.2021.113643

49. Ross MG. Forensic Analysis of Umbilical and Newborn Blood Gas Values for Infants at Risk of Cerebral Palsy. *J Clin Med*. 2021;10(8):1676. doi:10.3390/jcm10081676

50. Pirnareva EB, Marinov null, Tsankova M. [ASPHYXIA IN INTRAUTERINE GROWTH RESTRICTION OF THE FETUS- CARDIOTOCOGRAPHY AND ULTRASOUND METHODS OF DIAGNOSIS.]. *Akush Ginekol (Sofiia)*. 2016;55 Suppl 2:23-27.

51. Clerici G, Koutras I, Luzietti R, Di Renzo GC. Multiple true umbilical knots: a silent risk for intrauterine growth restriction with anomalous hemodynamic pattern. *Fetal Diagn Ther*. 2007;22(6):440-443. doi:10.1159/000106351

52. Armengaud JB, Yzydorczyk C, Siddeek B, Peyter AC, Simeoni U. Intrauterine growth restriction: Clinical consequences on health and disease at adulthood. *Reprod Toxicol*. 2021;99:168-176. doi:10.1016/j.reprotox.2020.10.005

53. Sacchi C, Marino C, Nosarti C, Vieno A, Visentin S, Simonelli A. Association of Intrauterine Growth Restriction and Small for Gestational Age Status With Childhood Cognitive Outcomes: A Systematic Review and Meta-analysis. *JAMA Pediatr*. 2020;174(8):772-781. doi:10.1001/jamapediatrics.2020.1097

54. Esih K, Trunk T, Osredkar D, et al. The impact of birthweight on the development of cerebral palsy: A population-based matched case-control study. *Early Hum Dev*. 2022;165:105533. doi:10.1016/j.earlhumdev.2021.105533

55. Bear JJ, Wu YW. Maternal Infections During Pregnancy and Cerebral Palsy in the Child. *Pediatr Neurol*. 2016;57:74-79. doi:10.1016/j.pediatrneurol.2015.12.018

56. Jacobsson B, Hagberg G, Hagberg H. Maternal infection and cerebral palsy in term infants with periventricular leucomalacia. *Am J Obstet Gynecol*. 2003;189(6, Supplement):S154. doi:10.1016/j.ajog.2003.10.337

57. Wu CS, Pedersen LH, Miller JE, et al. Risk of Cerebral Palsy and Childhood Epilepsy Related to Infections before or during Pregnancy. *PLOS ONE*. 2013;8(2):e57552. doi:10.1371/journal.pone.0057552

58. Tsimis ME. Intrauterine Infection and Cerebral Palsy. In: Panteliadis CP, ed. *Cerebral Palsy: A Multidisciplinary Approach*. Springer International Publishing; 2018:59-63. doi:10.1007/978-3-319-67858-0_7

59. Hermansen MC, Hermansen MG. Perinatal Infections and Cerebral Palsy. *Clin Perinatol*. 2006;33(2):315-333. doi:10.1016/j.clp.2006.03.002

60. Ayubi E, Sarhadi S, Mansori K. Maternal Infection During Pregnancy and Risk of Cerebral Palsy in Children: A Systematic Review and Meta-analysis. *J Child Neurol*. 2021;36(5):385-402. doi:10.1177/0883073820972507

61. Dunn AB, Jordan S, Baker BJ, Carlson NS. The Maternal Infant Microbiome: Considerations for Labor and Birth. *MCN Am J Matern Nurs*. 2017;42(6):318. doi:10.1097/NMC.0000000000000373

62. Spittle AJ, Morgan C, Olsen JE, Novak I, Cheong JLY. Early Diagnosis and Treatment of Cerebral Palsy in Children with a History of Preterm Birth. *Clin Perinatol*. 2018;45(3):409-420. doi:10.1016/j.clp.2018.05.011

63. Luu TM, Katz SL, Leeson P, Thébaud B, Nuyt AM. Preterm birth: risk factor for early-onset chronic diseases. *CMAJ*. 2016;188(10):736-746. doi:10.1503/cmaj.150450

64. Aleya L, Uddin MdS. Environmental pollutants and the risk of neurological disorders. *Environ Sci Pollut Res*. 2020;27(36):44657-44658. doi:10.1007/s11356-020-11272-3

65. Hu Y, Zhang Y, Talarico R, et al. Prenatal Exposure to Ambient Air Pollution and Offspring Cerebral Palsy in Ontario, Canada: A Population-Based Cohort Study. *ISEE Conf Abstr*. Published online September 18, 2022. doi:10.1289/isee.2022.P-0481

66. Miron-Celis M, Talarico R, Villeneuve PJ, et al. Critical windows of exposure to air pollution and gestational diabetes: assessing effect modification by maternal pre-existing conditions and environmental factors. *Environ Health*. 2023;22(1):26. doi:10.1186/s12940-023-00974-z

67. Johnson M, Shin HH, Roberts E, et al. Critical Time Windows for Air Pollution Exposure and Birth Weight in a Multicity Canadian Pregnancy Cohort. *Epidemiology*. 2022;33(1):7. doi:10.1097/EDE.0000000000001428

68. Rosa MJ, Hair GM, Just AC, et al. Identifying critical windows of prenatal particulate matter (PM2.5) exposure and early childhood blood pressure. *Environ Res*. 2020;182:109073. doi:10.1016/j.envres.2019.109073

69. Astell-Burt T, Feng X. Association of Urban Green Space With Mental Health and General Health Among Adults in Australia. *JAMA Netw Open*. 2019;2(7):e198209. doi:10.1001/jamanetworkopen.2019.8209

70. Cohen-Cline H, Turkheimer E, Duncan GE. Access to green space, physical activity and mental health: a twin study. *J Epidemiol Community Health*. 2015;69(6):523-529. doi:10.1136/jech-2014-204667

71. McCormick R. Does Access to Green Space Impact the Mental Well-being of Children: A Systematic Review. *J Pediatr Nurs*. 2017;37:3-7. doi:10.1016/j.pedn.2017.08.027

72. Pagalan L, Oberlander TF, Hanley GE, et al. The association between prenatal greenspace exposure and Autism spectrum disorder, and the potentially mediating role of air pollution reduction: A population-based birth cohort study. *Environ Int*. 2022;167:107445. doi:10.1016/j.envint.2022.107445

73. Elten M, Benchimol EI, Fell DB, et al. Residential Greenspace in Childhood Reduces Risk of Pediatric Inflammatory Bowel Disease: A Population-Based Cohort Study. *Off J Am Coll Gastroenterol ACG*. 2021;116(2):347. doi:10.14309/ajg.0000000000000990

74. Mah SM, Dasgupta K, Akbari A, Ross NA, Fry R. An international comparative study of active living environments and hospitalization for Wales and Canada. *SSM - Popul Health*. 2022;18:101048. doi:10.1016/j.ssmph.2022.101048

75. Ballabh P, de Vries LS. White matter injury in infants with intraventricular haemorrhage: mechanisms and therapies. *Nat Rev Neurol*. 2021;17(4):199-214. doi:10.1038/s41582-020-00447-8

76. Gotardo JW, Volkmer N de FV, Stangler GP, Dornelles AD, Bohrer BB de A, Carvalho CG. Impact of peri-intraventricular haemorrhage and periventricular leukomalacia in the neurodevelopment of preterms: A systematic review and meta-analysis. *PLOS ONE*. 2019;14(10):e0223427. doi:10.1371/journal.pone.0223427

77. Vohr BR. Neurodevelopmental outcomes of premature infants with intraventricular hemorrhage across a lifespan. *Semin Perinatol*. 2022;46(5):151594. doi:10.1016/j.semperi.2022.151594

78. Honnorat M, Plaisant F, Serret-Larmande A, Claris O, Butin M. Neurodevelopmental Outcome at Two Years for Preterm Infants With Intraventricular Hemorrhage: A Case-Control Study. *Pediatr Neurol*. 2023;141:52-57. doi:10.1016/j.pediatrneurol.2023.01.013

79. Scott TE, Aboudi D, Kase JS. Low-Grade Intraventricular Hemorrhage and Neurodevelopmental Outcomes at 24-42 Months of Age. *J Child Neurol*. 2020;35(9):578-584. doi:10.1177/0883073820922638

80. Reis JS, Pereira IA, Lira J, et al. Intraventricular hemorrhage in preterm infants: risk factors and neurodevelopmental outcomes. *J Pediatr Neonatal Individ Med JPNIM*. 2023;12(1):e120118-e120118. doi:10.7363/120118

81. Glass HC, Bonifacio SL, Chau V, et al. Recurrent Postnatal Infections Are Associated With Progressive White Matter Injury in Premature Infants. *Pediatrics*. 2008;122(2):299-305. doi:10.1542/peds.2007-2184

82. Cai S, Thompson DK, Anderson PJ, Yang JYM. Short- and Long-Term Neurodevelopmental Outcomes of Very Preterm Infants with Neonatal Sepsis: A Systematic Review and Meta-Analysis. *Children*. 2019;6(12):131. doi:10.3390/children6120131

83. Kelley KW, Pașca SP. Human brain organogenesis: Toward a cellular understanding of development and disease. *Cell*. 2022;185(1):42-61. doi:10.1016/j.cell.2021.10.003

84. Jiang XQ, Mei XD, Feng D. Air pollution and chronic airway diseases: what should people know and do? *J Thorac Dis*. 2016;8(1). doi:10.3978/j.issn.2072-1439.2015.11.50

85. Almetwally AA, Bin-Jumah M, Allam AA. Ambient air pollution and its influence on human health and welfare: an overview. *Environ Sci Pollut Res*. 2020;27(20):24815-24830. doi:10.1007/s11356-020-09042-2

86. US EPA O. Criteria Air Pollutants. April 9, 2014. Accessed August 23, 2023. https://www.epa.gov/criteria-air-pollutants

87. Government of Canada E and CC. Common air contaminants. June 3, 2004. Accessed August 23, 2023. https://www.canada.ca/en/environment-climate-change/services/air-pollution/pollutants/common-contaminants.html

88. Donaldson K, MacNee W, Stone V. ENVIRONMENTAL POLLUTANTS | Particulate Matter, Ultrafine Particles. In: Laurent GJ, Shapiro SD, eds. *Encyclopedia of Respiratory Medicine*. Academic Press; 2006:104-110. doi:10.1016/B0-12-370879-6/00132-0

89. Xing YF, Xu YH, Shi MH, Lian YX. The impact of PM2.5 on the human respiratory system. *J Thorac Dis*. 2016;8(1). doi:10.3978/j.issn.2072-1439.2016.01.19

90. Dockery DW, Pope CA, Xu X, et al. An Association between Air Pollution and Mortality in Six U.S. Cities. *N Engl J Med*. 1993;329(24):1753-1759. doi:10.1056/NEJM199312093292401

91. Burnett R, Chen H, Szyszkowicz M, et al. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proc Natl Acad Sci*. 2018;115(38):9592-9597. doi:10.1073/pnas.1803222115

92. Cohen AJ, Brauer M, Burnett R, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *The Lancet*. 2017;389(10082):1907-1918. doi:10.1016/S0140-6736(17)30505-6

93. Meng X, Zhang Y, Yang KQ, Yang YK, Zhou XL. Potential Harmful Effects of PM2.5 on Occurrence and Progression of Acute Coronary Syndrome: Epidemiology, Mechanisms, and Prevention Measures. *Int J Environ Res Public Health*. 2016;13(8):748. doi:10.3390/ijerph13080748

94. Liu Y, Wang L, Wang F, Li C. Effect of Fine Particulate Matter (PM2.5) on Rat Placenta Pathology and Perinatal Outcomes. *Med Sci Monit*. 2016;22:3274-3280. doi:10.12659/MSM.897808

95. Ghosh R, Causey K, Burkart K, Wozniak S, Cohen A, Brauer M. Ambient and household PM2.5 pollution and adverse perinatal outcomes: A meta-regression and analysis of attributable global burden for 204 countries and territories. *PLOS Med*. 2021;18(9):e1003718. doi:10.1371/journal.pmed.1003718

96. Kim H, Kim WH, Kim YY, Park HY. Air Pollution and Central Nervous System Disease: A Review of the Impact of Fine Particulate Matter on Neurological Disorders. *Front Public Health*. 2020;8. Accessed August 23, 2023. https://www.frontiersin.org/articles/10.3389/fpubh.2020.575330

97. Rahman MM, Shu YH, Chow T, et al. Prenatal Exposure to Air Pollution and Autism Spectrum Disorder: Sensitive Windows of Exposure and Sex Differences. *Environ Health Perspect*. 130(1):017008. doi:10.1289/EHP9509

98. Bernardina Dalla MD, Ayala CO, Cristina de Abreu Quintela Castro F, et al. Environmental pollution and attention deficit hyperactivity disorder: A meta-analysis of cohort studies. *Environ Pollut*. 2022;315:120351. doi:10.1016/j.envpol.2022.120351

99. Odo DB, Yang IA, Dey S, et al. Ambient air pollution and acute respiratory infection in children aged under 5 years living in 35 developing countries. *Environ Int*. 2022;159:107019. doi:10.1016/j.envint.2021.107019

100. Lavigne É, Talarico R, van Donkelaar A, et al. Fine particulate matter concentration and composition and the incidence of childhood asthma. *Environ Int*. 2021;152:106486. doi:10.1016/j.envint.2021.106486

101. Zhang Z, Weichenthal S, Kwong JC, et al. A Population-Based Cohort Study of Respiratory Disease and Long-Term Exposure to Iron and Copper in Fine Particulate Air Pollution and Their Combined Impact on Reactive Oxygen Species Generation in Human Lungs. *Environ Sci Technol*. 2021;55(6):3807-3818. doi:10.1021/acs.est.0c05931

102. Zhang T, Sun L, Wang T, et al. Gestational exposure to PM2.5 leads to cognitive dysfunction in mice offspring via promoting HMGB1-NLRP3 axis mediated hippocampal inflammation. *Ecotoxicol Environ Saf*. 2021;223:112617. doi:10.1016/j.ecoenv.2021.112617

103. Ramanathan V, Carmichael G. Global and regional climate changes due to black carbon. *Nat Geosci*. 2008;1(4):221-227. doi:10.1038/ngeo156

104. California Air Resources Board. Sulfate & Health. Accessed November 20, 2023. https://ww2.arb.ca.gov/resources/sulfate-and-health

105. Wyer KE, Kelleghan DB, Blanes-Vidal V, Schauberger G, Curran TP. Ammonia emissions from agriculture and their contribution to fine particulate matter: A review of implications for human health. *J Environ Manage*. 2022;323:116285. doi:10.1016/j.jenvman.2022.116285

106. Environment and Climate Change Canada. Nitrogen oxides: main emission sources. June 3, 2004. Accessed November 20, 2023. https://www.canada.ca/en/environment-climate-

change/services/air-pollution/pollutants/common-contaminants/nitrogen-oxides/main-emission-sources.html

107. US EPA O. What are volatile organic compounds (VOCs)? February 19, 2019. Accessed August 23, 2023. https://www.epa.gov/indoor-air-quality-iaq/what-are-volatile-organic-compounds-vocs

108. Zhang Y, Yang L, Bie S, et al. Chemical compositions and the impact of sea salt in atmospheric PM1 and PM2.5 in the coastal area. *Atmospheric Res*. 2021;250:105323. doi:10.1016/j.atmosres.2020.105323

109. Liu X, Turner JR, Hand JL, Schichtel BA, Martin RV. A Global-Scale Mineral Dust Equation. *J Geophys Res Atmospheres*. 2022;127(18):e2022JD036937. doi:10.1029/2022JD036937

110. Jarvis DJ, Adamkiewicz G, Heroux ME, Rapp R, Kelly FJ. Nitrogen dioxide. In: *WHO Guidelines for Indoor Air Quality: Selected Pollutants*. World Health Organization; 2010. Accessed November 20, 2023. https://www.ncbi.nlm.nih.gov/books/NBK138707/

111. Fraser Valley Regional District. Air Pollutants & Sources. https://www.fvrd.ca. Accessed August 23, 2023. https://www.fvrd.ca/EN/main/services/AirQualityandClimate/AirQualityandClimate/air-pollutants-and-sources.html

112. Korsiak J, Lavigne E, You H, et al. Air Pollution and Pediatric Respiratory Hospitalizations: Effect Modification by Particle Constituents and Oxidative Potential. *Am J Respir Crit Care Med*. 2022;206(11):1370-1378. doi:10.1164/rccm.202205-0896OC

113. Masselot P, Sera F, Schneider R, et al. Differential Mortality Risks Associated With PM2.5 Components: A Multi-Country, Multi-City Study. *Epidemiology*. 2022;33(2):167. doi:10.1097/EDE.0000000000001455

114. Jung CR, Lin YT, Hwang BF. Air Pollution and Newly Diagnostic Autism Spectrum Disorders: A Population-Based Cohort Study in Taiwan. *PLOS ONE*. 2013;8(9):e75510. doi:10.1371/journal.pone.0075510

115. Zhan Y, Liu J, Lu Z, Yue H, Zhang J, Jiang Y. Influence of residential greenness on adverse pregnancy outcomes: A systematic review and dose-response meta-analysis. *Sci Total Environ*. 2020;718:137420. doi:10.1016/j.scitotenv.2020.137420

116. Taylor L, Hochuli DF. Defining greenspace: Multiple uses across multiple disciplines. *Landsc Urban Plan*. 2017;158:25-38. doi:10.1016/j.landurbplan.2016.09.024

117. Lavigne E, Shin H, Murphy M, Abdulaziz K, Wen SW. Early Life Exposure to Greenspace and Autism Spectrum Disorder and the Mediating Effects of Air Pollution in Ontario, Canada. *ISEE Conf Abstr*. Published online September 18, 2022. doi:10.1289/isee.2022.O-OP-207

118. GISGeography. What is NDVI (Normalized Difference Vegetation Index)? GIS Geography. May 9, 2017. Accessed December 11, 2023. https://gisgeography.com/ndvi-normalized-difference-vegetation-index/

119. Zhu H, Nan X, Yang F, Bao Z. Utilizing the green view index to improve the urban street greenery index system: A statistical study using road patterns and vegetation structures as entry points. *Landsc Urban Plan*. 2023;237:104780. doi:10.1016/j.landurbplan.2023.104780

120. Diener A, Mudu P. How can vegetation protect us from air pollution? A critical review on green spaces' mitigation abilities for air-borne particles from a public health perspective - with implications for urban planning. *Sci Total Environ*. 2021;796:148605. doi:10.1016/j.scitotenv.2021.148605

121. Ponette-González AG, Chen D, Elderbrock E, et al. Urban edge trees: Urban form and meteorology drive elemental carbon deposition to canopies and soils. *Environ Pollut*. 2022;314:120197. doi:10.1016/j.envpol.2022.120197

122. Yao J, Wu S, Cao Y, et al. Dry deposition effect of urban green spaces on ambient particulate matter pollution in China. *Sci Total Environ*. 2023;900:165830. doi:10.1016/j.scitotenv.2023.165830

123. Yang L, Zhang L, Li Y, Wu S. Water-related ecosystem services provided by urban green space: A case study in Yixing City (China). *Landsc Urban Plan*. 2015;136:40-51. doi:10.1016/j.landurbplan.2014.11.016

124. Rojas-Rueda D, Nieuwenhuijsen MJ, Gascon M, Perez-Leon D, Mudu P. Green spaces and mortality: a systematic review and meta-analysis of cohort studies. *Lancet Planet Health*. 2019;3(11):e469-e477. doi:10.1016/S2542-5196(19)30215-3

125. Irga PJ, Burchett MD, Torpy FR. Does urban forestry have a quantitative effect on ambient air quality in an urban environment? *Atmos Environ*. 2015;120:173-181. doi:10.1016/j.atmosenv.2015.08.050

126. Ai H, Zhang X, Zhou Z. The impact of greenspace on air pollution: Empirical evidence from China. *Ecol Indic*. 2023;146:109881. doi:10.1016/j.ecolind.2023.109881

127. Son JY, Choi HM, Fong KC, Heo S, Lim CC, Bell ML. The roles of residential greenness in the association between air pollution and health: a systematic review. *Environ Res Lett*. 2021;16(9):093001. doi:10.1088/1748-9326/ac0e61

128. Zhao Y, Bao WW, Yang BY, et al. Association between greenspace and blood pressure: A systematic review and meta-analysis. *Sci Total Environ*. 2022;817:152513. doi:10.1016/j.scitotenv.2021.152513

129. Stanescu C, Talarico R, Weichenthal S, et al. Early life exposure to pollens and increased risks of childhood asthma: a prospective cohort study in Ontario children. *Eur Respir J*. 2024;63(4). doi:10.1183/13993003.01568-2023

130. Hartley K, Ryan PH, Gillespie GL, et al. Residential greenness, asthma, and lung function among children at high risk of allergic sensitization: a prospective cohort study. *Environ Health*. 2022;21:52. doi:10.1186/s12940-022-00864-w

131. Kumakoshi Y, Chan SY, Koizumi H, Li X, Yoshimura Y. Standardized Green View Index and Quantification of Different Metrics of Urban Green Vegetation. *Sustainability*. 2020;12(18):7434. doi:10.3390/su12187434

132. Yu H, Hu LW, Zhou Y, et al. Association between eye-level greenness and lung function in urban Chinese children. *Environ Res*. 2021;202:111641. doi:10.1016/j.envres.2021.111641

133. Orstad SL, Szuhany K, Tamura K, Thorpe LE, Jay M. Park Proximity and Use for Physical Activity among Urban Residents: Associations with Mental Health. *Int J Environ Res Public Health*. 2020;17(13):4885. doi:10.3390/ijerph17134885

134. Cardinali M, Beenackers MA, van Timmeren A, Pottgiesser U. The relation between proximity to and characteristics of green spaces to physical activity and health: A multi-dimensional sensitivity analysis in four European cities. *Environ Res*. 2024;241:117605. doi:10.1016/j.envres.2023.117605

135. Pasanen TP, White MP, Elliott LR, et al. Urban green space and mental health among people living alone: The mediating roles of relational and collective restoration in an 18-country sample. *Environ Res*. 2023;232:116324. doi:10.1016/j.envres.2023.116324

136. Ross N, Wasfi R, Herrmann T, Gleckner W. Canadian Active Living Environments Database (Can-ALE) User Manual. Published online 2018.

137. Mah SM, Sanmartin C, Riva M, Dasgupta K, Ross NA. Active living environments, physical activity and premature cardiometabolic mortality in Canada: a nationwide cohort study. *BMJ Open*. 2020;10(11):e035942. doi:10.1136/bmjopen-2019-035942

Chapter 3. Data Sources and Cohort Overview

3.1 Study design

This thesis will consist of two retrospective cohort studies that will aim to answer each of the two thesis objectives. The study will include full-term live births that took place in Ontario, Canada between April 2002, and December 2020. Through analysis of secondary data from population-based health administrative databases and external environmental exposure data over almost 20 years, this thesis will be able to thoroughly assess the impacts of $PM_{2.5}$ mass concentration, composition, and greenspace exposures on CP outcomes in this population.

3.2 Data sources

The data sources involved in creation of the cohort for this thesis were accessed through ICES, formerly known as the Institute of Clinical and Evaluative Sciences (ICES), a non-profit research institute that stores and maintains an extensive repository of demographic and health-related data on the Ontarian population.[1] ICES provides patient-level data that is coded with unique identifiers. These unique identifiers, which are also known as ICES Key Numbers (IKN), are assigned to all eligible individuals in Ontario who have provincial health insurance, allowing for linkage of individual-level data across various data sources.[2] This data linkage then provides researchers with the ability to study associations between outcomes, exposures, and other influential factors.

In addition to ICES administrative data, project specific data (PSD) for air pollution, greenspace, and ALE exposure measures were brought into the ICES environment for linkage with the cohort. These measures came from external data sources, which will be described in sections 3.2.10 and 13.2.11.

Overall, the following sections will offer an overview of the specific data sources to better understand the study population and the cohort used for this thesis.

3.2.1 MOMBABY

The MOMBABY database, sourced from the Canadian Institute of Health Information Discharge Abstract Database (CIHI-DAD), is a comprehensive repository that holds vital information on hospital admissions and discharges for delivering mothers and their newborns.[3] Using this maternal-infant IKN linked database, the baseline of the study cohort was created. Variables such as GA, maternal age, birthweight, and parity were also obtained from this database for analysis.

3.2.2 ICES Registered Persons Database (RPDB)

The ICES Registered Persons Database (RPDB) encompasses demographic information for all Ontario residents with a provincial health card.[4] This repository includes crucial information such as age, gender, address, IKNs, and notably annual 6-digit postal codes for each individual. Utilizing the RPDB, the sex of the baby, and regions of residence were linked with environmental exposures. The inclusion of annual 6-digit postal codes in the RPDB not only facilitates the linkage of regions of residence with environmental exposures but also enables a temporal understanding of individuals' geographic contexts over time. For this thesis, the centroid of the 6-digit postal codes were used to assign environmental exposures to the cohort. This temporal dimension allows for tracking changes in residents' environmental exposures, considering potential shifts in residential locations and associated variations in environmental factors, as residential locations are updated every year on July 1st.

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

The CIHI-DAD serves as a comprehensive repository of hospital discharge information in Canada, offering a wealth of data on patients' diagnoses, procedures, and demographic details.[5] Through the use of standard diagnostic ICD-10-CA codes (the Canadian implementation of the International Classification of Diseases, 10th Revision) and procedural or interventional CCI codes (Canadian Classification of Health Interventions),[6] a broad spectrum of medical conditions and procedures can be recorded in this database. This allowed for identification and extraction of CP diagnoses from the database, facilitating a thorough examination of CP cases for the purpose of outcome ascertainment in this thesis. The specific diagnosis code utilized for CP in this thesis is ICD-10 code G80, ensuring a standardized approach to data extraction and analysis.

3.2.4 Ontario Health Insurance Plan (OHIP) claims database

The Ontario Health Insurance Plan (OHIP) Database serves as a comprehensive repository compiling healthcare billing data submitted by physicians and healthcare providers for service reimbursement, thereby offering a detailed account of medical encounters.[7] Within this repository, crucial information includes diagnoses, indicating the reasons for patient visits, types of services rendered, and the associated billing codes. For this thesis, OHIP fee code 343 was used to obtain CP diagnoses for outcome ascertainment. This multifaceted approach of utilizing the OHIP and CIHI-DAD database helps to enhance the depth and specificity of our analyses.

3.2.5 National Ambulatory Care Reporting System (NACRS)

The National Ambulatory Care Reporting System (NACRS) is another administrative database which provides a comprehensive repository of data on ambulatory care services. It was developed by CIHI, and contains information from various outpatient care settings, including hospital-based clinics and community health centers.[8] For this thesis, NACRS data was used to

obtain diagnoses of CP, as medical visits and diagnostic procedures are recorded in this database. The same ICD-10 code from the CIHI-DAD was used to identify the CP diagnoses. These records were then linked to the cohort using IKNs.

3.2.6 CENSUS

The CENSUS database is sourced from Statistics Canada and records information every five years for geographical variables such as postal codes and rural/urban residential status.[9] For this thesis, information for only 2006 was included to maintain consistency in the variables over the study period and was linked to the study cohort through their 6-digit postal code at birth.

3.2.7 Better Outcomes Registry and Network (BORN)

The Better Outcomes Registry and Network, also known as the BORN information system, is another administrative database that houses information on maternal, perinatal, and fetal health outcomes for the Ontarian population.[10] One notable strength of this registry is that it captures approximately >99% of all births in the province of Ontario, including hospital births, as well as midwifery-attended home and birth-centre births.[10] Using this database, we were able to obtain covariate information pertaining to maternal health from the years April 2006 to December 2020. Variables such as maternal smoking status and maternal body mass index (BMI) were obtained and linked to the study population using IKNs.

3.2.8 Ontario Marginalization Index (ON-Marg)

The Ontario Marginalization Index (ON-Marg) database is sourced from Statistics Canada census data and contains key indicators of four distinct dimensions of marginalization (household/dwellings, material resources, age/labour force, and racialized/newcomer populations).[11] These variables are available as quintiles. For this thesis, information on SES

variables were extracted and linked to the cohort using IKNs. This integration of ON-Marg data enhanced the depth of our research, providing a more holistic understanding of the complex interplay between marginalization and health within the context of this thesis.

3.2.9 Maternal chronic disorder data

3.2.9.1 Ontario Diabetes Database (ODD)

As mentioned earlier, pre-existing maternal health disorders such as diabetes can affect the risk of certain health outcomes, thus the Ontario Diabetes Database (ODD) was used to extract information on maternal diabetes diagnosis for use in the analysis. ODD is an ICES-derived cohort database that houses confirmed diabetes diagnoses of Ontario residents, validated through administrative healthcare databases maintained by ICES.[12] Individuals are included in the database if they had either one hospitalization record or two physician billing claims indicating a diabetes diagnosis within a two-year period.

3.2.9.2 Ontario Hypertension dataset

The Ontario Hypertension dataset (HYPER) is an additional cohort derived from ICES, serving as a repository for capturing information related to maternal disorder status, particularly hypertension. In this dataset, the utilization of administrative claims data ensures the precise and reliable recording of hypertension diagnoses.[13] Using the HYPER dataset contributes to a comprehensive understanding of the prevalence and impact of hypertension within maternal populations on CP outcomes.

These maternal disorders were identified prior to conception, meaning the individuals had the condition before becoming pregnant. This distinction is important because it helps to clarify that the disorders were not a result of pregnancy, but rather pre-existing conditions that could

influence pregnancy outcomes. By identifying these disorders beforehand, this thesis can better isolate the potential impact of these conditions on CP outcome, ensuring that any associations observed are not confounded by the onset of these conditions during gestation.

3.2.10 Ambient Air Pollution Exposure Data

3.2.10.1 $PM_{2.5}$ mass and composition data

North American bi-weekly estimates of $PM_{2.5}$ mass and it's composition, which includes SO_4, NH_4, NO_3, OM, BC, SS, and dust, at 1×1 km resolution were obtained and evaluated for exposure level from Health Canada (version V5.NA.04.02).[14,15] Retrieval of the $PM_{2.5}$ mass and composition data was done by van Donkelaar et al., through a vast number of techniques, including satellite retrievals, chemical transport models and ground monitors.[16] Bi-weekly and annual total $PM_{2.5}$ mass concentrations and its components across North America from 2000 to 2020 were generated from satellite observations of aerosol optical depth (AOD) obtained from multiple instruments (MODIS, MISR, SeaWiFS) and algorithms (Dark Target, Deep Blue, MAIAC).[14,16] To establish a relationship between satellite AOD observations and ground-level $PM_{2.5}$ concentrations, a high-performance GEOS-Chem chemical transport model (GCHP) in a stretched grid format specifically over Canada was employed.[17,18] Statistical integration of ground-based observations from the United States' Environmental Protection Agency's Air Quality System (AQS) and Environment Canada's National Air Pollution Surveillance (NAPS) program further refined the estimates, considering both total $PM_{2.5}$ mass concentrations and individual component contributions.[14,16]

This bi-weekly data for Ontario was brought into the ICES environment as PSD and was assigned to the study population using the 6-digit postal code and the mother's residence recorded at time of delivery.

3.2.10.2 NO_2 data

Measures of weekly NO_2 exposure levels were obtained from Health Canada and transferred to ICES as PSD. These measures were obtained using an advanced spatiotemporal interpolation technique.[19] A long-term average of NO_2 measures for the year 2020 was obtained from Health Canada using a nationwide land-use regression (LUR) model at the postal code level. The nationwide LUR model incorporated data from the NAPS network, satellite-derived estimates from 2020, road lengths within 10 km, area of industrial land use within 2 km, and the mean summer rainfall.[20–22] This LUR model was then combined with a weekly scaling surface, which was calculated from scaling factors of weekly average measures of NO_2 obtained from the NAPS monitoring network and satellite data.[19,23]

The calculation for obtaining the scaling surface is shown in equation 1. Overall, the scaling factor was generated by calculating a ratio of weekly mean NO_2 concentrations from NAPS monitors in Ontario to annual values for year 2020 LUR model estimates at the locations of each monitor.

Equation 1. Scaling factor calculation

$$SF_{iw} = \frac{C_{im}}{LUR_{2020}(x_i)} \qquad (1)$$

In equation 1, SF_{iw} is the scaling factor for the monitor i and week w, C_{iw} is the weekly mean monitor concentration, and $LUR_{2020}(x_i)$ is the year 2020 LUR model estimate at the specific monitor location i. The scaling surface for each week was then created for the entire time period

by applying an inverse distance weighting (IDW) spatial interpolation using the postal code locations that were within 25 km of a NAPS station for the scaling factors. These weekly scaling surfaces were then multiplied to the yearly LUR estimates to obtain weekly NO_2 estimates per gestational week. The calculation for obtaining the final weekly pollutant measure is shown in equation 2.

Equation 2. Weekly NO_2 estimate calculation

$$LUR(x)_w = LUR(x)_{2020} \times SS(x)_w \quad (2)$$

In equation 2, $LUR(x)_w$ represents the LUR model estimate for the week at point *x*. $LUR(x)_{2020}$ is the year 2020 LUR model estimate at point *x*, and $SS(x)_w$ is the scaling surface value for week *w* at point *x*, which was interpolated from the scaling factor (SF_{iw}).[19,24]

These weekly NO_2 estimates were available for the period between January 1, 1995, and December 31, 2020 and were linked to the cohort using 6-digit postal code and date.

3.2.10.3 O_3 data

Weekly measures of O_3 were obtained in a similar manner, using the average of annual LUR measures from the Canadian Urban Environmental Health Research Consortium (CANUE) data from 2002 to 2015. Using 21 km grid values, these measures were obtained from the average daily maximum O_3 concentrations during May 1st to October 31st, which are also considered the warm seasons.[22] Similar to NO_2, spatiotemporal interpolation was performed using data from monitors in the NAPS network to obtain weekly estimates. This was also done by calculating a scaling factor using equation 1, and then multiplying by the LUR value for each postal code, using equation 2.[19,25]

Overall, weekly O_3 estimates were available for the period between January 1, 1995, and December 31, 2020 and were linked to the cohort by postal code and date.

3.2.11 Greenspace Exposure Data

3.2.11.1 Normalized Difference Vegetation Index (NDVI)

The Normalized Difference Vegetation Index, also known as NDVI, is a very common greenspace measure used in environmental studies. NDVI is a numerical indicator used in remote sensing to assess and quantify the health and abundance of vegetation.[26] It is derived from the contrast between the reflectance of near-infrared and red light wavelengths in satellite imagery.[27] NDVI values range from -1 to 1, with higher NDVI values indicating healthier and denser vegetation, and lower values suggesting less vegetation or non-vegetated surfaces.[28]

For this thesis, NDVI values were obtained from CANUE using annual Landsat 5 and 8 data, with a spatial resolution of 30 metres. The annual average NDVI values within a 250-metre radius of each residential postal code was used for each year.[29] The linkage of NDVI values to the study population was done through the 6-digit postal codes and dates.

3.2.11.2 Green View Index (GVI)

The Green View Index, also known as GVI, is another numerical measure that quantifies the proportion of visible greenery within a specific environment or landscape.[30] The GVI was calculated by measuring the amount of green vegetation visible in a particular area using street-level imagery or photographs from Google Street View (GSV).[31] This involved analyzing the proportion of green pixels within the defined field of view, which was then converted into a numerical index representing the degree of greenery for each coordinate.[30] GVI values range from 0 to 100, with increasing values for higher proportions of green pixels identified.

For this thesis, GVI data was obtained from CANUE as an average long-term value for each postal code. This was one measurement that was taken between 2010 and 2017, at a spatial resolution of 30m x 30m averaged across postal code boundaries. This data was then transferred to ICES as PSD and linked to the cohort using postal codes.

3.2.12 Active Living Environment Exposure data

3.2.12.1 Park Proximity

In this thesis, park proximity measures were used as a proxy for ALEs. Park proximity measures identify how close a specific area, such as a neighbourhood or dissemination block, is to the nearest park. Essentially, it measures the closeness of greenspaces, such as parks, for individuals in the area. This is an important measure because living closer to a park may encourage its use, which may influence physical activity and overall well-being.[32]

For this thesis, park proximity measures were obtained from CANUE. These were available as normalized values for one long term measurement taken in 2019, at spatial resolutions of 1 km circular buffers around a centroid of a dissemination area. This measure was obtained by CANUE from a collection of authoritative open data sources and OpenStreetMap. The data was transferred to ICES as PSD and assigned to the cohort using postal codes at time of birth.

3.2.12.2 Canadian Active Living Environments (Can-ALE)

The Canadian Active Living Environments (Can-ALE) index is a tool used to assess the quality of the physical environment in relation to active living and health in communities. It takes into account various aspects of urban and rural settings, including connectiveness of street patterns, the presence of sidewalks and bike paths, public transport use, and overall walkability.[33] These are

all factors that can determine the level of health and active living in a community. The Can-ALE index is presented as quintiles, ranging from 1 (very low) to 5 (very high).

The Can-ALE index data was obtained from CANUE. These measures were available from the census year 2016, as 1 km circular buffers around a centroid of a dissemination area. Similar to the other external datasets used in this thesis, the Can-ALE quintile data was transferred to ICES as PSD and linked to the cohort based on postal code at time of birth.

Overall, using multiple metrics when analyzing greenspace exposures provides a broader exposure framework and helps maintains data consistency.[34,35]

3.3 Privacy and Ethical considerations

Ethics approval for the use of air pollution and greenspace data was obtained through the Health Canada Research Ethics Board. In addition, the project was reviewed and approved by an ICES privacy officer.

3.4 Cohort Overview

Since the same source cohort was utilized for both manuscripts in this thesis, this section will focus on a brief overview and description of the cohort. Firstly, the source cohort for this thesis included all registered births from Ontario, Canada from April 1st, 2002 to December 31st, 2020. April 1st 2002 was chosen as the start date, as it was the earliest date at which GA was available in the MOMBABY database. Similarly, December 31st, 2020 was chosen as the end date, as the exposure data for air pollution was available until that date.

Once the base cohort (2 484 025 mother-infant pairs) was selected from the administrative data, the following exclusion criteria were applied, in this respective order, to obtain our source cohort:

1. Mother or child have an invalid identification number/ IKN
    - An invalid identification number, or IKN, prevents the linkage of vital information such as outcomes, covariates, and exposures. As such, 7 764 (0.31%) mother-infant pairs were removed at this step.
2. Part of a multiple birth
    - Multiple births are births in which more than one offspring is produced, such as twins, triplets, or more. In the literature, multiple births have been found to differ in certain health outcomes such as GA and birthweight, when compared to singleton births.[36] Thus, to prevent challenges in the analysis, 110 939 (4.47%) multiple births were excluded at this step.
3. Invalid information on biological sex
    - Biological sex of the child was important for our studies as it can influence CP development.[37] As such, 362 (0.01%) births were removed at this step.
4. Ineligible for provincial health insurance at birth
    - Eligibility for provincial health insurance allows for the documentation of administrative data. Those who become ineligible for provincial health data, often due to a change in residential postal code following relocation, are at risk of having missing information on health outcomes and other covariates. Thus, 1 727 (0.07%) pairs were removed due to the mother not residing in Ontario or missing postal code at birth, and an additional 88 153 (3.55%) were removed for not having continuous OHIP eligibility during the study period.
5. Stillbirth delivery

- For this thesis, only live term births were considered during analysis to ensure a more homogeneous study population, reducing potential biases and confounding factors associated with non-live births. As such, 690 (0.03%) stillborn births were removed at this step.

6. Preterm birth
    - Preterm births have been found to be associated with pregnancy complications, thus they were removed from the study.[38] As such, 80 963 (3.26%) preterm births were removed at this step.

Following these exclusions, 2 193 427 mother-infant pairs were remaining in the source cohort, which was used to address the thesis objectives.

7. Missing exposure data
    - The source cohort was then linked to the exposure data, and pairs with missing exposure data were removed. No additional records were excluded for missing air pollution exposure data for study population 1, which was used in Chapter 4. And 757 016 (34.5%) additional records were removed for missing greenspace exposure data for study population 2, which was used in Chapter 5. These study populations are described in more detail in their respective chapters.

Figure 3 is a flow-diagram that visually depicts the exclusion steps that were applied to derive the source cohort.

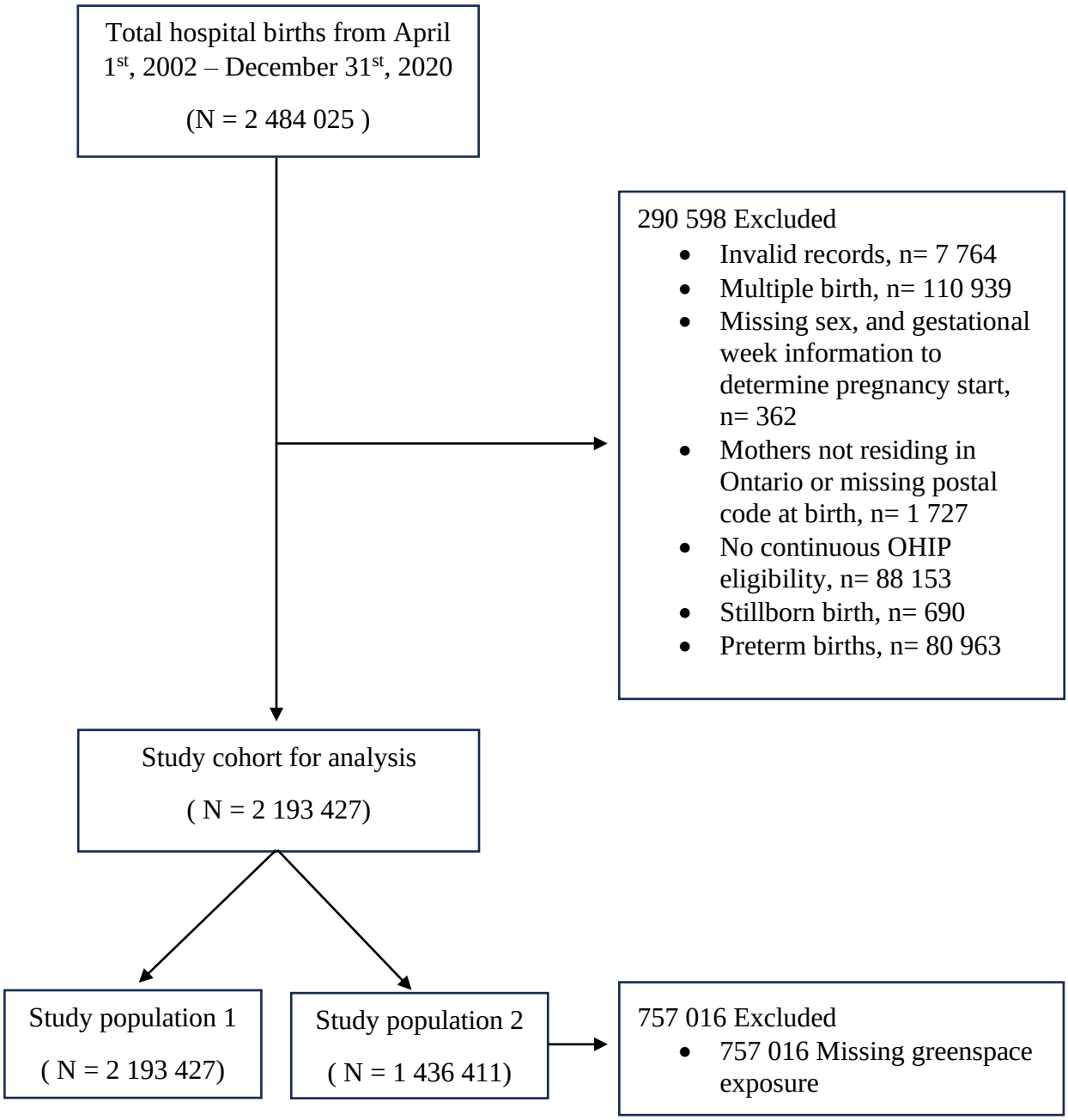


Figure 3. Flow-diagram of the inclusion and exclusion of the source cohort

Table 1 displays the baseline characteristics of the source cohort, stratified by the outcome, prior to the exclusion of missing exposures. Descriptive tables for baseline characteristics for study population 1 and 2 can be found in Chapter 4 and Chapter 5, respectively.

Table 1. Characteristics of the source cohort at birth, stratified by CP status

Characteristic		CP cases (N= 3907)	Non-CP cases (N=2 189 520)
Mom's age at delivery, mean (SD)		29.9 (5.86)	30.33 (5.39)
Gestational age in weeks, mean (SD)		38.86 (1.38)	39.09 (1.24)
Birth weight (grams)		3304.36 (582.81)	3429.23 (486.56)
Sex, n (%)			
Male		2200 (56.31%)	1120535 (51.18%)
Female		1707 (43.69%)	1068985 (48.82%)
Parity, n (%)			
0		1824 (46.69%)	949802 (43.38%)
1		1298 (33.22%)	805143 (36.77%)
>= 2		785(20.09%)	434575 (19.85%)
Maternal disorder status, n (%)			
Diabetes	**Yes**	98 (2.51%)	30048 (1.37%)
	No	3809 (97.49%)	2159472 (98.63%)
Hypertension	**Yes**	111 (2.84%)	47309 (2.16%)
	No	3796 (97.16%)	2142211 (97.84%)
Maternal smoking, n (%)			
Yes		356 (9.11%)	168820 (7.71%)
No		2274 (58.20%)	1513054 (69.10%)
Missing		1277 (32.68%)	505646 (23.19%)
Season of birth, n (%)			
Fall		986 (25.24%)	558544 (25.51%)
Spring		968 (24.78%)	548405 (25.05%)
Summer		1022 (26.16%)	585368 (26.73%)
Winter		931 (23.83%)	497203 (22.71%)
Instability quintile [a], n (%)			
1		734 (18.79%)	454033 (20.74%)
2		724 (18.53%)	405791 (18.53%)
3		685 (17.53%)	390349 (17.83%)
4		772 (19.76%)	415144 (18.96%)
5		928 (23.75%)	493308 (22.53%)
Missing		64 (1.64%)	30895 (1.41%)
Deprivation quintile [a], n (%)			
1		703 (17.99%)	437362 (19.98%)
2		666 (17.05%)	408469 (18.66%)
3		717 (18.35%)	404981 (18.5%)
4		745 (19.07%)	412253 (18.83%)
5		1012 (25.9%)	495560 (22.63%)
Missing		64 (1.64%)	30895 (1.41%)
Dependency quintile [a], n (%)			
1		1157 (29.61%)	700342 (31.99%)
2		857 (21.93%)	468146 (21.38%)
3		694 (17.76%)	378953 (17.31%)
4		623 (15.95%)	328175 (14.99%)

5	512 (13.10%)	283009 (12.93%)
Missing	64 (1.64%)	30895 (1.41%)
Ethnic concentration quintile [a], n (%)		
1	516 (13.21%)	286345 (13.08%)
2	598 (15.31%)	324242 (14.81%)
3	706 (18.07%)	364285 (16.64%)
4	802 (20.53%)	462232 (21.11%)
5	1221 (31.25%)	721521 (32.95%)
Missing	64 (1.64%)	30895 (1.41%)

Findings are presented as counts (percentages) for categorical variables or means (standard deviations) for continuous variables.

[a] These quintiles were created by sorting the marginalization data into five groups, ranked from one (least marginalized) to five (most marginalized).

Overall, table 1 shows that the source cohort for this thesis had 2 193 427 mother-infant pairs, 3902 (0.18%) of whom were diagnosed with CP after birth. The average (±standard deviation) maternal age at delivery was slightly lower for CP cases, 29.9 (5.86) compared to non-CP cases 30.33 (5.39). This was also the case for gestational week at delivery, which was 38.86 (1.38) for CP cases, and 39.09 (1.24) for non-CP cases. In addition, as found in the literature, there was a higher proportion of males who were observed to have CP, 56.31%, compared to females, 43.69%. Table 1 also shows that the numbers of both CP cases and non-cases were observed to decrease as parity increased in the source cohort. In comparison to non-CP cases, children with CP were generally slightly more likely to be born with a higher marginalized index, and there was a slight increased proportion of births occurring in summer for both CP and non-CP cases.

3.5 References

1. ICES. Data Privacy and Security. ICES. Accessed December 10, 2023. https://www.ices.on.ca/data-privacy/

2. ICES. Use ICES Data | Working With ICES Data. ICES. Accessed December 10, 2023. https://www.ices.on.ca/use-ices-data/working-with-ices-data/

3. ICES. ICES Data Dictionary for MOMBABY. Accessed December 10, 2023. https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library=MOMBABY

4. Schull MJ, Azimaee M, Marra M, et al. ICES: Data, Discovery, Better Health. *Int J Popul Data Sci*. 2019;4(2). doi:10.23889/ijpds.v4i2.1135

5. ICES. Canadian Institute for Health Information Discharge Abstract Database: A Validation Study. ICES. Accessed December 10, 2023. https://www.ices.on.ca/publications/research-reports/canadian-institute-for-health-information-discharge-abstract-database-a-validation-study/

6. CIHI. Codes and classifications for clinical health data. Accessed December 10, 2023. https://www.cihi.ca/en/submit-data-and-view-standards/codes-and-classifications

7. OHDP. OHDP - Researchers - Datasets. OHDP. Accessed December 10, 2023. https://ohdp.ca/datasets/

8. CIHI. National Ambulatory Care Reporting System (NACRS) metadata | CIHI. Accessed December 12, 2023. https://www.cihi.ca/en/national-ambulatory-care-reporting-system-nacrs-metadata

9. ICES. ICES Data Dictionary for CENSUS. Accessed December 10, 2023. https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library=CENSUS

10. Murphy MSQ, Fell DB, Sprague AE, et al. Data Resource Profile: Better Outcomes Registry & Network (BORN) Ontario. *Int J Epidemiol*. 2021;50(5):1416-1425. doi:10.1093/ije/dyab033

11. Public Health Ontario. Ontario Marginalization Index (ON-Marg). Public Health Ontario. Accessed December 10, 2023. https://www.publichealthontario.ca/en/Data-and-Analysis/Health-Equity/Ontario-Marginalization-Index

12. Lipscombe LL. ICES Report: The Growing Prevalence of Diabetes in Ontario: Are We Prepared? *Healthc Q*. 2007;10(3). Accessed December 10, 2023. https://www.longwoods.com/content/18920/healthcare-quarterly/ices-report-the-growing-prevalence-of-diabetes-in-ontario-are-we-prepared-

13. ICES. ICES Data Dictionary for HYPER. Accessed December 10, 2023. https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library=HYPER

14. van Donkelaar A, Martin RV, Li C, Burnett RT. Regional Estimates of Chemical Composition of Fine Particulate Matter Using a Combined Geoscience-Statistical Method with Information from Satellites, Models, and Monitors. *Environ Sci Technol*. 2019;53(5):2595-2611. doi:10.1021/acs.est.8b06392

15. van Donkelaar A, Hammer MS, Bindle L, et al. Monthly Global Estimates of Fine Particulate Matter and Their Uncertainty. *Environ Sci Technol*. 2021;55(22):15287-15300. doi:10.1021/acs.est.1c05309

16. van Donkelaar A, Martin RV, Brauer M, et al. Global Estimates of Fine Particulate Matter using a Combined Geophysical-Statistical Method with Information from Satellites, Models, and Monitors. *Environ Sci Technol*. 2016;50(7):3762-3772. doi:10.1021/acs.est.5b05833

17. Paciorek CJ, Liu Y, HEI Health Review Committee. Assessment and statistical modeling of the relationship between remotely sensed aerosol optical depth and PM2.5 in the eastern United States. *Res Rep Health Eff Inst*. 2012;(167):5-83; discussion 85-91.

18. van Donkelaar A, Martin RV, Brauer M, et al. Global Estimates of Ambient Fine Particulate Matter Concentrations from Satellite-Based Aerosol Optical Depth: Development and Application. *Environ Health Perspect*. 2010;118(6):847-855. doi:10.1289/ehp.0901623

19. Bechle MJ, Millet DB, Marshall JD. National Spatiotemporal Exposure Surface for NO2: Monthly Scaling of a Satellite-Derived Land-Use Regression, 2000-2010. *Environ Sci Technol*. 2015;49(20):12297-12305. doi:10.1021/acs.est.5b02882

20. Zhang Y, Hu Y, Talarico R, et al. Prenatal Exposure to Ambient Air Pollution and Cerebral Palsy. *JAMA Netw Open*. 2024;7(7):e2420717. doi:10.1001/jamanetworkopen.2024.20717

21. Hystad P, Setton E, Cervantes A, et al. Creating National Air Pollution Models for Population Exposure Assessment in Canada. *Environ Health Perspect*. 2011;119(8):1123-1129. doi:10.1289/ehp.1002976

22. Elten M, Benchimol E, Fell D, et al. Ambient air pollution and the risk of pediatric-onset inflammatory bowel disease: A population-based cohort study. *Environ Int*. 2020;138:105676. doi:10.1016/j.envint.2020.105676

23. Lavigne E, Lima I, Hatzopoulou M, et al. Spatial variations in ambient ultrafine particle concentrations and risk of congenital heart defects. *Environ Int*. 2019;130:104953. doi:10.1016/j.envint.2019.104953

24. Lavigne É, Bélair MA, Do MT, et al. Maternal exposure to ambient air pollution and risk of early childhood cancers: A population-based study in Ontario, Canada. *Environ Int*. 2017;100:139-147. doi:10.1016/j.envint.2017.01.004

25. Wang J, Cohan DS, Xu H. Spatiotemporal ozone pollution LUR models: Suitable statistical algorithms and time scales for a megacity scale. *Atmos Environ*. 2020;237:117671. doi:10.1016/j.atmosenv.2020.117671

26. CANUE. Green/Blue Space. CANUE. Accessed November 20, 2023. https://canue.ca/greenness/

27. NASA. Measuring Vegetation (NDVI & EVI). August 30, 2000. Accessed November 20, 2023. https://earthobservatory.nasa.gov/features/MeasuringVegetation/measuring_vegetation_2.php

28. GISGeography. What is NDVI (Normalized Difference Vegetation Index)? GIS Geography. May 9, 2017. Accessed December 11, 2023. https://gisgeography.com/ndvi-normalized-difference-vegetation-index/

29. Gorelick N, Hancher M, Dixon M, Ilyushchenko S, Thau D, Moore R. Google Earth Engine: Planetary-scale geospatial analysis for everyone. *Remote Sens Environ*. 2017;202:18-27. doi:10.1016/j.rse.2017.06.031

30. Puppala H, Tamvada JP, Kim B, Peddinti PRT. Enhanced green view index. *Methods X*. 2022;9. doi:10.1016/j.mex.2022.101824

31. Li X, Zhang C, Li W, Ricard R, Meng Q, Zhang W. Assessing street-level urban greenery using Google Street View and a modified green view index. *Urban For Urban Green*. 2015;14(3):675-685. doi:10.1016/j.ufug.2015.06.006

32. Kaczynski AT, Besenyi GM, Stanis SAW, et al. Are park proximity and park features related to park use and park-based physical activity among adults? Variations by multiple socio-demographic characteristics. *Int J Behav Nutr Phys Act*. 2014;11(1):146. doi:10.1186/s12966-014-0146-4

33. Ross N, Wasfi R, Herrmann T, Gleckner W. Canadian Active Living Environments Database (Can-ALE) User Manual. Published online 2018.

34. Yin P. Comparison of greenness measures in assessing the association between urban residential greenness and birth weight. *Urban For Urban Green*. 2019;46:126519. doi:10.1016/j.ufug.2019.126519

35. Labib SM, Lindley S, Huck JJ. Estimating multiple greenspace exposure types and their associations with neighbourhood premature mortality: A socioecological study. *Sci Total Environ*. 2021;789:147919. doi:10.1016/j.scitotenv.2021.147919

36. Kalikkot Thekkeveedu R, Dankhara N, Desai J, Klar AL, Patel J. Outcomes of multiple gestation births compared to singleton: analysis of multicenter KID database. *Matern Health Neonatol Perinatol*. 2021;7:15. doi:10.1186/s40748-021-00135-5

37. Park MS. Sex/Gender Differences in Cerebral Palsy. In: Kim N, ed. *Sex/Gender-Specific Medicine in Clinical Areas*. Springer Nature; 2024:337-342. doi:10.1007/978-981-97-0130-8_18

38. Vogel JP, Oladapo OT, Manu A, Gülmezoglu AM, Bahl R. New WHO recommendations to improve the outcomes of preterm birth. *Lancet Glob Health*. 2015;3(10):e589-e590. doi:10.1016/S2214-109X(15)00183-7

Ch. 4 Ambient Air Pollution and Cerebral Palsy

4.1 Preface

This chapter includes a manuscript titled "*Prenatal exposure to fine particulate matter composition and risk of cerebral palsy: A population-based retrospective cohort study in Ontario, Canada*", which will be formatted for submission to the journal Environmental Pollution. This manuscript addresses objective 1 of this thesis, which aims to investigate the associations between gestational exposure to ambient air pollution and the risk of CP. Ethics approval for this study was granted by the Research Ethics Boards of Health Canada. The authors declare they have no competing interests.

4.2 List of authors and contributions

Amrin Ahmed[1,2], Steven Hawken[2,3], Anna Gunz[4,5], Robert Talarico[6], Chengchun Yu[6], Carmen Messerlian[7,8,9], Yu Zhang[7], Hong Chen[1,6,10], Scott Weichenthal[11], Aaron van Donkelaar[12], Randall V. Martin[12], Éric Lavigne[1,2]

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

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

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

[4] Children's Health Research Institute, London, Ontario, Canada

[5] Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

[6] ICES uOttawa, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

[7] Department of Environmental Health, Harvard T.H. Chan School of Public Heath, Boston, Massachusetts, United States of America

[8] Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, United States of America

[9] Massachusetts General Hospital Fertility Center, Department of Obstetrics and Gynecology, Boston, Massachusetts, United States of America

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

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

[12] Department of Energy, Environmental, and Chemical Engineering McKelvey School of Engineering, St. Louis, Missouri, United States of America

Amrin Ahmed: Conceptualization, Writing- Original draft preparation, Methodology, Formal analysis; Writing- Reviewing and Editing; Steven Hawken: Writing- Reviewing and

Editing; Anna Gunz: Writing- Reviewing and Editing; Robert Talarico: Data preparation, Writing- Reviewing and Editing; Chengchun Yu: Formal analysis, Data preparation, Writing- Reviewing and Editing; Carmen Messerlian: Writing- Reviewing and Editing; Yu Zhang: Writing- Reviewing and Editing; Hong Chen: Writing- Reviewing and Editing; Scott Weichenthal: Writing- Reviewing and Editing; Aaron van Donkelaar: Methodology, Data preparation, Writing- Reviewing and Editing; Randall Martin: Methodology, Data preparation, Writing- Reviewing and Editing; Éric Lavigne: Conceptualization, Methodology, Formal analysis; Writing- Reviewing and Editing.

4.3 Abstract

Background: Existing literature suggests an association between prenatal exposure to fine particulate air pollution ($PM_{2.5}$) and cerebral palsy (CP). However, the impact of individual $PM_{2.5}$ components (SO_4, NH_4, NO_3, SS, BC, dust, OM) on CP risk remains unknown.

Objective: To examine the associations between prenatal exposure to $PM_{2.5}$ components, and risk of CP among term births in Ontario, Canada.

Methods: This was a retrospective cohort study that examined term births (gestational age ≥ 37 completed weeks) from April 2002 to December 2020. $PM_{2.5}$ total mass and composition measures were assigned to maternal residence at birth using satellite-based estimates and ground-level monitoring data. Cohort data were compiled using health administrative databases. Single-pollutant distributed lag cox proportional hazard models, with and without additional adjustment for $PM_{2.5}$ residuals, were used to investigate the associations between gestational exposures to $PM_{2.5}$ total mass, its components, NO_2, and O_3.

Results: 2,193,427 mother-infant pairs were identified, of which 3,907 were diagnosed with CP during the follow-up period. Increased risk of CP was found for SO_4 exposure during early pregnancy in both residual-adjusted (HR: 1.052, 95% CI: 1.009-1.097, per IQR=0.94 ug/m^3), and non-adjusted models (HR: 1.050, 95% CI: 1.007- 1.095, per IQR=0.94 ug/m^3). The concentration-response relationship between the sensitive window found for SO_4 and CP risk (weeks 4 to 9 of gestation) showcased a supralinear pattern, with HRs increasing steeply at lower concentrations before plateauing at higher levels.

Conclusions: Prenatal exposure to SO_4 may be associated with increased CP risk during the early pregnancy period. Associations between prenatal $PM_{2.5}$ total mass and composition exposure and CP risk should be further investigated.

Keywords: $PM_{2.5}$ components, prenatal exposure, cerebral palsy

Abbreviations: ammonium, NH_4^+; black carbon, BC; confidence interval, CI; cerebral palsy, CP; hazard ratio, HR; mineral dust, dust; nitrate, NO_3^-; nitrogen dioxide, NO_2; organic matter, OM; ozone, O_3; particulate matter with a mean aerodynamic diameter less than 2.5 micrometres, $PM_{2.5}$; sea salt, SS; sulfate, SO_4;

4.4 Introduction

Cerebral palsy (CP) stands as the most frequently diagnosed physical disability during childhood.[1] It encompasses a group of diverse neurodevelopmental disorders characterized by non-progressive manifestations that present with a range of clinical features, primarily affecting motor function. The diverse clinical features of CP can include muscle spasticity, involuntary movements, and difficulties in coordination, all of which substantially impact the quality of life of those affected.[2] With an incidence rate between approximately 2 and 3 out of every 1,000 live births, the etiology of CP remains unclear due to the complex nature of the disease.[3] Nonetheless, due to its early diagnosis, it is recognized that prenatal factors play a substantial role in CP risk, highlighting the potential for prevention through the identification and comprehension of these risk factors.

In recent years, maternal exposure to environmental factors has been proven to potentially influence neurological conditions. Ambient air pollution, which has diverse sources including vehicle emissions, industrial processes, and natural elements, is a leading environmental risk factor for global burden of disease.[4,5] Notably, emerging evidence suggests that prenatal exposure to fine particulate matter with a diameter less than 2.5 μm ($PM_{2.5}$) may have a profound impact on the development of CP and other neurological disorders.[6,7] These disorders include stroke, dementia, Alzheimer's disease, autism spectrum disorder (ASD), and Parkinson's disease.[8] Additionally, exposure to $PM_{2.5}$ during pregnancy has been associated with various reproductive outcomes, such as low birth weight and preterm birth, which are risk factors for CP.[9] One recent and novel study found prenatal residential $PM_{2.5}$ exposure to be associated with a 1.12-fold increase in the risk of CP per increasing interquartile range (IQR).[10] Suspected mechanisms by which $PM_{2.5}$ is thought to cause these health outcomes is through epigenetic alterations, pro-inflammatory pathway

activations, and the induction of oxidative stress.[11–13] Along with $PM_{2.5}$, prenatal exposure to nitrogen dioxide (NO_2) and ozone (O_3) have also been associated with similar birth outcomes, especially in women with pre-existing maternal comorbidities such as diabetes and preeclampsia during the gestational period.[14] However, while the association between $PM_{2.5}$ and CP risk have been studied, there still exists a gap in knowledge regarding the specific $PM_{2.5}$ components associated with cerebral palsy. The various major components of $PM_{2.5}$ include sulfate (SO_4); ammonium (NH_4); nitrate (NO_3); sea salt (SS); black carbon (BC); mineral dust (dust); and organic matter (OM).[15] Individually, these pollutants have been found to have harmful effects on human health, including increased mortalilty,[16] thus, investigating these components is important because they have distinct chemical properties, origins, and health effects, which may enable more targeted efforts to address specific pollution sources.

To address these gaps, we conducted a population-based retrospective cohort study to investigate the relationships between maternal exposures to components of $PM_{2.5}$, NO_2, and O_3 and the risk of developing CP among live term births. We utilized population-based health administrative data from the province of Ontario, Canada, spanning the years 2002 to 2020. In addition, critical periods of exposure were investigated and the associated effects at different weeks of pregnancy were estimated. By identifying specific $PM_{2.5}$ components and critical windows of weekly exposure during gestation that are associated with increased CP risk, this study could help support public health efforts to reduce the burden of CP by informing targeted preventive measures and regulations to decrease exposure to ambient air pollutants.

4.5 Methods

Study population and data sources

This was a retrospective cohort study comprised of all live term births (gestational age ≥ 37 completed weeks) that occurred in hospitals in Ontario, Canada between April 1st, 2002 and December 31st, 2020. We conducted our analysis using administrative health data from ICES, which is a non-profit research institute that compiles and analyzes healthcare and demographic data for over 99% of Ontario's population.[17]

Maternal demographic and health data were linked to mother-infant pairs using the Registered Persons Database (RPDB), which includes demographic information on those registered for health insurance, and the MOMBABY cohort, an ICES-derived dataset that links hospital admission records of mothers and their newborns for all hospital births in the province, based on Discharge Abstract Database from the Canadian Institute for Health Information (CIHI-DAD) information. Additional variables such as maternal smoking and body mass index were available from 2006-2020 from the Better Outcomes Registry and Network (BORN). The Ontario Diabetes Database (ODD) and the Ontario Hypertension Dataset (HYPER) were also used to obtain information on maternal chronic disorders. The Ontario Marginalization Index (ON-Marg) was used to obtain area-level socioeconomic status variables. Outcome ascertainment utilized the National Ambulatory Care Reporting System (NACRS), Discharge Abstract Database from the Canadian Institute for Health Information (CIHI-DAD) and the Ontario Health Insurance Plan (OHIP) Records Database, which contains health services billing data from all physicians in Ontario.

The study excluded mother-infant pairs involving multiple births, preterm births, invalid health card numbers, missing postal codes for exposure assessment, and those lacking essential covariates and exposures. Additionally, individuals ineligible for provincial health insurance

(OHIP) at birth were excluded (Supplementary Figure S1). These datasets were linked using unique encoded identifiers and analyzed at ICES.

Exposure assessment

Exposure to the ambient air pollutants in the population was assigned using the geographic centre of each 6-digit postal code area for maternal residence at delivery. Weekly and bi-weekly average concentrations of the exposures were available from the date of conception until the end of the 36^{th} week of gestation for each pregnancy using the recorded gestational age in the MOMBABY dataset from 2002 to 2020. Due to the early diagnosis of CP (within the first 2 years of life) and literature highlighting the probability of disease development during the prenatal period, exposures were only assigned during the prenatal period and not throughout childhood.[3]

North American bi-weekly total and component (SO_4, NH_4, NO_3, SS, BC, dust, OM) $PM_{2.5}$ mass concentrations at 1×1 km resolution, version V5.NA.04.02, were derived by combining satellite retrievals of aerosol optical depth (AOD) with simulated output from the GEOS-Chem chemical transport model, and ground-based measurements. Utilized satellite instrumentation included the NASA VIIRS, MODIS, MISR, and SeaWiFS instruments with the Dark Target, Deep Blue, MAIAC, and MISR AOD retrieval algorithms. Simulated output was used to provide an additional AOD dataset, relate AOD to total $PM_{2.5}$ concentrations, and provide an initial compositional breakdown of total $PM_{2.5}$. Total and component $PM_{2.5}$ concentrations were refined by statistically incorporating ground-based observations from the United States EPA Air Quality System and the Canadian National Air Pollution Surveillance (NAPS) network using a geographically weighted regression.[18,19]

Weekly NO_2 concentration levels were measured using a national land-use regression (LUR) model incorporating data from the NAPS network, satellite-derived estimates from 2020,

road lengths within 10 km, area of industrial land use within 2 km, and the mean summer rainfall.[6,20,21] Weekly O_3 concentration measurements followed a similar approach, using 21 km grid values which were estimated from the average daily maximum O_3 concentrations during the warm seasons (May 1st to October 31st). Since these were annual concentration estimates, LUR data from the Canadian Urban Environmental Health Research Consortium (CANUE) from the years 2002 to 2015 and spatiotemporal interpolation techniques based on NAPS monitor data was used to obtain the concentration measures at the weekly level.[21]

Outcome ascertainment

The outcome for this study is defined as a diagnosis of CP before the age of 18 years old. This was characterized using a case algorithm, which included a single inpatient hospitalization diagnosis using the ICD-10-CA code G80 from CIHI-DAD, or two or more outpatient diagnoses, with a minimum two-week interval, documented in physician billing claims with the modified ICD-9 code 343 from OHIP.[22]

Covariates

Our analysis incorporated several key covariates to account for potential confounding factors. These covariates included maternal age, parity, infant sex, birth weight, socioeconomic variables (residential instability, quintile groups of maternal deprivation, dependency, and ethnic concentration), geographic location (rural/urban), season of birth and year of birth. Maternal comorbidities, such as diabetes and hypertension, were also included as covariates in the models, as they have been found to be associated with other neurodevelopmental disorders.[23,24] Overall, these covariates were chosen based on existing literature,[25–27] and a directed acyclic graph was conceptualized (Supplementary Figure S2).

Statistical Analyses

In this study, cox proportional hazards models were used to investigate the associations between exposure to ambient air pollutants during the gestational period and CP risk. The follow-up time was measured in days from birth, until their first diagnosis of CP, death, loss of eligibility for provincial health insurance, their 18th birthday, or the conclusion of the follow-up period (December, 2020), similar to a previous study.[6]

Single-pollutant models were examined with and without additional adjustment for the residuals from linear models that regressed total outdoor $PM_{2.5}$ concentrations on the concentrations of each component. This approach captured the variation in $PM_{2.5}$ not explained by its components and was preferable to multi-pollutant models (ie. including total $PM_{2.5}$ mass and its components in the same model), which faced multi-collinearity issues and the risk of over-adjusting for the same components.[28] Hazard ratios (HRs) for the $PM_{2.5}$ residuals were also examined per IQR increase. Models including NO_2 and O_3 individually, and with additional adjustment for total outdoor $PM_{2.5}$ were also assessed.

The single-pollutant models were fitted with an extension of the distributed lag non-linear model (DLNM) to also simultaneously investigate each of the first 37 weeks of exposure during pregnancy to assess specific windows of susceptibility.[29] The DLNM incorporated average concentrations of $PM_{2.5}$, SO_4, NH_4, NO_3, OM, BC, SS, dust, NO_2, and O_3 throughout gestational weeks 0-36 as separate cross-bases, assuming a smooth function. This smooth function was modelled using natural splines.[30,31] The degrees of freedom for the natural spline was selected based on the lowest Akaike Information Criterion (AIC).[32] Based on the AIC, the linear model provided the best fit for $PM_{2.5}$, NH_4, OM, BC, SS, dust, NO_2, and O_3, while a model with 3 degrees of freedom provided best fit for SO_4 and NO_3. From the models, a sensitive window was identified when the 95% confidence interval (CI) did not contain unity.

We conducted several additional and sensitivity analyses. Due to the identification of sex-differences for CP in previous studies, models were stratified by infant sex and further assessed for effect modification by including an air pollutant × sex interaction term in the stratified models.[33] Effect modification by rural/urban place of residence was also assessed. Effect measure modification was considered present if the Wald chi-square p-value was <0.05.

Additional analyses were done by further adjusting the models for maternal smoking, a risk factor for CP development.[34] The cohort adjusted for maternal smoking was limited to infants born after 2006, as data was unavailable before this time frame. Associations in full term births (≥39 weeks of gestation) was also explored, as previous literature has found risk differences for CP in children born at 37 weeks compared to 40 weeks.[35] Finally, due to the potential variation in outcomes based on follow-up length, we further explored associations by limiting maximum follow-up time to 6 years of age.

Data management steps and descriptive statistics were completed in SAS EG version 7.1 (SAS Institute). All other statistical analyses were conducted using R (version 3.1.2), and the dlnm package (version 2.1.3) was employed for the DLNMs.

4.6 Results

Descriptive statistics

A total of 2,193,427 mother-infant pairs were identified between April 1st 2002 and December 31st 2020 in the province of Ontario, Canada (Table 1). In this cohort, 3,907 children were diagnosed with CP during the follow-up period. The mean (±SD) maternal age at delivery was 30.33 years (±5.39) for the entire cohort. The mean (±SD) gestational age at birth was 39.09 weeks (±1.24) across the cohort, with children with CP being born slightly earlier on average

(38.86 ±1.38). Among children with CP, a higher proportion were male (56.31%) compared to female (43.69%).

The mean (±SD) concentration of $PM_{2.5}$ during the prenatal period was 7.42 μg/m³ (± 2.84), with higher average levels among mothers of children with CP (7.87 μg/m³, ± 2.98). Mean NO_2 and O_3 concentrations were 5.66 ppb (± 2.91) and 46.50 ppb (± 9.26) respectively. Mean prenatal concentrations for the components of $PM_{2.5}$ (SO_4, NH_4, NO_3, SS, BC, dust, OM) are described in Supplementary Table S1. Strong correlations were found between prenatal total mass concentrations of $PM_{2.5}$ and mass concentration of NH_4 (r = 0.89), SO_4 (r = 0.83), and OM (r = 0.79). Strong correlations were also found between $PM_{2.5}$ components such as NO_3 and NH_4 (r = 0.75), OM and SO_4 (r = 0.71), and NH_4 and SO_4 (r = 0.70). The correlations between $PM_{2.5}$ and NO_2 (r = 0.12) and O_3 (r = 0.03) were weak, similar to the correlation between NO_2 and O_3 averaged across gestation (r = 0.02) (Supplementary Table S2).

Associations between CP and prenatal ambient air pollution concentrations

Figure 1 visually summarizes the overall estimated HRs and 95% CIs from the models for $PM_{2.5}$ and each component, with and without additional adjustment for $PM_{2.5}$ residuals. Overall, HRs for the components showed minimal change after additional adjustment for $PM_{2.5}$ residuals in the models. $PM_{2.5}$ components, including $PM_{2.5}$ itself, did not exhibit statistically significant associations with CP in both residual adjusted and non-adjusted models when assessing overall gestational risk.

The $PM_{2.5}$ residual variations accounting for SO_4 and NH_4 showed significant associations with increased risk (HR_{SO4}: 1.045, 95% CI: 1.001-1.091, per IQR=0.94 ug/m^3 increase; HR_{NH4}: 1.110, 95% CI: 1.030-1.186, per IQR=0.5 ug/m^3). However, significant associations were not found for both SO_4 and NH_4 when further adjusting for these residual variations in the single-

pollutant models, though HRs were elevated compared to other pollutants (HR_{SO4}: 1.059, 95% CI: 0.990- 1.133, per IQR=0.94 ug/m^3 increase; HR_{NH4}: 1.031, 95% CI: 0.989- 1.076, per IQR=0.5 ug/m^3) (Supplementary Table S3). Interestingly, OM demonstrated a similar pattern, with a significant protective effect when accounting for its $PM_{2.5}$ residual variation (HR: 0.929, 95% CI: 0.892- 0.967, per IQR=1.39 ug/m^3 increase), but demonstrating a non-significant effect when further adjusting for this residual variation in the single-pollutant model (HR: 0.919, 95% CI: 0.835-1.011, per IQR=1.39 ug/m^3 increase) (Supplementary Table S3).

Sensitive windows during gestation were consistently identified for SO_4 across both models, indicating that it may play a key role in driving CP risk during critical periods of fetal development. Figure 2 illustrates the estimated HRs for SO_4 as a function of gestational week after adjusting for covariates in the single-pollutant and residual-adjusted model. The overall residual-adjusted model for SO_4 had a slighter higher risk (HR: 1.059, 95% CI: 0.990- 1.133, per IQR=0.94 ug/m^3 increase) compared to the non residual-adjusted model (HR: 1.055, 95% CI: 0.987-1.129, per IQR=0.94 ug/m^3 increase), though both overall HRs were non-significant. While overall HRs for the two models differed slightly, both models presented a sensitive window between weeks 4-9 that showed a significant increased risk for CP ($HR_{non\text{-}adjusted}$: 1.05, 95% CI: 1.007-1.095, per IQR=0.94 ug/m^3 increase; $HR_{adjusted}$: 1.052, 95% CI: 1.009-1.097, per IQR=0.94 ug/m^3 increase), as shown by CIs above unity. Furthermore, the concentration-response curve for SO_4 during the sensitive window (weeks 4-9) in both models showed a supralinear pattern, with a sharp increase in risk at lower concentrations, followed by a steady rise as concentrations continued to increase (Figure 3).

Additional models adjusting for NO_2 and O_3 did not significantly alter the associations observed with $PM_{2.5}$. Overall, the findings from the main analyses suggest that certain components

of $PM_{2.5}$, such as SO_4, especially during critical periods of gestation, may be more relevant to CP risk than $PM_{2.5}$ mass concentration alone.

Additional and sensitivity analyses

Following stratification by infant sex, sensitive windows of exposure were identified among boys for SO_4 (HR: 1.061, 95% CI: 1.009-1.115, per IQR=0.94 ug/m^3 increase, P=0.08) and dust (HR: 1.069, 95% CI: 1.007-1.136, per IQR=0.3 ug/m^3 increase, P=0.004) between gestational weeks 4 to 8, and 23 to 36, respectively. Among girls, OM exposure during gestational weeks 20 to 22 indicated a significant association (HR: 0.986, 95% CI: 0.972-1, per IQR=1.39 ug/m^3 increase, P=0.70). Only the p-value for dust exposure in boys during the sensitive window was found to be significant for effect modification (Supplementary Table S4). Similar results were found in the residual-adjusted models for overall risk of CP and each pollutant (Supplementary Table S5). When assessing the effect modification by rural/urban residence of birth, no significant p-values were observed between the interaction and pollutant terms suggesting that the observed associations might be influenced by other factors, though a sensitive window was observed for dust exposure during weeks 22 to 36 in rural residents (HR: 1.191, 95% CI: 1.023-1.385, per IQR=0.3 ug/m^3 increase, p-value=0.76) (Supplementary Table S6). Interestingly, significant associations were found for overall SO_4 when further adjusting for residuals (HR: 1.077, 95% CI: 1.004-1.154, per IQR=0.94 ug/m^3 increase), in the urban population (Supplementary Table S7).

When further adjusting for maternal smoking (Supplementary Tables S8 and Supplementary Table S9), SO_4 indicated increased risk of CP in single-pollutant ($HR_{week\ 4\text{-}7}$: 1.046, 95% CI: 1.005-1.089, per IQR= 0.49 ug/m^3 increase) and residual-adjusted models ($HR_{overall}$: 1.099, 95% CI: 1.003-1.203, per IQR= 0.49 ug/m^3 increase), with significant associations in both. Additionally, OM was associated with a reduced risk of CP in both models. Sensitivity analyses

that only included full term births (≥39 weeks of gestation) found protective associations for BC (HR: 0.983, 95% CI: 0.968-0.998, per IQR=0.49 ug/m^3 increase), and OM (HR: 0.871, 95% CI: 0.771-0.984, per IQR=1.39 ug/m^3 increase) during the mid-pregnancy periods in the single-pollutant models (Supplementary Table S10). Similar results were found in the residual-adjusted models (Supplementary Table S11). Notable significant positive associations were not found in the sensitivity analyses that limited follow-up to 6 years of age, in both single-pollutant and residual-adjusted models (Supplementary Table S12 and Supplementary Table S13).

4.7 Discussion

In this large retrospective cohort study, we observed a consistent association between prenatal exposure to SO_4 during the pregnancy period and increased CP risk across all models and additional analyses. Increased associations for CP risk were found for mineral dust exposure in boys and rural residents, however overall adverse effects for dust were inconsistent across models. The findings from our study did not confirm results from a previous study that found significant positive associations between $PM_{2.5}$ total mass exposure and CP risk, however similar results for NO_2 and O_3 exposure having null association with CP risk were found.[6]

Prenatal exposure to SO_4 has been linked to an increased risk of undergrowth in fetal abdominal circumference, head circumference, femur length, and estimated fetal weight.[36] Fetal growth restriction and undergrowth during the early-pregnancy period (trimester 1) has been shown to increase the risk of neurodevelopmental disorders, including CP, due to the reduction in placental perfusion as a result of a decrease in villous cross-sectional vascular area, limiting neurodevelopmental potential.[37,38] SO_4 concentrations are mainly attributed to the burning of fossil fuels, which can result from coal burning, industrial processes, and vehicular emissions.[39] In recent

years, the burning of fossil fuels has been associated with adverse health effects in children, such as lowered birth weight, deficits in lung function, respiratory symptoms, and developmental disorders.[40,41] In addition, coal burning has shown to be a major contributor to ambient $PM_{2.5}$ and studies have found it to be linked to neurobehavioral problems, such as social problems and anxiety.[41]

In the GEOS-Chem model used for obtaining the air pollution measures, dust concentrations were found to be primarily arising from long-range transport from the United States (US). Thus, while our analyses found an increased risk of CP for dust exposure in some stratified populations, it may not be attributed to likely sources of mineral dust such as road dust and forest fires,[42] but instead serves as a tracer of long-range transport of aged pollution from the US. Nonetheless, dust exposure has been linked to various negative health outcomes, such as respiratory issues, cardiovascular problems, and exacerbation of asthma and other chronic lung diseases.[43,44] The fine particulate nature allows for penetration into the respiratory system, causing inflammation and oxidative stress, which can lead to long-term health complications.[45–47]

The potential link between prenatal exposure to these air pollutants and the risk of CP can be explained through several underlying biological mechanisms. One key mechanism involves the impairment of placental function. As mentioned earlier, reduction in placental blood flow can lead to insufficient oxygen and nutrient delivery to the developing fetus, resulting in fetal growth restriction and underdevelopment of critical organs, including the brain.[48] Additionally, air pollutants, such as SO_4 and dust, can induce oxidative stress and inflammation in both the mother and the fetus.[49] Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them, which can damage cellular structures, including DNA, proteins, and lipids, leading to cellular dysfunction and death.[50] In the

context of fetal development, oxidative stress can disrupt the delicate processes of neurogenesis, synaptogenesis, and myelination, which are essential for proper brain development.[51–53] Maternal exposure to pollutants can also activate inflammatory pathways, leading to the release of pro-inflammatory cytokines.[54] These cytokines can cross the placenta and enter the fetal circulation, causing inflammation in fetal tissues, including the developing brain.[55,56] Chronic inflammation during critical periods of brain development can impair neural connectivity and function, increasing the risk of neurodevelopmental disorders such as CP.[57–59]

While the findings of OM providing protective effects are not consistent with the literature, which generally reports adverse health effects associated with particulate matter,[60,61] several factors could explain this discrepancy. One possible explanation is potential increased exposure misclassification present for OM. This misclassification might arise from the variability in sources and composition of OM, making it difficult to accurately measure and characterize its true impact. Additionally, OM from natural sources, such as biogenic emissions, might have different health implications compared to OM from anthropogenic sources. Variations in the chemical composition of OM can lead to differing biological effects, with some organic compounds potentially having less harmful or even protective properties. Further research is needed to better understand these complex interactions and the specific components of OM that may contribute to its protective effects.

This study has several significant strengths that enhance its contributions to understanding the association between prenatal air pollution exposure and CP. First, the large cohort size of over 2 million mother-infant pairs provides robust statistical power and allows for precise estimation of risk associations, ensuring that the findings are generalizable across a broader population. Furthermore, the extended study period of nearly two decades (2002-2020) captures a wide range

of exposure scenarios and temporal variations in air pollution levels, which strengthens the temporal validity of the results. In addition, the use of sophisticated analysis techniques, such as distributed lag models allowed us to estimate effects at the weekly level, which helped identify specific critical windows of exposure during pregnancy. The use of $PM_{2.5}$ residual-adjusted models and sensitivity analyses further validates the robustness of the associations observed.

Limitations in the study could include uncertainties related to the representation of air pollution, which, although comprehensive, may not accurately reflect individual-level exposure due to spatial and temporal variability in air pollution levels, or other sources of uncertainty associated with the satellite retrievals, models, and measurements upon which it is constructed. Additionally, while the study adjusts for numerous confounders, there remains the potential for misclassification bias in the diagnosis of CP, as it relies on administrative health data which may vary in accuracy. The exposure assessment is based on maternal residential address at birth, which does not account for potential changes in residence during pregnancy, leading to possible exposure misclassification. Furthermore, the generalizability of the findings may be limited to populations with similar environmental and sociodemographic characteristics as Ontario, Canada, potentially limiting the applicability of the results to other regions with different pollution profiles and health care systems. Another limitation is the inability to account for all possible interactions between different pollutants, as the focus on individual pollutants may overlook the complex mixture effects of multiple air pollutants. Lastly, due to a lack of data, we were unable to account for some individual level factors such as race/ethnicity, BMI, and lifestyle factors, which may be determinants of CP risk.

In this study, prenatal exposure to SO_4 was found to be notably associated with an increased risk of CP. These findings highlight the need to further research in the area of CP and ambient air

pollution, to better support implementation of targeted public health interventions and policy change.

4.8 Acknowledgements

Parts of this material are based on data and/or information compiled and provided by CIHI and the Ontario Ministry of Health. The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. This study is based in part on data provided by Better Outcomes Registry and Network ("BORN"), part of the Children's Hospital of Eastern Ontario. The interpretation and conclusions contained herein do not necessarily represent those of BORN Ontario. This document used data adapted from the Statistics Canada Postal Code^OM Conversion File, which is based on data licensed from Canada Post Corporation, and/or data adapted from the Ontario Ministry of Health Postal Code Conversion File, which contains data copied under license from ©Canada Post Corporation and Statistics Canada. We thank the Toronto Community Health Profiles Partnership for providing access to the Ontario Marginalization Index.

This study was supported by a research grant from Health Canada. RVM acknowledges support from NASA Grant 80NSSC21K0508.

4.9 Tables and figures

Table 1. Characteristics of term births with and without a CP diagnosis born in Ontario, Canada, between 2002-2020.

Characteristics		Without CP (N= 2189520)	With CP (N= 3907)	Total (N= 2193427)
Individual-level characteristics				
Maternal age at delivery, mean (SD)		30.33 (5.39)	29.90 (5.86)	30.33 (5.39)
Maternal pre-pregnancy BMI, n (%)				
< 18.5 (underweight)		47238 (2.16%)	65 (1.66%)	47303 (2.16%)
18.5 – 24.9 (healthy weight)		478906 (21.87%)	553 (14.15%)	479459 (21.86%)
25.0 – 29.9 (overweight)		234021 (10.69%)	281 (7.19%)	234302 (10.68%)
≥ 30.0 (obesity)		191060 (8.73%)	287 (7.35%)	191347 (8.72%)
Missing		1238295 (56.55%)	2721 (69.65%)	1241016 (56.58%)
Maternal pre-existing health condition, n (%)				
Pre-pregnancy diabetes	Yes	30048 (1.37%)	98 (2.51%)	30146 (1.37%)
	No	2159472 (98.63%)	3809 (97.49%)	2163281 (98.63%)
Pre-pregnancy hypertension	Yes	47309 (2.16%)	111 (2.84%)	47420 (2.16)
	No	2142211 (97.84%)	3796 (97.16%)	2146007 (97.84%)
Maternal smoking during pregnancy, n (%)				
Yes		168820 (7.71%)	356 (9.11%)	169176 (7.71%)
No		1513054 (69.10%)	2274 (58.20%)	1515328 (69.08%)
Unknown		507646 (23.19%)	1277 (32.68%)	508923 (23.21%)
Follow-up year after birth, mean (SD)		8.94 (5.16)	10.79 (4.51)	8.95 (5.16)
Infant sex, n (%)				
Male		1120535 (51.18%)	2200 (56.31%)	1122735 (51.19%)
Female		1068985 (48.82%)	1707 (43.69%)	1070692 (48.81%)
Gestational age in weeks, mean (SD)		39.09 (1.24)	38.86 (1.38)	39.09 (1.24)
Birth weight (grams) (SD)		3429.23 (486.56)	3304.36 (582.81)	3429.00 (486.77)
Parity, n (%)				
0		949802 (43.48%)	1824 (46.69%)	951626 (43.39%)
1		805143 (36.77%)	1298 (33.22%)	806441 (36.77%)
≥ 2		434575 (19.85%)	785 (20.09)	435360 (19.85%)
Season of birth, n (%)				
Spring		548405 (25.05%)	968 (24.78%)	549373 (25.05%)
Summer		595368 (26.69%)	1022 (26.16%)	586390 (26.73%)
Fall		558544 (25.51%)	986 (25.24%)	559530 (25.51%)
Winter		497203 (22.71%)	931 (23.83%)	498134 (22.71%)
Neighbourhood-level characteristics				
Residence at birth				
Urban		1963567 (89.68%)	3479 (89.05%)	1967046 (89.68%)
Rural		224525 (10.25%)	426 (10.9%)	224951 (10.26%)
Unknown		1428 (0.07%)	2 (0.05%)	1430 (0.07%)

Instability quintile[a], n (%)			
Quintile 1	454033 (20.74%)	734 (18.79%)	454767 (20.73%)
Quintile 2	405791 (18.53%)	724 (18.53%)	406515 (18.53%)
Quintile 3	390349 (17.83%)	685 (17.53%)	391034 (17.83%)
Quintile 4	415144 (18.96%)	772 (19.76%)	415916 (18.96%)
Quintile 5	493308 (22.53%)	928 (23.75%)	494236 (22.53%)
Unknown	30895 (1.41%)	64 (1.64%)	30959 (1.41%)
Deprivation quintile[a], n (%)			
Quintile 1	437362 (19.98%)	703 (17.99%)	438065 (19.97%)
Quintile 2	408469 (18.66%)	666 (17.05%)	409135 (18.65%)
Quintile 3	404981 (18.50%)	717 (18.35%)	405698 (18.50%)
Quintile 4	412253 (18.83%)	745 (19.07%)	412998 (18.83%)
Quintile 5	495560 (22.63%)	1012 (25.90%)	496572 (22.64%)
Unknown	30895 (1.41%)	64 (1.64%)	30959 (1.41%)
Dependency quintile[a], n (%)			
Quintile 1	700342 (31.99%)	1157 (29.61%)	701499 (31.98%)
Quintile 2	468146 (21.38%)	857 (21.93%)	469003 (21.38%)
Quintile 3	378953 (17.31%)	694 (17.76%)	379647 (17.31%)
Quintile 4	328175 (14.99%)	623 (15.95%)	328798 (14.99%)
Quintile 5	283009 (12.93%)	512 (13.10%)	283521 (12.93%)
Unknown	30895 (1.41%)	64 (1.64%)	30959 (1.41%)
Ethnic concentration quintile[a], n (%)			
Quintile 1	286345 (13.08%)	516 (13.21%)	286861 (13.08%)
Quintile 2	324242 (14.81%)	598 (15.31%)	324840 (14.81%)
Quintile 3	364285 (16.64%)	706 (18.07%)	364991 (16.64%)
Quintile 4	462232 (21.11%)	802 (20.53%)	463034 (21.11%)
Quintile 5	721521 (32.95%)	1221 (31.25%)	722742 (32.95%)
Unknown	30895 (1.41%)	64 (1.64%)	30959 (1.41%)
Averaged levels during pregnancy			
$PM_{2,5}$, $\mu g/m^3$, mean (SD)	7.42 (2.84)	7.87 (2.98)	7.42 (2.84)
NO_2, ppb, mean (SD)	5.66 (2.91)	5.62 (2.88)	5.66 (2.91)
O_3, ppb, mean (SD)	46.50 (9.26)	47.33 (8.81)	46.50 (9.26)

Abbrev. CP, cerebral palsy; $PM_{2.5}$, fine particulate matter with a diameter ≤ 2.5 μm; NO_2, nitrogen dioxide; O_3, ozone; SD, standard deviation.

[a] These quintiles have been created by sorting the marginalization data into five groups, ranked from one (least marginalized) to five (most marginalized).

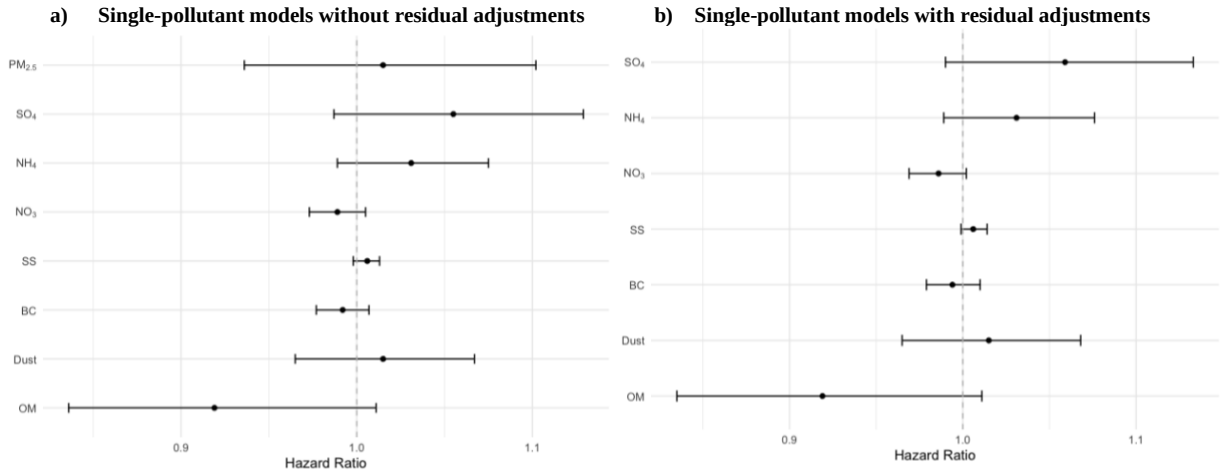


Figure 1. Weekly associated hazard ratios (HRs) and 95% confidence intervals (CIs) describing the association between prenatal outdoor $PM_{2.5}$ mass concentrations and CP per interquartile range increase in a) single-pollutant models without residual adjustments, and b) single-pollutant models with residual adjustments. All models were adjusted for maternal age at delivery (continuous), infant sex (binary), urban/rural (binary), seasons of birth (categorical), calendar years of birth (categorical), parity (categorical), maternal comorbidities (binary), residential instability (categorical), and quintile groups of maternal deprivation (categorical), dependency (categorical), and ethnic concentration (categorical).

Note: CP, cerebral palsy; IQR, interquartile range; $PM_{2.5}$, fine particulate matter with a diameter ≤ 2.5 μm; SO_4, sulphate; NH_4, ammonium, NO_3, nitrate; SS, sea salt; BC, black carbon, OM, organic matter; NO_2, nitrogen dioxide; O_3, ozone;

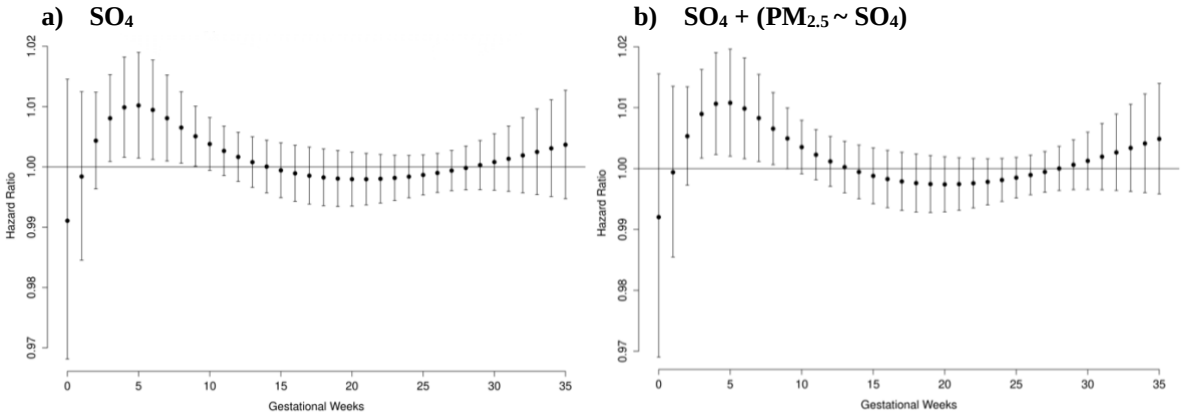


Figure 2. Weekly associated hazard ratios (HRs) for CP per interquartile range increase in prenatal exposure to a) SO_4 and b)SO_4 with additional adjustment for residual $PM_{2.5}$. All models were adjusted for maternal age at delivery (continuous), infant sex (binary), urban/rural (binary), seasons of birth (categorical), calendar years of birth (categorical), parity (categorical), maternal comorbidities (binary), residential instability (categorical), and quintile groups of maternal deprivation (categorical), dependency (categorical), and ethnic concentration (categorical).

Note: $PM_{2.5}$, fine particulate matter with a diameter ≤ 2.5 μm; SO_4, sulphate;

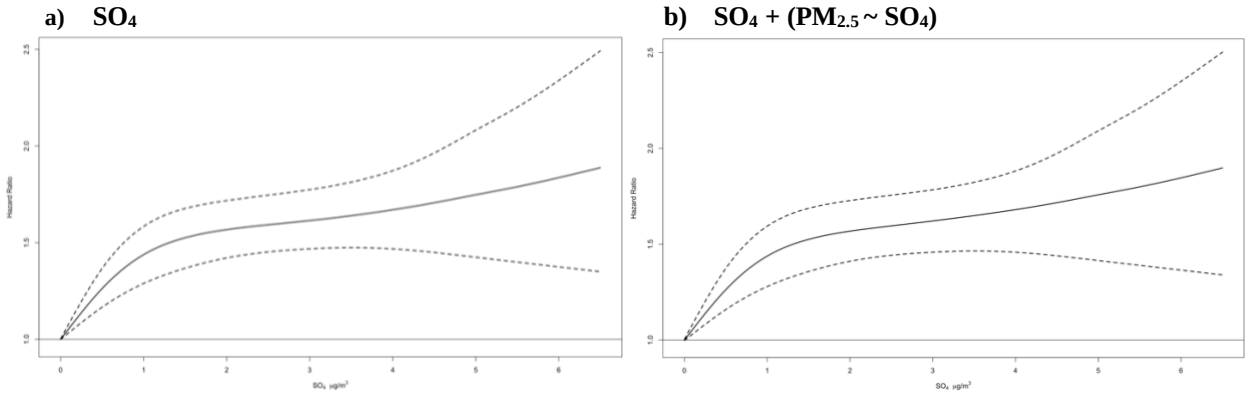
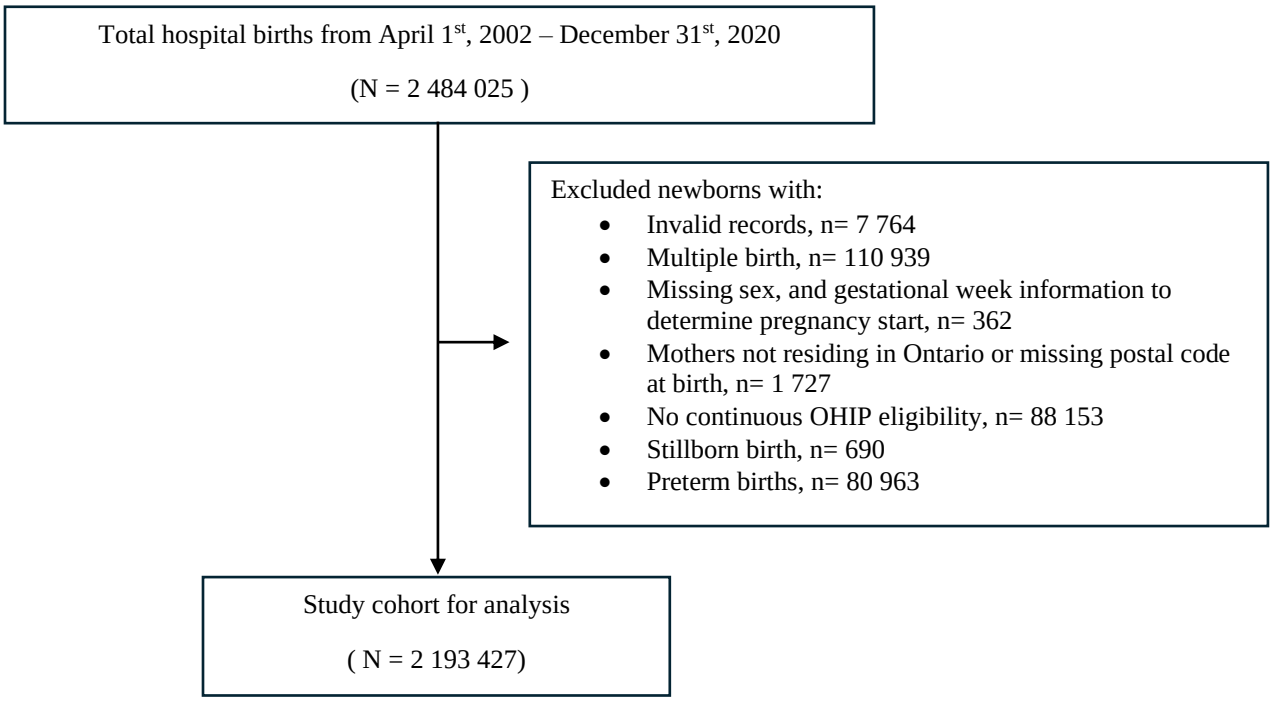


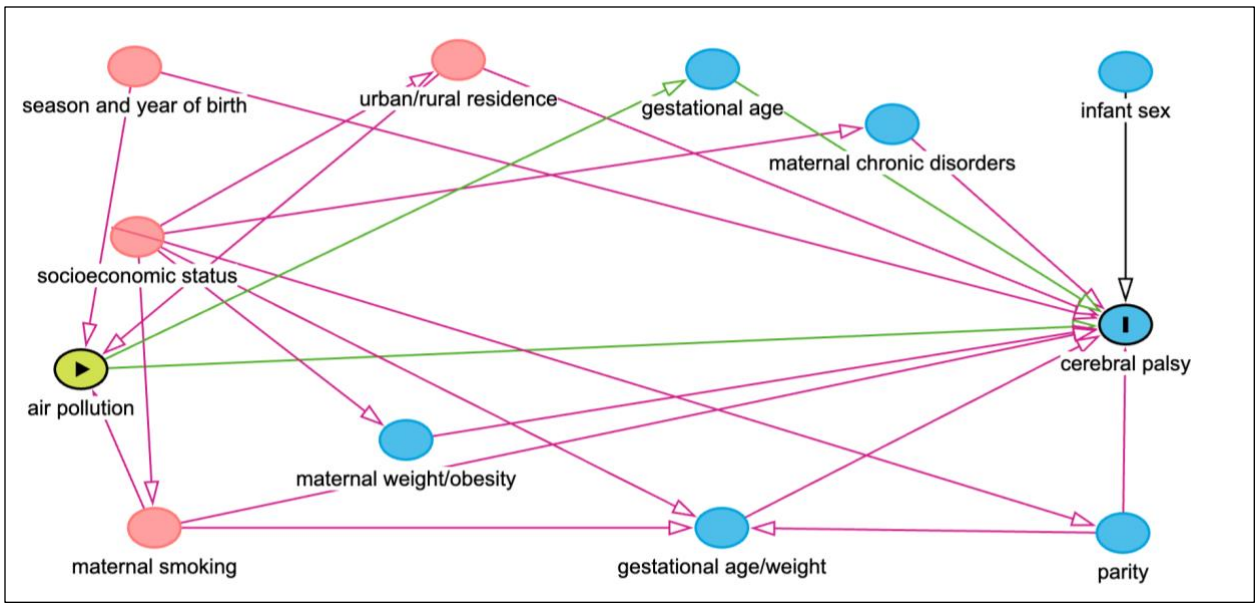
Figure 3. Concentration-response function for the association between SO_4 during the sensitive window (weeks 4 to 9 of gestation) and the risk of CP a) without $PM_{2.5}$ residual adjustment, and b) with $PM_{2.5}$ residual adjustment. Models were adjusted for maternal age at delivery (continuous), infant sex (binary), urban/rural (binary), seasons of birth (categorical), calendar years of birth (categorical), parity (categorical), maternal comorbidities (binary), residential instability (categorical), and quintile groups of maternal deprivation (categorical), dependency (categorical), and ethnic concentration (categorical). Dashed lines indicate 95% confidence intervals.

Note: $PM_{2.5}$, fine particulate matter with a diameter ≤ 2.5 μm; SO_4, sulphate;

4.10 Supplementary materials



Supplementary Figure S1. Flowchart of the inclusion and exclusion of the study population.



Supplementary Figure S2. Directed acyclic graph (DAG) for estimating the effect of ambient air pollution on CP in children. (1) Nodes: parameters in red are potential confounding factors, and parameters in blue are ancestors of the outcome only (i.e., cause of the outcome but not of the exposure). (2) Edges (arrows): causal relationships. (3) Exposure (focal predictor): ambient air pollution ($PM_{2.5}$, its components (SO_4, NH_4, NO_3, SS, BC, dust, OM), NO_2, and O_3). (4) Response (health outcome): CP in children.

Supplementary Table S1. Average prenatal concentrations of ambient $PM_{2.5}$, its components (SO_4, NH_4, NO_3, SS, BC, dust, OM), NO_2, and O_3 across pregnancy and per trimester by CP status.

Pollutant	Non-CP cases Mean ± SD	CP cases Mean ± SD	Total Mean ± SD
$PM_{2.5}$ (ug/m^3)	7.42 ± 1.81	7.88 ± 1.84	7.42 ± 1.81
1st trimester	7.45 ± 2.08	7.91 ± 2.16	7.45 ± 2.08
2nd trimester	7.41 ± 2.03	7.89 ± 2.07	7.41 ± 2.03
3rd trimester	7.41 ± 2.05	7.86 ± 2.11	7.41 ± 2.05
SO_4 (ug/m^3)	0.59 ± 0.23	0.64 ± 0.24	0.59 ± 0.23
1st trimester	1.79 ± 0.49	1.94 ± 0.50	1.79 ± 0.49
2nd trimester	1.79 ± 0.64	1.94 ± 0.68	1.79 ± 0.64
3rd trimester	1.78 ± 0.62	1.93 ± 0.65	1.78 ± 0.62
NH_4 (ug/m^3)	0.79 ± 0.27	0.86 ± 0.28	0.79 ± 0.27
1st trimester	0.80 ± 0.31	0.87 ± 0.32	0.80 ± 0.31
2nd trimester	0.79 ± 0.31	0.87 ± 0.31	0.79 ± 0.31
3rd trimester	0.78 ± 0.31	0.85 ± 0.32	0.78 ± 0.31
NO_3 (ug/m^3)	1.01 ± 0.44	1.08 ± 0.46	1.01 ± 0.44
1st trimester	1.03 ± 0.72	1.10 ± 0.74	1.03 ± 0.72
2nd trimester	1.03 ± 0.71	1.09 ± 0.71	1.03 ± 0.71
3rd trimester	0.98 ± 0.70	1.05 ± 0.71	0.98 ± 0.70
SS (ug/m^3)	0.09 ± 0.04	0.10 ± 0.04	0.09 ± 0.04
1st trimester	0.09 ± 0.06	0.10 ± 0.06	0.09 ± 0.06
2nd trimester	0.09 ± 0.06	0.10 ± 0.06	0.09 ± 0.06
3rd trimester	0.09 ± 0.06	0.10 ± 0.06	0.09 ± 0.06
BC (ug/m^3)	0.59 ± 0.23	0.64 ± 0.24	0.59 ± 0.23
1st trimester	0.59 ± 0.26	0.64 ± 0.28	0.59 ± 0.26
2nd trimester	0.59 ± 0.26	0.64 ± 0.27	0.59 ± 0.26
3rd trimester	0.59 ± 0.26	0.64 ± 0.27	0.59 ± 0.26
dust (ug/m^3)	0.46 ± 0.12	0.48 ± 0.12	0.46 ± 0.12
1st trimester	0.46 ± 0.16	0.48 ± 0.16	0.46 ± 0.16
2nd trimester	0.46 ± 0.15	0.48 ± 0.16	0.46 ± 0.15
3rd trimester	0.46 ± 0.15	0.48 ± 0.16	0.46 ± 0.15
OM (ug/m^3)	2.69 ± 0.50	2.79 ± 0.50	2.69 ± 0.50
1st trimester	2.68 ± 0.78	2.79 ± 0.80	2.68 ± 0.78
2nd trimester	2.67 ± 0.75	2.78 ± 0.76	2.67 ± 0.75
3rd trimester	2.71 ± 0.75	2.80 ± 0.77	2.71 ± 0.75
NO_2 (ppb)	5.66 ± 2.91	5.62 ± 2.88	5.66 ± 2.91
1st trimester	5.68 ± 3.44	5.66 ± 3.44	5.68 ± 3.44
2nd trimester	5.71 ± 3.39	5.65 ± 3.38	5.71 ± 3.39
3rd trimester	5.61 ± 3.36	5.57 ± 3.31	5.61 ± 3.36

O_3 (ppb)	46.50 ± 9.26	47.33 ± 8.81	46.50 ± 9.26
1st trimester	45.97 ± 11.78	46.93 ± 11.73	45.98 ± 11.78
2nd trimester	46.68 ± 11.83	47.51 ± 11.57	46.68 ± 11.83
3rd trimester	46.74 ± 11.75	47.48 ± 11.49	46.74 ± 11.75

Abbrev. $PM_{2.5}$, fine particulate matter with a diameter ≤ 2.5 μm; SO_4, sulphate; NH_4, ammonium, NO_3, nitrate; SS, sea salt; BC, black carbon, OM, organic matter; NO_2, nitrogen dioxide; O_3, ozone; CP, cerebral palsy.

Supplementary Table S2. Pearson correlation coefficients between the average prenatal concentrations of $PM_{2.5}$ its components (SO_4, NH_4, NO_3, SS, BC, dust, OM), NO_2, and O_3.

Air pollutants	$PM_{2·5}$	SO_4	NH_4	NO_3	SS	BC	dust	OM	NO_2	O_3
$PM_{2·5}$	1.00									
SO_4	0.83	1.00								
NH_4	0.89	0.70	1.00							
NO_3	0.57	0.16	0.75	1.00						
SS	0.36	0.08	0.46	0.62	1.00					
BC	0.71	0.53	0.50	0.23	0.22	1.00				
dust	0.67	0.61	0.51	0.17	0.16	0.51	1.00			
OM	0.79	0.71	0.48	0.07	0.00	0.65	0.57	1.00		
NO_2	0.12	-0.07	0.23	0.40	0.33	0.02	-0.01	-0.12	1.00	
O_3	0.03	0.09	0.10	0.04	0.01	-0.09	0.05	-0.05	0.02	1.00

Abbrev. $PM_{2.5}$, fine particulate matter with a diameter ≤ 2.5 μm; SO_4, sulphate; NH_4, ammonium, NO_3, nitrate; SS, sea salt; BC, black carbon, OM, organic matter; NO_2, nitrogen dioxide; O_3, ozone; CP, cerebral palsy.

Supplementary Table S3. Hazard ratios (95% confidence intervals) describing the association between prenatal outdoor $PM_{2.5}$ mass and component concentrations with CP in single-pollutant models, $PM_{2.5}$ residual-adjusted models, $PM_{2.5}$ residual variation models, and additional models for the entire pregnancy and DLM-identified sensitive windows.

Outdoor $PM_{2.5}$ mass and component models	HR (95% CI)
Single-pollutant models	
$PM_{2.5}$	1.015 (0.936-1.102)
SO_4	1.055 (0.987-1.129)
Sensitive window	1.050 (1.007-1.095)[a]
NH_4	1.031 (0.989-1.075)
NO_3	0.989 (0.973-1.005)
SS	1.006 (0.998-1.013)
BC	0.992 (0.977-1.007)
dust	1.015 (0.965-1.067)
OM	0.919 (0.836-1.011)
$PM_{2.5}$ residual-adjusted models	
SO_4	1.059 (0.990- 1.133)
Sensitive window	1.052 (1.009- 1.097)[b]
NH_4	1.031 (0.989- 1.076)
NO_3	0.986 (0.969- 1.002)
SS	1.006 (0.999- 1.014)
BC	0.994 (0.979- 1.010)
dust	1.015 (0.965- 1.068)
OM	0.919 (0.835- 1.011)
$PM_{2.5}$ residual variation models	
$PM_{2.5} \sim SO_4$	1.045 (1.001- 1.091)
$PM_{2.5} \sim NH_4$	1.110 (1.030- 1.186)
$PM_{2.5} \sim NO_3$	1.030 (0.991- 1.074)
$PM_{2.5} \sim SS$	0.976 (0.949- 1.004)
$PM_{2.5} \sim BC$	0.969 (0.939-1.000)
$PM_{2.5} \sim$ dust	1.003 (0.964- 1.001)
$PM_{2.5} \sim OM$	0.929 (0.892- 0.967)
Additional models	
Single-pollutant models	
NO_2	1.000 (1.000-1.000)
O_3	1.026 (0.966-1.089)
Multi-pollutant models	
$PM_{2.5} + NO_2 + O_3$	1.007 (0.927-1.094)
$PM_{2.5} + NO_2$	1.016 (0.936-1.103)
$PM_{2.5} + O_3$	1.006 (0.926-1.092)

Note: All hazard ratios are scaled by the interquartile range of each pollutant: $PM_{2.5}$ (3.5 ug/m^3), SO_4 (0.94 ug/m^3), NH_4 (0.5 ug/m^3), NO_3 (1.2 ug/m^3), SS (0.1 ug/m^3), BC (0.49 ug/m^3), dust (0.3 ug/m^3), OM (1.39 ug/m^3), NO_2 (5.26 ppb), and O_3 (19.94 ppb). All the models were adjusted for maternal age at delivery, rurality, seasons of birth, birth year, birth weight, parity, maternal comorbidities, infant sex, residential instability, quintile groups of maternal deprivation, dependency, and ethnic concentration. Abbrev. CP, cerebral palsy; IQR, interquartile range; $PM_{2.5}$, fine particulate matter with a diameter $\leq$ 2.5 μm; SO_4, sulphate; NH_4, ammonium, NO_3, nitrate; SS, sea salt; BC, black carbon, OM, organic matter; NO_2, nitrogen dioxide; O_3, ozone;

[a] HR for the DLM-identified sensitive windows 4–9 wk of gestation.
[b] HR for the DLM-identified sensitive windows 4–9 wk of gestation.

Supplementary Table S4. Hazard ratios (95% confidence intervals) associated with $PM_{2.5}$ and its components (SO_4, NH_4, NO_3, SS, BC, dust, OM), with risk of CP stratified by infant sex for the entire pregnancy and DLM-identified sensitive windows from single-pollutant models.

Exposure	Boys		Girls		P-value[a]
	Cohort size (cases)	HR (95% CI)	Cohort size (cases)	HR (95% CI)	
$PM_{2.5}$	1 122 735 (2 200)	1.038 (0.931-1.155)	1 070 692 (1 707)	0.994 (0.874-1.13)	0.69
SO_4		1.066 (0.975-1.166)		1.056 (0.951-1.173)	0.80
Sensitive window		1.061 (1.009-1.115)[b]		—	0.08
NH_4		1.044 (0.987-1.103)		1.02 (0.956-1.088)	0.67
NO_3		0.989 (0.967-1.01)		0.988 (0.964-1.014)	0.75
SS		1.006 (0.995-1.016)		1.006 (0.994-1.017)	0.75
BC		0.993 (0.972-1.014)		0.989 (0.966-1.013)	0.75
DUST		1.045 (0.978-1.117)		0.987 (0.911-1.07)	0.67
Sensitive window		1.069 (1.007-1.136)[c]		—	0.004
OM		0.964 (0.852-1.091)		0.867 (0.744-1.01)	0.73
Sensitive window		—		0.986 (0.972-1)[d]	0.70

Note: All hazard ratios are scaled by the interquartile range of each pollutant: $PM_{2.5}$ (3.5 ug/m^3), SO_4 (0.94 ug/m^3), NH_4 (0.5 ug/m^3), NO_3 (1.2 ug/m^3), SS (0.1 ug/m^3), BC (0.49 ug/m^3), dust (0.3 ug/m^3), and OM (1.39 ug/m^3). All the models were adjusted for maternal age at delivery, rurality, seasons of birth, birth year, birth weight, parity, maternal comorbidities, residential instability, quintile groups of maternal deprivation, dependency, and ethnic concentration. Abbrev. CP, cerebral palsy; —, not applicable; $PM_{2.5}$, fine particulate matter with a diameter ≤ 2.5 μm; SO_4, sulphate; NH_4, ammonium, NO_3, nitrate; SS, sea salt; BC, black carbon, OM, organic matter;

[a] P-values correspond to the multiplicative air pollutant×sex interaction term using air pollution level averaged over the DLM-identified sensitive window.
[b] HR for the DLM-identified sensitive windows 4–8 wk of gestation for boys.
[c] HR for the DLM-identified sensitive windows 23–36 wk of gestation for boys.
[d] HR for the DLM-identified sensitive windows 20–22 wk of gestation for girls.

Supplementary Table S5. Hazard ratios (95% confidence intervals) for the association between residual variations in total outdoor $PM_{2.5}$ mass concentrations, $PM_{2.5}$ residual-adjusted models for each component (SO_4, NH_4, NO_3, SS, BC, dust, OM), and the risk of CP stratified by infant sex.

Exposure	Boys		Girls		P-value[a]
	Cohort size (cases)	HR (95% CI)	Cohort size (cases)	HR (95% CI)	
$PM_{2.5}$ ~ SO_4		1.029 (0.970-1.093)		1.071 (1.002-1.145)	0.92
SO_4		1.070 (0.978-1.170)		1.058 (0.952-1.172)	0.79
$PM_{2.5}$ ~ NH_4		1.110 (1.017-1.211)		1.109 (1.001-1.229)	0.71
NH_4		1.044 (0.987-1.104)		1.018 (0.953-1.088)	0.68
$PM_{2.5}$ ~ NO_3		1.013 (0.961-1.068)		1.049 (0.985-1.118)	0.77
NO_3		0.987 (0.965-1.010)		1.003 (0.991-1.015)	0.75
$PM_{2.5}$ ~ SS	1 122 735	0.968 (0.934-1.004)	1 070 692	0.983 (0.942-1.027)	0.60
SS	(2 200)	1.007 (0.996-1.017)	(1 707)	1.006 (0.995-1.017)	0.73
$PM_{2.5}$ ~ BC		0.957 (0.917-1.000)		0.973 (0.928-1.022)	0.35
BC		0.995 (0.975-1.016)		0.992 (0.968-1.016)	0.75
$PM_{2.5}$ ~ dust		1.018 (0.966-1.073)		0.990 (0.930-1.053)	0.96
dust		1.048 (0.980-1.12)		0.986 (0.910-1.068)	0.67
$PM_{2.5}$ ~ OM		0.939 (0.889-0.991)		0.941 (0.858-0.973)	0.77
OM		0.963 (0.850-1.092)		0.870 (0.747-1.013)	0.73

Note: All hazard ratios are scaled by the interquartile range of each pollutant: $PM_{2.5}$ (3.5 ug/m^3), SO_4 (0.94 ug/m^3), NH_4 (0.5 ug/m^3), NO_3 (1.2 ug/m^3), SS (0.1 ug/m^3), BC (0.49 ug/m^3), dust (0.3 ug/m^3), and OM (1.39 ug/m^3). All the models were adjusted for maternal age at delivery, rurality, seasons of birth, birth year, birth weight, parity, maternal comorbidities, residential instability, quintile groups of maternal deprivation, dependency, and ethnic concentration. Abbrev. CP, cerebral palsy; $PM_{2.5}$, fine particulate matter with a diameter ≤ 2.5 μm; SO_4, sulphate; NH_4, ammonium, NO_3, nitrate; SS, sea salt; BC, black carbon, OM, organic matter;

[a] P-values correspond to the multiplicative air pollutant×interaction term using air pollution level averaged over the DLM-identified sensitive window.

Supplementary Table S6. Hazard ratios (95% confidence intervals) associated with $PM_{2.5}$ and its components (SO_4, NH_4, NO_3, SS, BC, dust, OM), with risk of CP stratified by rural/urban residence at birth for the entire pregnancy and DLM-identified sensitive windows from single-pollutant models.

Exposure	Rural		Urban		P-value[a]
	Cohort size (cases)	HR (95% CI)	Cohort size (cases)	HR (95% CI)	
$PM_{2.5}$	224 951 (426)	1.046 (0.867-1.263)	1 967 046 (3 479)	1.026 (0.937-1.124)	0.85
SO_4		0.997 (0.851-1.167)		1.070 (0.998-1.146)	0.91
Sensitive window		—		1.051 (1.007-1.096)[b]	0.73
NH_4		1.017 (0.967-1.068)		1.038 (0.989-1.089)	0.98
NO_3		0.976 (0.934-1.019)		0.991 (0.977-1.004)	0.86
SS		0.893 (0.713- 1.119)		1.002 (0.999-1.004)	0.61
BC		1.057 (0.97-1.151)		0.982 (0.948-1.018)	0.77
dust		1.096 (0.931-1.291)		1.015 (0.958-1.076)	0.83
Sensitive window		1.191 (1.023-1.385)[c]		—	0.76
OM		0.933 (0.753-1.156)		0.929 (0.83-1.039)	0.51

Note: All hazard ratios are scaled by the interquartile range of each pollutant: $PM_{2.5}$ (3.5 ug/m^3), SO_4 (0.94 ug/m^3), NH_4 (0.5 ug/m^3), NO_3 (1.2 ug/m^3), SS (0.1 ug/m^3), BC (0.49 ug/m^3), dust (0.3 ug/m^3), and OM (1.39 ug/m^3). All the models were adjusted for maternal age at delivery, seasons of birth, birth year, birth weight, parity, maternal comorbidities, infant sex, residential instability, quintile groups of maternal deprivation, dependency, and ethnic concentration. Abbrev. CP, cerebral palsy; $PM_{2.5}$, fine particulate matter with a diameter ≤ 2.5 μm; SO_4, sulphate; NH_4, ammonium, NO_3, nitrate; SS, sea salt; BC, black carbon, OM, organic matter;

[a] P-values correspond to the multiplicative air pollutant×interaction term using air pollution level averaged over the DLM-identified sensitive window.

[b] HR for the DLM-identified sensitive windows 4–9 wk of gestation for urban residents.

[c] HR for the DLM-identified sensitive windows 22–36 wk of gestation for rural residents.

Supplementary Table S7. Hazard ratios (95% confidence intervals) for the association between residual variations in total outdoor $PM_{2.5}$ mass concentrations, $PM_{2.5}$ residual-adjusted models for each component (SO_4, NH_4, NO_3, SS, BC, dust, OM), and the risk of CP stratified by rural/urban residence at birth.

Exposure	Rural		Urban		P-value[a]
	Cohort size (cases)	HR (95% CI)	Cohort size (cases)	HR (95% CI)	
$PM_{2.5}$ ~ SO_4	224 951 (426)	0.912 (0.761-1.093)	1 967 046 (3 479)	1.047 (1.001-1.096)	0.52
SO_4		0.983 (0.838-1.153)		1.077 (1.004-1.154)	0.38
$PM_{2.5}$ ~ NH_4		1.114 (0.867-1.431)		1.098 (1.024-1.177)	0.85
NH_4		1.019 (0.969-1.072)		1.041 (0.992-1.093)	0.51
$PM_{2.5}$ ~ NO_3		1.069 (0.937-1.219)		1.021 (0.978-1.065)	0.86
NO_3		0.974 (0.932-1.018)		0.988 (0.974-1.002)	0.99
$PM_{2.5}$ ~ SS		1.003 (0.923-1.089)		0.971 (0.942-1.000)	0.67
SS		0.893 (0.713-1.119)		1.002 (1.000-1.004)	0.74
$PM_{2.5}$ ~ BC		1.061 (0.946-1.190)		0.963 (0.931-0.996)	0.24
BC		1.050 (0.961-1.147)		0.988 (0.954-1.024)	0.77
$PM_{2.5}$ ~ dust		1.038 (0.917-1.174)		0.993 (0.951-1.037)	0.54
dust		1.098 (0.932-1.295)		1.014 (0.957-1.075)	0.82
$PM_{2.5}$ ~ OM		0.880 (0.763-1.014)		0.932 (0.893-0.973)	0.90
OM		0.897 (0.720-1.116)		0.927 (0.828-1.037)	0.51

Note: All hazard ratios are scaled by the interquartile range of each pollutant: $PM_{2.5}$ (3.5 ug/m^3), SO_4 (0.94 ug/m^3), NH_4 (0.5 ug/m^3), NO_3 (1.2 ug/m^3), SS (0.1 ug/m^3), BC (0.49 ug/m^3), dust (0.3 ug/m^3), and OM (1.39 ug/m^3). All the models were adjusted for maternal age at delivery, rurality, seasons of birth, birth year, birth weight, parity, maternal comorbidities, infant sex, residential instability, quintile groups of maternal deprivation, dependency, and ethnic concentration. Abbrev. CP, cerebral palsy; $PM_{2.5}$, fine particulate matter with a diameter ≤ 2.5 μm; SO_4, sulphate; NH_4, ammonium, NO_3, nitrate; SS, sea salt; BC, black carbon, OM, organic matter;

[a] P-values correspond to the multiplicative air pollutant×interaction term using air pollution level averaged over the DLM-identified sensitive window.

Supplementary Table S8. Hazard ratios (95% confidence intervals) associated with $PM_{2.5}$ and its components (SO_4, NH_4, NO_3, SS, BC, dust, OM), with risk of CP when further adjusting for maternal smoking, for the entire pregnancy and DLM-identified sensitive windows in single-pollutant models.

Exposure	Cohort size (cases)	Overall HR (95% CI)
$PM_{2.5}$	1 684 504 (2 630)	1.015 (0.91-1.133)
SO_4		1.09 (0.996-1.193)
Sensitive window		1.046 (1.005-1.089)[a]
NH_4		1.037 (0.989-1.087)
NO_3		0.987 (0.969-1.006)
SS		1.012 (0.998-1.026)
BC		0.982 (0.951-1.013)
dust		1.007 (0.95-1.068)
OM		0.871 (0.766-0.99)
Sensitive window		0.977 (0.956-0.998)[b]

Note: All hazard ratios are scaled by the interquartile range of each pollutant: $PM_{2.5}$ (3.5 ug/m^3), SO_4 (0.94 ug/m^3), NH_4 (0.5 ug/m^3), NO_3 (1.2 ug/m^3), SS (0.1 ug/m^3), BC (0.49 ug/m^3), dust (0.3 ug/m^3), and OM (1.39 ug/m^3). All the models were adjusted for maternal age at delivery, rurality, seasons of birth, birth year, birth weight, parity, maternal comorbidities, infant sex, residential instability, quintile groups of maternal deprivation, dependency, and ethnic concentration. Abbrev. CP, cerebral palsy; $PM_{2.5}$, fine particulate matter with a diameter ≤ 2.5 μm; SO_4, sulphate; NH_4, ammonium, NO_3, nitrate; SS, sea salt; BC, black carbon, OM, organic matter;

[a] HR for the DLM-identified sensitive windows 4–7 wk of gestation.
[b] HR for the DLM-identified sensitive windows 14–19 wk of gestation.

Supplementary Table S9. Hazard ratios (95% confidence intervals) for the association between residual variations in total outdoor $PM_{2.5}$ mass concentrations, $PM_{2.5}$ residual-adjusted models for each component (SO_4, NH_4, NO_3, SS, BC, dust, OM), and the risk of CP stratified when further adjusting for maternal smoking.

Exposure	Cohort size (cases)	HR (95% CI)
$PM_{2.5}$ ~ SO_4	1 684 504 (2 630)	1.078 (1.018-1.141)
SO_4		1.099 (1.003-1.203)
$PM_{2.5}$ ~ NH_4		1.160 (1.063-1.265)
NH_4		1.037 (0.989-1.088)
$PM_{2.5}$ ~ NO_3		1.049 (0.991-1.111)
NO_3		0.981 (0.962-1.001)
$PM_{2.5}$ ~ SS		0.965 (0.928-1.004)
SS		1.012 (0.999-1.026)
$PM_{2.5}$ ~ BC		0.958 (0.917-1.001)
BC		0.978 (0.955-1.019)
$PM_{2.5}$ ~ dust		0.995 (0.943-1.050)
dust		1.007 (0.949-1.068)
$PM_{2.5}$ ~ OM		0.907 (0.859-0.956)
OM		0.867 (0.762-0.985)

Note: All hazard ratios are scaled by the interquartile range of each pollutant: $PM_{2.5}$ (3.5 ug/m^3), SO_4 (0.94 ug/m^3), NH_4 (0.5 ug/m^3), NO_3 (1.2 ug/m^3), SS (0.1 ug/m^3), BC (0.49 ug/m^3), dust (0.3 ug/m^3), and OM (1.39 ug/m^3). All the models were adjusted for maternal age at delivery, rurality, seasons of birth, birth year, birth weight, parity, maternal comorbidities, infant sex, residential instability, quintile groups of maternal deprivation, dependency, and ethnic concentration. Abbrev. CP, cerebral palsy; $PM_{2.5}$, fine particulate matter with a diameter ≤ 2.5 μm; SO_4, sulphate; NH_4, ammonium, NO_3, nitrate; SS, sea salt; BC, black carbon, OM, organic matter;

Supplementary Table S10. Hazard ratios (95% confidence intervals) associated with $PM_{2.5}$ and its components (SO_4, NH_4, NO_3, SS, BC, dust, OM), with risk of CP when only full-term births (≥ 39 gestational weeks) were included for the entire pregnancy and DLM-identified sensitive windows in single-pollutant models.

Exposure	Cohort size (cases)	HR (95% CI)
$PM_{2.5}$	1 523 258 (2410)	0.949 (0.855-1.054)
SO_4		0.993 (0.913-1.079)
NH_4		0.996 (0.942-1.052)
NO_3		0.999 (0.979-1.020)
SS		1.010 (1.000-1.020)
BC		0.978 (0.959-0.998)
Sensitive window		0.998 (0.996-1.000)[a]
dust		0.976 (0.915-1.041)
OM		0.879 (0.777-0.993)
Sensitive window		0.977 (0.957-0.998)[b]

Note: All hazard ratios are scaled by the interquartile range of each pollutant: $PM_{2.5}$ (3.5 ug/m^3), SO_4 (0.94 ug/m^3), NH_4 (0.5 ug/m^3), NO_3 (1.2 ug/m^3), SS (0.1 ug/m^3), BC (0.49 ug/m^3), dust (0.3 ug/m^3), and OM (1.39 ug/m^3). All the models were adjusted for maternal age at delivery, rurality, seasons of birth, birth year, birth weight, parity, maternal comorbidities, infant sex, residential instability, quintile groups of maternal deprivation, dependency, and ethnic concentration. Abbrev. CP, cerebral palsy; IQR, interquartile range; $PM_{2.5}$, fine particulate matter with a diameter ≤ 2.5 μm; SO_4, sulphate; NH_4, ammonium, NO_3, nitrate; SS, sea salt; BC, black carbon, OM, organic matter;

[a] HR for the DLM-identified sensitive windows 16–18 wk of gestation.
[b] HR for the DLM-identified sensitive windows 17-22 wk of gestation.

Supplementary Table S11. Hazard ratios (95% confidence intervals) for the association between residual variations in total outdoor $PM_{2.5}$ mass concentrations, $PM_{2.5}$ residual-adjusted models for each component (SO_4, NH_4, NO_3, SS, BC, dust, OM), and the risk of CP stratified when only full-term births (≥ 39 gestational weeks) were included.

Exposure	Cohort size (cases)	HR (95% CI)
$PM_{2.5}$ ~ SO_4		1.052 (0.993-1.113)
SO_4		0.995 (0.915-1.083)
$PM_{2.5}$ ~ NH_4		1.114 (1.025-1.212)
NH_4		0.996 (0.941-1.053)
$PM_{2.5}$ ~ NO_3		1.059 (1.006-1.116)
NO_3		0.995 (0.974-1.017)
$PM_{2.5}$ ~ SS	1 523 258	0.994 (0.959-1.031)
SS	(2410)	1.010 (1.000-1.020)
$PM_{2.5}$ ~ BC		0.973 (0.935-1.014)
BC		0.980 (0.961-1.000)
$PM_{2.5}$ ~ dust		1.017 (0.967-1.071)
dust		0.977 (0.916-1.042)
$PM_{2.5}$ ~ OM		0.956 (0.907-1.009)
OM		0.882 (0.780-0.997)

Note: All hazard ratios are scaled by the interquartile range of each pollutant: $PM_{2.5}$ (3.5 ug/m^3), SO_4 (0.94 ug/m^3), NH_4 (0.5 ug/m^3), NO_3 (1.2 ug/m^3), SS (0.1 ug/m^3), BC (0.49 ug/m^3), dust (0.3 ug/m^3), and OM (1.39 ug/m^3). All the models were adjusted for maternal age at delivery, rurality, seasons of birth, birth year, birth weight, parity, maternal comorbidities, infant sex, residential instability, quintile groups of maternal deprivation, dependency, and ethnic concentration. Abbrev. CP, cerebral palsy; IQR, interquartile range; $PM_{2.5}$, fine particulate matter with a diameter ≤ 2.5 μm; SO_4, sulphate; NH_4, ammonium, NO_3, nitrate; SS, sea salt; BC, black carbon, OM, organic matter;

Supplementary Table S12. Hazard ratios (95% confidence intervals) for associations between exposure to air pollutants and risk of CP before age 6 for the entire pregnancy and DLM-identified sensitive windows from single-pollutant models.

Exposure	Cohort Size (cases)	HR (95% CI)
$PM_{2.5}$	744 438 (3 433)	0.988 (0.793-1.231)
SO_4		1.081 (0.916-1.275)
NH_4		1.054 (0.955-1.163)
NO_3		0.996 (0.952-1.043)
SS		1.019 (0.969-1.07)
BC		0.943 (0.876-1.015)
dust		1.002 (0.835-1.203)
OM		0.795 (0.599-1.054)

Note: All hazard ratios are scaled by the interquartile range of each pollutant: $PM_{2.5}$ (3.5 ug/m^3), SO_4 (0.94 ug/m^3), NH_4 (0.5 ug/m^3), NO_3 (1.2 ug/m^3), SS (0.1 ug/m^3), BC (0.49 ug/m^3), dust (0.3 ug/m^3), and OM (1.39 ug/m^3). All the models were adjusted for maternal age at delivery, rurality, seasons of birth, birth year, birth weight, parity, maternal comorbidities, infant sex, residential instability, quintile groups of maternal deprivation, dependency, and ethnic concentration. Abbrev. CP, cerebral palsy; $PM_{2.5}$, fine particulate matter with a diameter ≤ 2.5 μm; SO_4, sulphate; NH_4, ammonium, NO_3, nitrate; SS, sea salt; BC, black carbon, OM, organic matter;

Supplementary Table S13. Hazard ratios (95% confidence intervals) for the association between residual variations in total outdoor $PM_{2.5}$ mass concentrations, $PM_{2.5}$ residual-adjusted models for each component (SO_4, NH_4, NO_3, SS, BC, dust, OM), and the risk of CP before age 6.

Exposure	Cohort size (cases)	HR (95% CI)
$PM_{2.5}$ ~ SO_4		1.091 (0.981-1.213)
SO_4		1.063 (0.899-1.258)
$PM_{2.5}$ ~ NH_4		1.339 (1.124-1.595)
NH_4		1.025 (0.926-1.134)
$PM_{2.5}$ ~ NO_3		1.098 (0.961-1.254)
NO_3		0.990 (0.944-1.038)
$PM_{2.5}$ ~ SS	744 438	0.981 (0.898-1.069)
SS	(3 433)	1.019 (0.969-1.071)
$PM_{2.5}$ ~ BC		0.927 (0.850-1.011)
BC		0.956 (0.886-1.032)
$PM_{2.5}$ ~ dust		1.018 (0.907-1.143)
dust		1.005 (0.836-1.207)
$PM_{2.5}$ ~ OM		0.905 (0.812-1.009)
OM		0.769 (0.580-1.018)

Note: All hazard ratios are scaled by the interquartile range of each pollutant: $PM_{2.5}$ (3.5 ug/m^3), SO_4 (0.94 ug/m^3), NH_4 (0.5 ug/m^3), NO_3 (1.2 ug/m^3), SS (0.1 ug/m^3), BC (0.49 ug/m^3), dust (0.3 ug/m^3), and OM (1.39 ug/m^3). All the models were adjusted for maternal age at delivery, rurality, seasons of birth, birth year, birth weight, parity, maternal comorbidities, infant sex, residential instability, quintile groups of maternal deprivation, dependency, and ethnic concentration. Abbrev. CP, cerebral palsy; $PM_{2.5}$, fine particulate matter with a diameter $\leq$ 2.5 μm; SO_4, sulphate; NH_4, ammonium, NO_3, nitrate; SS, sea salt; BC, black carbon, OM, organic matter;

4.11 References

1. Van Naarden Braun K, Doernberg N, Schieve L, Christensen D, Goodman A, Yeargin-Allsopp M. Birth Prevalence of Cerebral Palsy: A Population-Based Study. *Pediatrics*. 2016;137(1):e20152872. doi:10.1542/peds.2015-2872

2. Appleton RE, Gupta R. Cerebral palsy: not always what it seems. *Arch Dis Child*. 2019;104(8):809-814. doi:10.1136/archdischild-2018-315633

3. Patel DR, Neelakantan M, Pandher K, Merrick J. Cerebral palsy in children: a clinical overview. *Transl Pediatr*. 2020;9(Suppl 1):S125-S12S135. doi:10.21037/tp.2020.01.01

4. Yuchi W, Sbihi H, Davies H, Tamburic L, Brauer M. Road proximity, air pollution, noise, green space and neurologic disease incidence: a population-based cohort study. *Environ Health*. 2020;19(1):8. doi:10.1186/s12940-020-0565-4

5. Dhimal M, Chirico F, Bista B, et al. Impact of Air Pollution on Global Burden of Disease in 2019. *Processes*. 2021;9(10):1719. doi:10.3390/pr9101719

6. Hu Y, Zhang Y, Talarico R, et al. Prenatal Exposure to Ambient Air Pollution and Offspring Cerebral Palsy in Ontario, Canada: A Population-Based Cohort Study. *ISEE Conf Abstr*. Published online September 18, 2022. doi:10.1289/isee.2022.P-0481

7. Xing YF, Xu YH, Shi MH, Lian YX. The impact of PM2.5 on the human respiratory system. *J Thorac Dis*. 2016;8(1). doi:10.3978/j.issn.2072-1439.2016.01.19

8. Fu P, Guo X, Cheung FMH, Yung KKL. The association between PM2.5 exposure and neurological disorders: A systematic review and meta-analysis. *Sci Total Environ*. 2019;655:1240-1248. doi:10.1016/j.scitotenv.2018.11.218

9. Bachwenkizi J, Liu C, Meng X, et al. Maternal exposure to fine particulate matter and preterm birth and low birth weight in Africa. *Environ Int*. 2022;160:107053. doi:10.1016/j.envint.2021.107053

10. Zhang Y, Hu Y, Talarico R, et al. Prenatal Exposure to Ambient Air Pollution and Cerebral Palsy. *JAMA Netw Open*. 2024;7(7):e2420717. doi:10.1001/jamanetworkopen.2024.20717

11. Ladd-Acosta C, Feinberg JI, Brown SC, et al. Epigenetic marks of prenatal air pollution exposure found in multiple tissues relevant for child health. *Environ Int*. 2019;126:363-376. doi:10.1016/j.envint.2019.02.028

12. Bolton JL, Huff NC, Smith SH, et al. Maternal Stress and Effects of Prenatal Air Pollution on Offspring Mental Health Outcomes in Mice. *Environ Health Perspect*. 2013;121(9):1075-1082. doi:10.1289/ehp.1306560

13. Saenen ND, Vrijens K, Janssen BG, et al. Placental Nitrosative Stress and Exposure to Ambient Air Pollution During Gestation: A Population Study. *Am J Epidemiol*. 2016;184(6):442-449. doi:10.1093/aje/kww007

14. Lavigne E, Yasseen AS, Stieb DM, et al. Ambient air pollution and adverse birth outcomes: Differences by maternal comorbidities. *Environ Res*. 2016;148:457-466. doi:10.1016/j.envres.2016.04.026

15. Dominici F, Wang Y, Correia AW, Ezzati M, Pope CAI, Dockery DW. Chemical Composition of Fine Particulate Matter and Life Expectancy: In 95 US Counties Between 2002 and 2007. *Epidemiology*. 2015;26(4):556. doi:10.1097/EDE.0000000000000297

16. Wang Y, Xiao S, Zhang Y, et al. Long-term exposure to PM2.5 major components and mortality in the southeastern United States. *Environ Int*. 2022;158:106969. doi:10.1016/j.envint.2021.106969

17. ICES. ICES | Our Organization | Mission, Vision & Values. ICES. Accessed April 26, 2023. https://www.ices.on.ca/our-organization/mission-and-vision/

18. van Donkelaar A, Martin RV, Li C, Burnett RT. Regional Estimates of Chemical Composition of Fine Particulate Matter Using a Combined Geoscience-Statistical Method with Information from Satellites, Models, and Monitors. *Environ Sci Technol*. 2019;53(5):2595-2611. doi:10.1021/acs.est.8b06392

19. van Donkelaar A, Hammer MS, Bindle L, et al. Monthly Global Estimates of Fine Particulate Matter and Their Uncertainty. *Environ Sci Technol*. 2021;55(22):15287-15300. doi:10.1021/acs.est.1c05309

20. Hystad P, Setton E, Cervantes A, et al. Creating National Air Pollution Models for Population Exposure Assessment in Canada. *Environ Health Perspect*. 2011;119(8):1123-1129. doi:10.1289/ehp.1002976

21. Elten M, Benchimol E, Fell D, et al. Ambient air pollution and the risk of pediatric-onset inflammatory bowel disease: A population-based cohort study. *Environ Int*. 2020;138:105676. doi:10.1016/j.envint.2020.105676

22. Ahmed A, Rosella LC, Oskoui M, Watson T, Yang S. Prevalence and temporal trends of cerebral palsy in children born from 2002 to 2017 in Ontario, Canada: Population-based cohort study. *Dev Med Child Neurol*. 2023;65(2):243-253. doi:10.1111/dmcn.15324

23. Rodolaki K, Pergialiotis V, Iakovidou N, Boutsikou T, Iliodromiti Z, Kanaka-Gantenbein C. The impact of maternal diabetes on the future health and neurodevelopment of the offspring: a review of the evidence. *Front Endocrinol*. 2023;14:1125628. doi:10.3389/fendo.2023.1125628

24. Chen KR, Yu T, Lien YJ, Chou YY, Kuo PL. Childhood neurodevelopmental disorders and maternal diabetes: A population-based cohort study. *Dev Med Child Neurol*. 2023;65(7):933-941. doi:10.1111/dmcn.15488

25. Steinle S, Johnston HJ, Loh M, et al. In Utero Exposure to Particulate Air Pollution during Pregnancy: Impact on Birth Weight and Health through the Life Course. *Int J Environ Res Public Health*. 2020;17(23):8948. doi:10.3390/ijerph17238948

26. Yuan L, Zhang Y, Gao Y, Tian Y. Maternal fine particulate matter (PM2.5) exposure and adverse birth outcomes: an updated systematic review based on cohort studies. *Environ Sci Pollut Res*. 2019;26(14):13963-13983. doi:10.1007/s11356-019-04644-x

27. Klepac P, Locatelli I, Korošec S, Künzli N, Kukec A. Ambient air pollution and pregnancy outcomes: A comprehensive review and identification of environmental public health challenges. *Environ Res*. 2018;167:144-159. doi:10.1016/j.envres.2018.07.008

28. Weichenthal S, Christidis T, Olaniyan T, et al. Epidemiological studies likely need to consider PM2.5 composition even if total outdoor PM2.5 mass concentration is the exposure of interest. *Environ Epidemiol*. 2024;8(4):e317. doi:10.1097/EE9.0000000000000317

29. Gasparrini A, Armstrong B, Kenward MG. Distributed lag non-linear models. *Stat Med*. 2010;29(21):2224-2234. doi:10.1002/sim.3940

30. Wu H, Jiang B, Zhu P, et al. Associations between maternal weekly air pollutant exposures and low birth weight: a distributed lag non-linear model. *Environ Res Lett*. 2018;13(2):024023. doi:10.1088/1748-9326/aaa346

31. Rahman MM, Shu YH, Chow T, et al. Prenatal Exposure to Air Pollution and Autism Spectrum Disorder: Sensitive Windows of Exposure and Sex Differences. *Environ Health Perspect*. 130(1):017008. doi:10.1289/EHP9509

32. Gasparrini A. Distributed Lag Linear and Non-Linear Models in R: The Package dlnm. *J Stat Softw*. 2011;43:1-20. doi:10.18637/jss.v043.i08

33. Romeo DM, Sini F, Brogna C, Albamonte E, Ricci D, Mercuri E. Sex differences in cerebral palsy on neuromotor outcome: a critical review. *Dev Med Child Neurol*. 2016;58(8):809-813. doi:10.1111/dmcn.13137

34. Ren S, Xie S, Li X, et al. The association between maternal exposure to secondhand smoke during pregnancy and their children's cerebral palsy, Shandong, China. *Tob Induc Dis*. 2020;18:87. doi:10.18332/tid/127872

35. Moster D, Wilcox AJ, Vollset SE, Markestad T, Lie RT. Cerebral Palsy Among Term and Postterm Births. *JAMA*. 2010;304(9):976-982. doi:10.1001/jama.2010.1271

36. Zhou S, Li T, Han N, et al. The associations of prenatal exposure to PM2.5 and its constituents with fetal growth: A prospective birth cohort in Beijing, China. *Environ Res*. 2022;214:114196. doi:10.1016/j.envres.2022.114196

37. Streja E, Miller JE, Wu C, et al. Disproportionate Fetal Growth and the Risk for Congenital Cerebral Palsy in Singleton Births. *PLoS ONE*. 2015;10(5):e0126743. doi:10.1371/journal.pone.0126743

38. Baschat AA. Neurodevelopment after Fetal Growth Restriction. *Fetal Diagn Ther*. 2013;36(2):136-142. doi:10.1159/000353631

39. McDuffie EE, Smith SJ, O'Rourke P, et al. A global anthropogenic emission inventory of atmospheric pollutants from sector- and fuel-specific sources (1970–2017): an application of the Community Emissions Data System (CEDS). *Earth Syst Sci Data*. 2020;12(4):3413-3442. doi:10.5194/essd-12-3413-2020

40. Perera FP. Multiple Threats to Child Health from Fossil Fuel Combustion: Impacts of Air Pollution and Climate Change. *Environ Health Perspect*. 2017;125(2):141-148. doi:10.1289/EHP299

41. Zhang Y, Han A, Deng S, et al. The impact of fossil fuel combustion on children's health and the associated losses of human capital. *Glob Transit*. 2023;5:117-124. doi:10.1016/j.glt.2023.07.001

42. Environment and Climate Change Canada. Air pollutant emissions. June 14, 2010. Accessed June 27, 2024. https://www.canada.ca/en/environment-climate-change/services/environmental-indicators/air-pollutant-emissions.html

43. Habybabady RH, Sis HN, Paridokht F, et al. Effects of Dust Exposure on the Respiratory Health Symptoms and Pulmonary Functions of Street Sweepers. *Malays J Med Sci MJMS*. 2018;25(6):76-84. doi:10.21315/mjms2018.25.6.8

44. Sadeghimoghaddam A, Khankeh H, Norozi M, Fateh S, Farrokhi M. Investigating the effects of dust storms on morbidity and mortality due to cardiovascular and respiratory diseases: A systematic review. *J Educ Health Promot*. 2021;10(1):191. doi:10.4103/jehp.jehp_1272_20

45. Nazari S, Kermani M, Fazlzadeh M, Matboo SA, Yari AR. The Origins and Sources of Dust Particles, Their Effects On Environment and Health, and Control Strategies: A Review. *J Air Pollut Health*. 2016;1(2):137-152.

46. Nishita-Hara C, Kobayashi H, Hara K, Hayashi M. Dithiothreitol-Measured Oxidative Potential of Reference Materials of Mineral Dust: Implications for the Toxicity of Mineral Dust Aerosols in the Atmosphere. *GeoHealth*. 2023;7(7):e2022GH000736. doi:10.1029/2022GH000736

47. Fussell JC, Kelly FJ. Mechanisms underlying the health effects of desert sand dust. *Environ Int*. 2021;157:106790. doi:10.1016/j.envint.2021.106790

48. Zhang S, Regnault TRH, Barker PL, et al. Placental Adaptations in Growth Restriction. *Nutrients*. 2015;7(1):360-389. doi:10.3390/nu7010360

49. Chiarello DI, Ustáriz J, Marín R, et al. Cellular mechanisms linking to outdoor and indoor air pollution damage during pregnancy. *Front Endocrinol*. 2023;14:1084986. doi:10.3389/fendo.2023.1084986

50. Pizzino G, Irrera N, Cucinotta M, et al. Oxidative Stress: Harms and Benefits for Human Health. *Oxid Med Cell Longev*. 2017;2017:8416763. doi:10.1155/2017/8416763

51. Komar-Fletcher M, Wojas J, Rutkowska M, Raczyńska G, Nowacka A, Jurek JM. Negative environmental influences on the developing brain mediated by epigenetic modifications. *Explor Neurosci*. 2023;2(5):193-211. doi:10.37349/en.2023.00021

52. Marzola P, Melzer T, Pavesi E, Gil-Mohapel J, Brocardo PS. Exploring the Role of Neuroplasticity in Development, Aging, and Neurodegeneration. *Brain Sci*. 2023;13(12):1610. doi:10.3390/brainsci13121610

53. Toboła-Wróbel K, Pietryga M, Dydowicz P, Napierała M, Brązert J, Florek E. Association of Oxidative Stress on Pregnancy. *Oxid Med Cell Longev*. 2020;2020:6398520. doi:10.1155/2020/6398520

54. Volk HE, Park B, Hollingue C, et al. Maternal immune response and air pollution exposure during pregnancy: insights from the Early Markers for Autism (EMA) study. *J Neurodev Disord*. 2020;12:42. doi:10.1186/s11689-020-09343-0

55. Zhou J, Tong J, Ru X, et al. Placental inflammatory cytokines mRNA expression and preschool children's cognitive performance: a birth cohort study in China. *BMC Med*. 2023;21(1):449. doi:10.1186/s12916-023-03173-2

56. Ratnayake U, Quinn T, Walker D, Dickinson H. Cytokines and the neurodevelopmental basis of mental illness. *Front Neurosci*. 2013;7. doi:10.3389/fnins.2013.00180

57. Jiang NM, Cowan M, Moonah SN, Petri WA. The Impact of Systemic Inflammation on Neurodevelopment. *Trends Mol Med*. 2018;24(9):794-804. doi:10.1016/j.molmed.2018.06.008

58. Dunn GA, Nigg JT, Sullivan EL. Neuroinflammation as a Risk Factor for Attention Deficit Hyperactivity Disorder. *Pharmacol Biochem Behav*. 2019;182:22-34. doi:10.1016/j.pbb.2019.05.005

59. Davis RL. Chapter Eight - Neurodevelopment: Inflammation Matters. In: Aschner M, Costa LG, eds. *Advances in Neurotoxicology*. Vol 2. Linking Environmental Exposure to Neurodevelopmental Disorders. Academic Press; 2018:227-264. doi:10.1016/bs.ant.2018.03.002

60. Manisalidis I, Stavropoulou E, Stavropoulos A, Bezirtzoglou E. Environmental and Health Impacts of Air Pollution: A Review. *Front Public Health*. 2020;8:14. doi:10.3389/fpubh.2020.00014

61. Kumar P, Singh AB, Arora T, Singh S, Singh R. Critical review on emerging health effects associated with the indoor air quality and its sustainable management. *Sci Total Environ*. 2023;872:162163. doi:10.1016/j.scitotenv.2023.162163

Ch. 5 Greenspaces, ALEs, and Cerebral Palsy

5.1 Preface

This chapter includes a manuscript titled "*Associations of prenatal exposure to residential greenspace, and active living environments with cerebral palsy: A population-based cohort study in Ontario, Canada"*, which will be formatted for submission to the journal Environmental Epidemiology. The manuscript addresses objective 2 of this thesis, which aims to investigate the associations between gestational exposure to greenspaces, ALEs, and the risk of CP. Ethics approval for this study was granted by the Research Ethics Boards of Health Canada. The authors declare they have no competing interests.

5.2 List of authors and contributions

Amrin Ahmed[1,2], Steven Hawken[2,3], Anna Gunz[4,5], Robert Talarico[6], Chengchun Yu[6], Hong Chen[1,6,7], Paul Villeneuve[8], Éric Lavigne[1,2]

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

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

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

[4] Children's Health Research Institute, London, Ontario, Canada

[5] Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

[6] ICES uOttawa, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

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

[8] Department of Neuroscience, Carleton University, Ottawa, Ontario, Canada

Amrin Ahmed: Conceptualization, Writing- Original draft preparation, Methodology, Formal analysis; Writing- Reviewing and Editing; Steven Hawken: Writing- Reviewing and Editing; Anna Gunz: Writing- Reviewing and Editing; Robert Talarico: Data preparation, Writing- Reviewing and Editing; Chengchun Yu: Writing- Reviewing and Editing; Hong Chen: Writing- Reviewing and Editing; Paul Villeneuve: Writing- Reviewing and Editing; Éric Lavigne: Conceptualization, Writing- Original draft preparation, Methodology, Formal analysis; Writing- Reviewing and Editing.

5.3 Abstract

Background: Prenatal exposure to environmental factors, such as greenspace and active living environments, have been linked to various protective effects, however associations with cerebral palsy (CP) risk remain unexplored.

Objective: To examine the associations between prenatal exposure to residential greenspaces, indicators of active living environments, and risk of CP among term births (gestational age ≥ 37 completed weeks) in Ontario, Canada.

Methods: We conducted a retrospective cohort study using health administrative data from Ontario, Canada, between April 1st, 2002 and December 31st, 2020. Exposures of interest included the normalized difference vegetation index (NDVI), Green View Index (GVI), and park proximity. The Canadian Active Living Environments (Can-ALE) index was also utilized. Cox proportional hazards models estimated hazard ratios (HRs) for CP risk associated with these environmental exposures, adjusting for potential confounders.

Results: Our analysis identified 1,436,411 mother-infant pairs, of which 2 883 were diagnosed with CP during the follow-up period. Interquartile range increases in NDVI (HR: 1.040, 95% CI: 0.987 - 1.096, per IQR=0.1) and GVI (HR: 0.989, 95% CI: 0.943 - 1.038, per IQR=10.05%) were not significantly associated with CP risk. Similar results were found for quartile increases of NDVI and GVI. Residential proximity to parks at birth was associated with a reduction in CP risk (HR: 0.946, 95% CI: 0.904 - 0.990, per 0.06 increase in park proximity index), after adjusting for ALE and air pollution.

Conclusions: Our study suggests that living closer to a park may help reduce CP risk. Further research should investigate these protective effects and consider other dimensions of greenspace quality and usability.

Keywords: Greenspace exposure, prenatal exposure, cerebral palsy, NDVI, GVI, ALE, park proximity

Abbreviations: Active Living Environments, ALE; Canadian Active Living Environments, Can-ALE; Cerebral Palsy, CP; Green View Index, GVI; Interquartile Range, IQR; Normalized Difference Vegetation Index, NDVI

5.4 Introduction

Cerebral palsy (CP) is a complex neurological disorder, characterized by limitations in movement and motor abilities.[1] It affects 2 to 3 out of 1000 individuals and is most often diagnosed during early childhood and persists throughout the individual's lifespan.[2] CP is a non-progressive disorder that differs in severity and manifestation.[1] Nonetheless, its chronic nature presents many societal and economic burdens. While the etiology of the disease is complex and remains poorly understood, there is substantial evidence that prenatal and postnatal exposure to certain environmental factors play a key role in its development. In general, prenatal exposure to air pollutants has been shown to have effects on various neurological conditions, including CP.[3] In recent years, exposure to greenspace and natural urban environments have also been investigated as a protective factor against various health outcomes.[4] These studies have found protective associations between greenspace exposure and certain neurological conditions, such as dementia and autism spectrum disorder (ASD).[5,6] Greenspaces have been found to improve health outcomes through mechanisms such as promoting physical activity, reducing stress, enhancing air quality, and fostering social interactions.[7–9] However, no studies have been done investigating the protective effects of greenspace exposure on the risk of CP.

Greenspaces are characterized as areas primarily covered with vegetation, such as parks, gardens, forests, meadows, and other natural or semi-natural spaces within urban or rural environments.[10] With an increase in urbanization, efforts to preserve and increase greenspace exposure has been identified as an important initiative in communities. While most studies focus on adult populations, an ecological study done in Berlin found that both socio-economic and environmental factors, including natural surroundings, may have an impact on fine and gross motor development in children.[11] In addition, another study done in Wuhan, China found increased

exposure to green spaces in residential surroundings, measured using the normalized difference vegetation index (NDVI), to be associated with improved early childhood neurodevelopment.[12] The NDVI uses remote sensing and land use data to provide a greenspace metric that quantifies the presence of vegetation canopy in an aerial view.[13] As such, differing vegetation types are not accounted for and presents limitations in some studies.[14] While most greenspace studies have been done looking at NDVI, other greenspace measures have been developed which take into account variations in greenspace presence, such as the Greenview index (GVI). GVI helps quantifies the proportion of visible green vegetation from a particular viewpoint, providing a measure of the visual accessibility of greenspaces within an environment.[15] The use of varying greenspace metrics provides a better understanding of the role that different types of vegetation play within urban environments.

In addition to greenspaces, evaluating Active Living Environments (ALE) is crucial due to their significant impact on health outcomes. ALE include factors such as walkability, access to recreational areas, residential proximity to parks, and the availability of greenspaces, which collectively influence physical activity levels, mental health, and overall well-being.[16] Understanding how these environments promote active lifestyles can help explain associations with CP risk.

In this study, we used population-based health administrative data from the province of Ontario, Canada to conduct a retrospective cohort study. The aim of this study was to investigate the association between prenatal exposure to greenspaces, ALEs, and the risk of CP, recognizing that understanding the potential influence of greenspace exposure during pregnancy on CP risk could lead to more informed public health strategies and urban planning efforts.

5.5 Methods

Study populations and data sources

We conducted a retrospective cohort study of all live term births (gestational age ≥ 37 completed weeks) that occurred in hospitals in Ontario, Canada between April 1st, 2002 and December 31st, 2020, using administrative health data from ICES, a non-profit research institute that compiles and analyzes healthcare and demographic data for over 99% of Ontario's population.[17]

The study cohort was created by linking various administrative datasets using unique encoded identifiers at ICES. MOMBABY, a database that links maternal and infant hospital admission records in Ontario using data from the Discharge Abstract Database (CIHI-DAD), was used as the base of the cohort. It was cross-referenced with the Registered Persons Database, which holds demographic information for those covered by provincial health insurance, and the Better Outcomes Registry & Network (BORN), a birth registry which contains data, from 2006 and onwards, on maternal demographics, health practices, obstetrical background, and prenatal care for all births occurring within the province of Ontario[18]. The Ontario Diabetes Database (ODD) and the Ontario Hypertension Dataset (HYPER) were also used for information on maternal chronic disorders. Furthermore, CP diagnosis was identified from the CIHI-DAD, Ontario Health Insurance Plan (OHIP), and the National Ambulatory Care Reporting System (NACRS) databases.

Mother-infant pairs with invalid identification numbers, instances of multiple-birth deliveries, preterm births, children with unrecorded or invalid biological sex information, and those who were ineligible for provincial health insurance at birth were removed from the study

population. This also included pairs with missing or invalid data on covariates and greenspace exposure (Supplementary Figure S1).

Outcome ascertainment

The outcome for this study was defined as a diagnosis of CP before the age of 18 years. This was determined using a case algorithm that included either a single inpatient hospitalization diagnosis recorded with the ICD-10-CA code G80 in the CIHI-DAD database or two or more outpatient diagnoses documented with the modified ICD-9 code 343 in OHIP physician billing claims, with a minimum interval of two weeks between diagnoses, whichever occurred first.[3]

Exposure assessment

Exposure data for greenspace and active living environments were sourced from the Canadian Urban Environmental Health Research Consortium (CANUE). The CANUE is a platform that contains a wide range of environmental and geospatial data intended to provide insights into the complex relationships between urban environments and human health.[19] These environmental exposure metrics include NDVI, GVI, park proximity and Canadian active living environment index (Can-ALE) measures, which were available at the postal code level for this study. These environmental exposures were linked to the ICES cohort using maternal postal codes at the time of birth.

Using remote sensing, the NDVI measures the health and density of vegetation across a particular area by analyzing the spectral reflectance of light in both the visible and near-infrared portions of the electromagnetic spectrum.[20] The index is calculated by taking the difference between these two types of light and dividing it by their sum. This simple mathematical operation results in a numerical value that typically falls within the range of -1 to +1. In this scale, a high

NDVI value, close to +1, indicates lush and healthy vegetation, while a low value, closer to -1, represents non-vegetated or barren surfaces. NDVI values between 0.2 and 0.4 often characterize grasslands and moderately dense vegetation.[14] For this study, annual average NDVI values were extracted from Landsat 5 and Landsat 8 data at a 30 metre (m) spatial resolution for the years of the study period. These average annual NDVI values were then assigned to the study population within a 250 m radius buffer around the corresponding location coordinates of each participant's residential postal code at time of birth.[21]

The GVI is another greenspace metric designed to evaluate the abundance and distribution of green vegetation in areas. The GVI is often derived from high-resolution satellite imagery, aerial photography, or other remote sensing techniques, and it provides a numerical score or value to represent the extent of greenery in a specific urban location. GVI measures were extracted from Google Street View (GSV) images by calculating the difference between green and red, and green and blue spectral bands to obtain the percentage of pixels of greenspace in the images.[15] This provided a coordinate specific GVI index representing the vegetation coverage as a long-term average value for each postal code. The GVI values range from 0 to 100%, with higher values indicating a greater proportion of visible vegetation. These coordinate specific values were available as an average within the boundaries of each postal code and were linked to the study population using the postal code at time of birth.

Indicators of neighborhood environments conducive to active living, such as the Canadian Active Living Environments (Can-ALE) index and park proximity measures, were also utilized for this study. The Can-ALE index ranges from 1 (very low) to 5 (very high), measuring the active living friendliness of Canadian communities, and was developed using validated metrics such as intersection density, dwelling density, points of interest, and measures of walkability.[22] The ALE

was calculated for the 2016 census year using 1 km circular buffers around the centroid of dissemination areas. The normalized value of proximity of dissemination blocks to parks was also extracted, measuring how close dissemination blocks were to a neighborhood park within a 1 km walking distance, with higher values indicating closer proximity.[23] This park proximity index measure was used as a proxy for ALE, alongside the Can-ALE.

To account for further potential confounding with air pollutants, we obtained average prenatal exposure data on fine particulate matter ($PM_{2.5}$) at the bi-weekly level, and gaseous pollutants (nitrogen dioxide (NO_2), ozone (O_3)) at the weekly level, using temporal scaling methods.[24] These measures were linked to the cohort using postal code at time of birth.

Covariates

This study integrated a set of essential covariates to address the possible influence of confounding variables. These covariates encompassed a range of factors, including maternal age, parity, birth weight, socioeconomic variables (residential instability, maternal deprivation, dependency, and ethnic concentration), geographic location (rural/urban), maternal comorbidities, season of birth and year of birth. These covariates were chosen based on previous literature,[25–27] and was guided by a directed acyclic graph (DAG) (Supplementary Figure S2). To evaluate the impact of sex differences on exposure risk, further adjustment with infant sex was done in a sensitivity analysis. Additionally, confounding resulting from prenatal ambient air pollutants (i.e. particulate matter with aerodynamic diameter <2.5 μm, nitrogen dioxide and ozone) was also explored in sensitivity analyses.

Statistical analysis

Cox proportional hazards models were used to investigate the associations between prenatal exposure to greenspace metrics, ALE, proximity to parks and CP risk. The follow-up time was measured in days from birth, until their first diagnosis of CP, death, loss of eligibility for provincial health insurance, their 18th birthday, or the conclusion of the follow-up period (December, 2020).[3]

Firstly, descriptive analyses were conducted to characterize the study population and gain insights into the distribution of key variables. Before beginning our modeling, we performed correlation and univariate analyses to assess the presence of collinearity among the independent variables.

Cox proportional hazards models were used to estimate hazard ratios (HRs) and associated 95% confidence intervals (CIs) in the study. The models were presented per interquartile range (IQR) increase for each greenspace metric. We began with a baseline model for each measure that included basic potential maternal and infant confounding variables, and then incrementally adjusted for additional variables. We explored CP risk by quintile of ALE for the baseline model, and with further adjustment for infant sex and air pollution exposure, as the impact of greenspace and ALE factors may vary depending on the type of urban setting.

To ensure the robustness of our study findings, we undertook several sensitivity and additional analyses. First, we conducted a sensitivity analysis by further adjusting the models for each greenspace and ALE measure with infant sex, to determine if there were any sex-differences in the results we found. Next, we stratified our analysis by urban and rural residence to explore the presence of effect modification present in the type of living environment. This was done by including an interaction term between the exposure metrics of interest and the rurality variable. Lastly, we restricted the follow-up period to 6 years of age to ensure that our results were not

influenced by exposures in later life. We considered effect measure modification to be significant if the Wald chi-square p-value was less than 0.05.

To further assess potential dose-response relationships, we also conducted a categorical analysis for NDVI and GVI by investigating by quartile increases of the greenspaces. Cox proportional hazard models were used to report the HRs and associated 95% CIs in the fully adjusted models. In addition, p-values for linear trend patterns were assessed in categorical results indicating a linear pattern, by treating the quartile/quintile variable as a continuous variable in the regression model to test for a linear association across exposure levels.

Data management steps and descriptive statistics were completed in SAS EG version 7.1 (SAS Institute). All other statistical analyses were conducted using R (version 3.1.2).

5.6 Results

Descriptive statistics

The study population included a total of 1 436 411 term births between April 1st 2002 and December 31st 2020 in the province of Ontario, Canada, of which 2 883 were diagnosed with CP. The mean maternal age at delivery was similar between CP and non-CP cases, with averages of 29.98 years (SD = 5.78) and 30.40 years (SD = 5.39), respectively. A higher proportion of males were noted in the CP group (55.81%) compared to the non-CP group (51.20%). Infants diagnosed with CP had a lower mean birth weight (3294.98 grams, SD = 567.08) compared to those without CP (3423 grams, SD = 484.18), and the mean gestational age at birth was slightly lower for those with CP (38.87 weeks, SD = 1.37) compared to those without CP (39.1 weeks, SD = 1.24) (Table 1).

We found weak to moderate correlations (r) between continuous greenspace metrics (Supplementary Table S1). For instance, GVI was weakly correlated with NDVI (r = 0.11), ALE (r = 0.001), and park proximity (r = -0.05), whereas ALE was moderately correlated with park proximity (r = 0.41). Additionally, NDVI was weakly correlated with ALE (r = -0.26) and park proximity (r = -0.17).

Associations between greenspaces, active living environments, and CP

Figure 1 visually summarizes the association between continuous greenspace metrics and CP with HRs and 95% CIs per IQR change. At baseline, NDVI was positively associated with the risk of CP (HR: 1.026, 95% CI: 0.979 - 1.075, per 0.1), but the association was not statistically significant. This positive non-significant association persisted after adjusting for ALE scores and air pollution. In contrast, we found protective effects for GVI in the baseline model (HR: 0.990, 95% CI: 0.947 - 1.037, per 10.05%), however these were also not found to be significant, even after adjusting for ALE and air pollution. When additionally adjusting for ALE and air pollution, we found that NDVI and GVI slightly increased the risk of CP, but effects were not significant (Supplementary Table S2).

Conversely, significant protective effects were found for park proximity. The baseline model showed a significant reduction in the risk of CP (HR: 0.937, 95% CI: 0.899 - 0.976, per 0.06), and remained significant after adjusting for ALE (HR: 0.945, 95% CI: 0.904 - 0.987, per 0.06), air pollution (HR: 0.939, 95% CI: 0.900 - 0.980, per 0.06), and both (HR: 0.946, 95% CI: 0.904 - 0.990, per 0.06) (Supplementary Table S2).

Figure 2 presents the adjusted HRs and 95% CIs for the risk of CP across quintiles of ALE. Overall, we found both positive (increasing) and negative (decreasing) associations between quintiles of ALE for the baseline model, and when further adjusting for infant sex and air pollution.

When compared to the lowest quintile of ALE, each increasing quintile of ALE was associated with a decreasing risk of CP. In the baseline model, the association for the highest ALE quintile (quintile 5) was 0.881 (95% CI: 0.706 - 1.101), 0.885 (95% CI: 0.737 - 1.062) for quintile 4, 1.009 (95% CI: 0.867 - 1.172) for quintile 3, and 1.073 (95% CI: 0.930 - 1.238) for quintile 2, indicating a linear trend pattern (p-value <0.0001). Similar associations and linear trend patterns were found when further adjusting the models for infant sex and air pollution, although none of the HR associations reached statistical significance (Supplementary Table S3).

Sensitivity and additional analyses

When additionally adjusting for infant sex, we did not find substantial significant change in the risk of CP among the continuous greenspace measures (Supplementary Table S4). When stratifying analysis by urban/rural residence, no significant associations were found in both groups. Due to small sample sizes in ALE quintiles 3 to 5 in the stratified rural population, only urban residents were considered when assessing ALE quintiles. Overall, p-values for effect modification were also not found to be significant (Supplementary Table S5). No significant associations were found in the sensitivity analyses that limited follow-up to 6 years of age, however this analysis was limited to only 413 cases, a substantially smaller sample size compared to the primary analysis which may diminish the statistical power of the sensitivity analysis (Supplementary Table S6).

The categorical analyses of the greenspace measures did not reveal any significant associations. For NDVI, when compared to the reference/lowest quartile, each quartile increase was associated with a slight increase in CP risk, with quartile 4 having the highest association (HR: 1.316, 95% CI: 0.977-1.671). A similar pattern was found for GVI (quartile 4: HR: 0.998 (0.899-1.108)), but associations were slightly protective across the quartiles (Supplementary Table S7). Overall, a

linear dose-relationship pattern was observed for both NDVI and GVI (p-value for linear trend <0.0001).

5.7 Discussion

In this retrospective cohort study, we investigated the association between prenatal exposures to residential greenspaces, ALEs, and the risk of CP. Our findings did not support a significant protective effect of overall prenatal residential greenspace exposure, as measured by NDVI and GVI, on CP risk. However, our findings may suggest that residential proximity to parks at birth, a proxy of ALEs, may be associated with a reduced risk of CP.

While there is currently very limited literature available on the associations between prenatal greenspace exposure and CP, our study adds to the growing body of literature examining the overall health benefits of greenspace exposure. Previous research has documented various positive health outcomes associated with residential greenspaces, including reduced risks of preterm birth, low birth weight, and decreased adverse mental health outcomes.[28] Low birth weight, also termed small for gestational age (SGA), is a high risk factor for CP development in infants, as it often leads to growth restrictions or adverse prenatal conditions that can affect brain development.[29] Thus, greenspace exposure during the prenatal period may exert indirect benefits on fetal development by reducing major CP risk factors. In one study, NDVI was found to reduce the risk of neurodegenerative diseases,[30] while another found GVI to have protective effects on childhood asthma.[31] The lack of significant associations for NDVI and GVI in our study contrasts with these findings but may be explained by differences in disease pathophysiology, study design, population characteristics, and the specific measures of greenspace used. However, similar to

another study that explored the associations between greenspaces, active living environments and the risk of ASD, protective effects were found to residential park proximity at birth.[32]

The protective association observed with park proximity may reflect several underlying mechanisms. Parks and accessible greenspaces can promote physical activity, reduce stress, and enhance social interactions, all of which contribute to improved maternal health during pregnancy. Proximity to parks and other green spaces can lead to increased physical activity among pregnant women, which is beneficial for both maternal and fetal health. Regular physical activity during pregnancy is known to improve cardiovascular health, regulate blood glucose levels, and reduce the risk of gestational hypertension and diabetes, conditions that are linked to adverse birth outcomes.[33,34] Furthermore, parks provide an environment for social interaction and community engagement, which can alleviate maternal stress and improve mental health. Lower stress levels during pregnancy have been associated with better fetal development and a reduced risk of neurodevelopmental disorders.[35] Additionally, parks often contribute to lower levels of air pollution and noise, both of which are detrimental to fetal development.[36,37] Reduced exposure to pollutants such as $PM_{2.5}$, O_3, and NO_2 can decrease the incidence of respiratory and cardiovascular issues in pregnant women, leading to better birth outcomes.[38,39] Noise reduction in greener areas also contributes to lower stress levels and improved sleep quality, further enhancing maternal and fetal health.[40] These combined effects can collectively contribute to the reduction in CP risk observed with greater park proximity.

However, in this study, it is important to consider that the park proximity measures did not account for factors of park use, such as accessibility, park quality, or safety. For instance, while an individual may reside close to a park, practical barriers such as busy roads, inadequate pedestrian infrastructure, or perceived safety concerns could limit access and use. Therefore, park proximity

alone may not fully capture the potential health benefits associated with greenspace exposure. Future research should consider more complex measures of park accessibility and usability to provide a more comprehensive assessment.

This study has several notable strengths that enhance the robustness and reliability of its findings. Firstly, the large sample size and long follow-up period allows for generalizability of the study results. We also used various greenspace measures and indicators of ALEs, which provides a thorough evaluation of different dimensions of greenspace exposure and their potential health impacts. Lastly, the comprehensive adjustment for air pollution further strengthens the analysis by accounting for an important environmental factor that could confound the relationship between greenspace and CP risk.

Potential limitations that should be considered in the study include, misclassification of cases due to the reliance on secondary health administrative data, which was not collected for research purposes. Additionally, the study does not account for potential changes in greenspace exposure over time, assuming that exposure at birth is representative of prenatal exposure throughout pregnancy. Another limitation is the potential for selection bias, as the study population is limited to term births in Ontario, which may not be representative of other regions or populations with different environmental or healthcare contexts. While the study adjusts for a range of covariates, it is possible that some important factors, such as detailed maternal health conditions or other environmental exposures, were not fully accounted for. In addition, the greenspace metrics used in the study may present limitations as well. NDVI captures overall vegetation density but does not distinguish between different types of greenspaces, such as parks, forests, or agricultural land. GVI, while providing a visual perspective of greenspace, may not fully capture the accessibility or usability of these spaces. Moreover, these metrics do not account for the quality or

functionality of greenspaces, which are important factors influencing their health benefits. Furthermore, in the study, GVI was not available as a buffer around the centroid, but as an average within postal code boundaries, which may lead to misclassification error. Similarly, park proximity was available at the dissemination block-level, and not at the postal code-level, which may warrant misclassification errors. Park proximity and Can-ALE measures in rural areas may also not be complete (e.g., isolated resort areas or remote communities not connected by road), affecting statistical analysis.

Overall, our findings suggest that while overall prenatal residential greenspace exposure may not significantly reduce CP risk, proximity to parks at birth may offer protective benefits. Future research should investigate the mechanisms underlying the protective effects of park proximity and explore other dimensions of environmental factors, such as quality, usability, and specific types of greenspaces. This can highlight the importance of accessible and well-maintained parks in urban planning and public health policies. Public health policies aimed at increasing access to parks and fostering active living environments could contribute to better health outcomes for mothers and children.

5.8 Acknowledgements

Greenspace metrics (i.e. NDVI and GVI) and environmental factors conducive to active living (i.e. ALE, proximity to parks) metrics, indexed to DMTI Spatial Inc. postal codes, were provided by CANUE (Canadian Urban Environmental Health Research Consortium). Parts of this material are based on data and/or information compiled and provided by CIHI and the Ontario Ministry of Health. The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. This study is based in part on data provided by Better Outcomes

Registry and Network (“BORN”), part of the Children’s Hospital of Eastern Ontario. The interpretation and conclusions contained herein do not necessarily represent those of BORN Ontario. This document used data adapted from the Statistics Canada Postal Code^OM Conversion File, which is based on data licensed from Canada Post Corporation, and/or data adapted from the Ontario Ministry of Health Postal Code Conversion File, which contains data copied under license from ©Canada Post Corporation and Statistics Canada. We thank the Toronto Community Health Profiles Partnership for providing access to the Ontario Marginalization Index. This study was supported by a research grant from Health Canada.

5.9 Tables and figures

Table 1. Maternal, infant, and environmental characteristics of term births with and without a Cerebral Palsy diagnosis born in Ontario, Canada, 2002-2020.

Characteristics		Without CP (N= 1 433 528)	With CP (N= 2 883)	Total (N= 1 436 411)
Maternal characteristics				
Maternal age, years				
Mean ± SD		30.40 (5.39)	29.98 (5.78)	30.40 (5.39)
Median (Q1-Q3)		31 (27-34)	30 (26-34)	31 (27-34)
Parity, n(%)				
0		630 394 (43.98)	1 342 (46.55)	631 736 (43.98)
1		531 140 (37.05)	966 (33.51)	532 106 (37.04)
≥2		271 994 (18.97)	575 (19.94)	272 569 (18.98)
Maternal pre-existing health conditions, n(%)				
Pre-pregnancy diabetes	Yes	2 805 (0.20)	78 (2.71)	2 883 (0.20)
	No	1 430 723 (99.80)	2 805 (97.29)	1 433 528 (99.80)
Pre-pregnancy hypertension	Yes	2 789 (0.19)	94 (3.26)	2 883 (0.20)
	No	1 430 739 (99.81)	2 789 (96.74)	1 433 528 (99.80)
Maternal smoking during pregnancy				
Yes		101 829 (7.10)	263 (9.12)	102 092 (7.11)
No		968 083 (67.53)	1 711 (59.35)	969 794 (67.52)
Missing		363 616 (25.37)	909 (31.53)	364 525 (25.38)
Follow-up year after birth, mean (SD)		10.29 (4.26)	11.13 (4.09)	10.30 (4.26)
Infant characteristics				
Birth Season, n(%)				
Spring (Mar-May)		361 368 (25.21)	708 (24.56)	362 076 (25.21)
Summer (June-Aug)		379 160 (26.45)	734 (25.46)	379 894 (26.45)
Fall (Sept-Nov)		360 863 (25.17)	737 (25.56)	361 600 (25.17)
Winter (Dec-Feb)		332 137 (23.17)	704 (24.42)	332 841 (23.17)
Infant sex, n(%)				
Male		733 899 (51.20)	1 609 (55.81)	735 508 (51.20)
Female		699 629 (48.80)	1 274 (44.19)	700 903 (48.80)
Infant birthweight, grams				
Mean ± SD		3423 (484.18)	3294.98 (567.08)	3422.89 (484.39)
Median (Q1-Q3)		3410 (3100-3730)	3285.5 (2940-3646)	3410 (3100-3730)
Gestational age at birth, weeks				
Mean ± SD		39.1 (1.24)	38.87 (1.37)	39.1 (1.24)
Median (Q1-Q3)		39 (38-40)	39 (38-40)	39 (38-40)
Environmental characteristics				
NDVI				
Mean ± SD		0.69 (0.08)	0.69 (0.08)	0.69 (0.08)
Median (Q1-Q3)		0.71 (0.65-0.75)	0.7 (0.64-0.75)	0.71 (0.65-0.75)
NDVI (quartiles), n(%)				
1 (lowest)		361 783 (25.24)	722 (25.04)	362 505 (25.24)
2		357 304 (24.92)	704 (24.42)	358 008 (24.92)

3	357 169 (24.92)	715 (24.80)	357 884 (24.92)
4 (highest)	357 272 (24.92)	742 (25.74)	358 014 (24.92)
GVI			
Mean ± SD	13.81 (8.19)	13.87 (8.24)	13.81 (8.19)
Median (Q1-Q3)	12.17 (7.92-17.97)	12.35 (7.98-18.22)	12.18 (7.92-17.97)
GVI quartiles, n(%)			
1 (lowest)	361 783 (25.24)	722 (25.04))	362 505 (25.24)
2	357 304 (24.92)	704 (24.42)	358 008 (24.92)
3	357 169 (24.92)	715 (24.80)	357 884 (24.92)
4 (highest)	357 272 (24.92)	742 (25.74)	358 014 (24.92)
ALE quintiles, n(%)			
1 (lowest)	149 662 (10.44)	301 (10.44)	149 963 (10.44)
2	460 355 (32.11)	961 (33.33)	461 316 (32.12)
3	531 294 (37.06)	1 090 (37.81)	532 384 (37.06)
4	192 833 (13.45)	357 (12.38)	193 190 (13.45)
5 (highest)	92 585 (6.46)	160 (5.55)	92 745 (6.46)
Missing	6 799 (0.47)	14 (0.49)	6 813 (.47)
Park proximity			
Mean ± SD	0.07 (0.06)	0.07 (.06)	0.07 (0.07)
Median (Q1-Q3)	0.05 (0.03-0.09)	0.05 (0.03-0.09)	0.05 (0.03-0.09)
Residence at birth			
Urban	1 372 787 (95.76)	2 742 (95.11)	1 375 529 (95.76)
Rural	60 337 (4.21)	141 (4.89)	60 478 (4.21)
Instability quintile, n (%)			
Quintile 1	303 649 (21.18)	550 (19.08)	304 199 (21.18)
Quintile 2	242 875 (16.94)	479 (16.61)	243 354 (16.94)
Quintile 3	234 209 (16.34)	479 (16.61)	234 688 (16.34)
Quintile 4	278 272 (19.41)	593 (20.74)	278 870 (19.41)
Quintile 5	367 156 (25.61)	760 (26.36)	367 916 (25.61)
Unknown	7 367 (0.51)	17 (0.59)	7 384 (0.51)
Deprivation quintile, n (%)			
Quintile 1	290 269 (20.25)	529 (18.35)	290 798 (20.24)
Quintile 2	251 385 (17.54)	458 (15.89)	251 843 (17.53)
Quintile 3	252 054 (17.58)	528 (18.31)	252 582 (17.59)
Quintile 4	273 433 (19.07)	541 (18.77)	273 974 (19.07)
Quintile 5	359 020 (25.05)	810 (28.10)	359 830 (25.06)
Unknown	7 367 (0.51)	17 (0.58)	7 384 (0.51)
Dependency quintile, n (%)			
Quintile 1	507 972 (35.44)	974 (33.78)	508 946 (35.43)
Quintile 2	319 764 (22.31)	633 (21.96)	320 397 (22.31)
Quintile 3	236 390 (16.49)	490 (17.0)	236 880 (16.49)
Quintile 4	194 982 (13.60)	417 (14.46)	195 399 (13.60)
Quintile 5	167 053 (11.65)	352 (12.21)	167 405 (11.65)
Unknown	7 367 (0.51)	17 (0.59)	7 384 (0.51)

Ethnic concentration quintile, n (%)			
Quintile 1	118 616 (8.27)	255 (8.84)	118 871 (8.28)
Quintile 2	177 490 (12.38)	399 (13.84)	177 889 (12.38)
Quintile 3	244 280 (17.04)	514 (17.83)	244 794 (17.04)
Quintile 4	339 323 (23.67)	660 (22.89)	339 983 (23.67)
Quintile 5	546 452 (38.13)	1 038 (36.0)	547 490 (38.12)
Unknown	7 367 (0.51)	17 (0.59)	7 384 (0.51)
Averaged levels during pregnancy			
$PM_{2,5}$, $\mu g/m^3$, mean (SD)	7.42 (2.84)	7.88 (2.99)	7.43 (2.84)
NO_2, ppb, mean (SD)	5.66 (3.89)	5.62 (3.90)	5.66 (3.90)
O_3, ppb, mean (SD)	46.50 (13.82)	47.33 (13.77)	46.50 (13.82)

SD: standard deviation
Q1: 25th percentile or lower quartile
Q3: 75th percentile or upper quartile
NDVI: Normalized Difference Vegetation Index
GVI: Green View Index
ALE: Active Living Environments

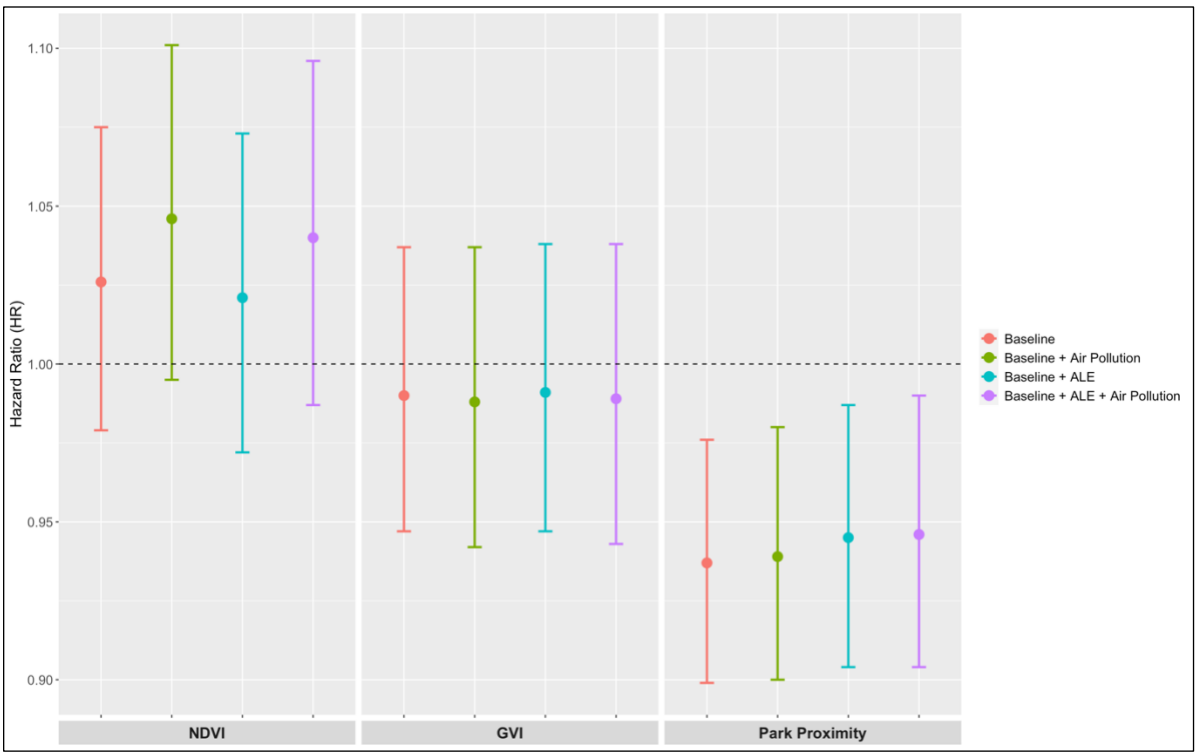


Figure 1. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for CP incidence per interquartile range (IQR) increase in continuous greenspace metrics (normalised difference vegetation index (NDVI), Greenview index (GVI), and park proximity).

Note: The baseline model includes maternal age at delivery, rurality, seasons of birth, birth year, birth weight, parity, residential instability, quintile groups of maternal deprivation, dependency (categorical), and ethnic concentration (categorical).

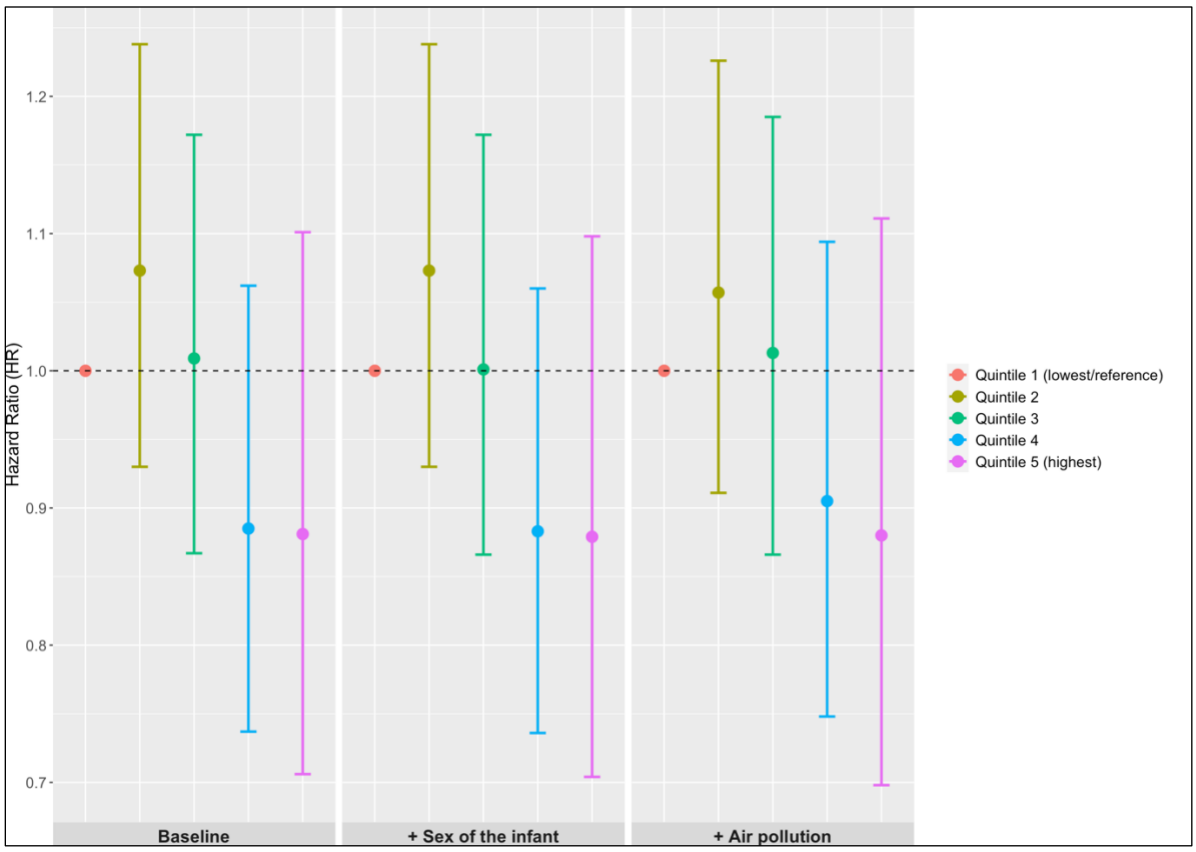
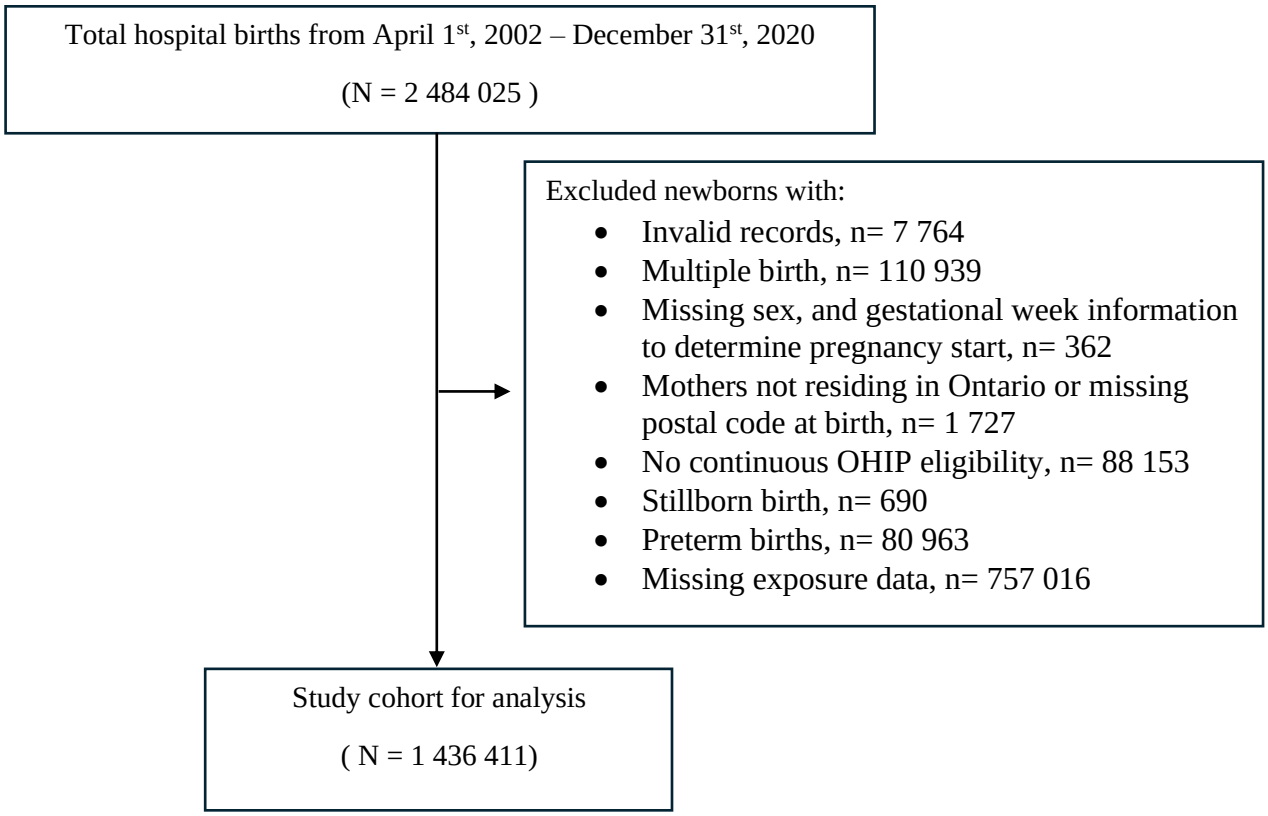


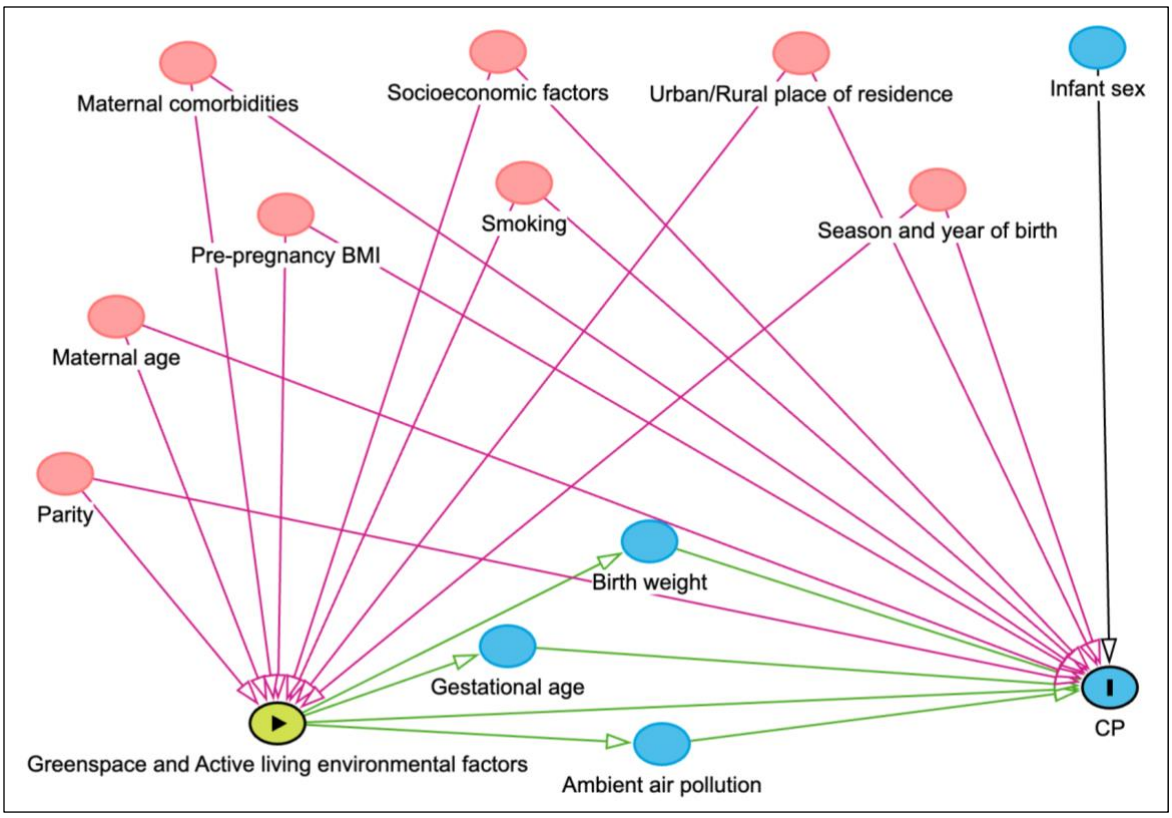
Figure 2. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for CP incidence by quintiles of active living environments (ALE).

Note: The baseline model includes maternal age at delivery, rurality, seasons of birth, birth year, birth weight, parity, residential instability, quintile groups of maternal deprivation, dependency (categorical), and ethnic concentration (categorical).

5.10 Supplementary materials



Supplementary Figure S1. Flowchart of the inclusion and exclusion of the study population.



Supplementary Figure S2. Directed acyclic graph (DAG) for estimating the effect of residential greenspace and active living environmental factors on CP in term births. (1) Nodes: parameters in red are potential confounding factors, and parameters in blue are ancestors of the outcome only (i.e., cause of the outcome but not of the exposure). (2) Edges (arrows): causal relationships. (3) Exposure (focal predictor): residential greenspace and active living environmental factors (i.e., green view index (GVI), normalized difference vegetation index (NDVI), active living environments index (ALE), and park proximity). (4) Response (health outcome): CP in term births.

Supplementary Table S1. Pearson correlation coefficients between continuous greenspace metrics.

	GVI	NDVI	ALE	Park proximity
GVI	1.00			
NDVI	0.11	1.00		
ALE	0.001	-0.26	1.00	
Park proximity	-0.05	-0.17	0.41	1.00

Supplementary Table S2. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of CP per interquartile range (IQR) increase in continuous greenspace metrics.

	HR (95% CI)
NDVI (per IQR = 0.1)	
Baseline model[1]	1.026 (0.979 - 1.075)
+ *Active living environments*[2]	1.021 (0.972 - 1.073)
+ *Air pollution*[3]	1.046 (0.995 - 1.101)
+ *Active living environments & Air pollution*[4]	1.040 (0.987 - 1.096)
GVI (per IQR = 10.05%)	
Baseline model[1]	0.990 (0.947 - 1.037)
+ Active living environments[2]	0.991 (0.947 – 1.038)
+ Air pollution[3]	0.988 (0.942 – 1.037)
+ Active living environments & Air pollution[4]	0.989 (0.943 – 1.038)
Park proximity (per IQR = 0.06)	
Baseline model[1]	0.937 (0.899 - 0.976)
+ *Active living environments*[2]	0.945 (0.904 - 0.987)
+ *Air pollution*[3]	0.939 (0.900 - 0.980)
+ *Active living environments & Air pollution*[4]	0.946 (0.904 - 0.990)

[1]Baseline model includes the following variables: maternal age at delivery, rurality, seasons of birth, birth year, birth weight, parity, residential instability, quintile groups of maternal deprivation, dependency (categorical), and ethnic concentration (categorical).
[2]Includes the baseline model and additional adjustment for Active Living Environments
[3]Includes the baseline model and additional adjustment for air pollution
[4] Includes the baseline model and additional adjustment for Active Living Environments and air pollution
NDVI: Normalized Difference Vegetation Index
GVI: Greenview Index

Supplementary Table S3. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of CP by quintiles of active living environments (ALE).

Model	*ALE quintiles*	HR (95% CI)	P-value for linear trend
Baseline model[1]	*1 (lowest)*	Ref.	<0.0001
	2	1.073 (0.930 - 1.238)	
	3	1.009 (0.867 - 1.172)	
	4	0.885 (0.737 - 1.062)	
	5 (highest)	0.881 (0.706 - 1.101)	
+ Sex of the infant[2]	*1 (lowest)*	Ref.	<0.0001
	2	1.073 (0.930 - 1.238)	
	3	1.001 (0.866 - 1.172)	
	4	0.883 (0.736 - 1.060)	
	5 (highest)	0.879 (0.704 - 1.098)	
+ Air pollution[3]	*1 (lowest)*	Ref.	<0.0001
	2	1.057 (0.911 - 1.226)	
	3	1.013 (0.866 - 1.185)	
	4	0.905 (0.748 - 1.094)	
	5 (highest)	0.880 (0.698 - 1.111)	

[1]Baseline model includes the following variables: maternal age at delivery, rurality, seasons of birth, birth year, birth weight, residential instability, quintile groups of maternal deprivation, dependency (categorical), and ethnic concentration (categorical).

[2] Includes the baseline model and additional adjustment for infant sex.

[3] Includes the baseline model and additional adjustment for air pollution.

Supplementary Table S4. Adjusted hazard ratios (ORs) and 95% confidence intervals (CIs) of CP in continuous greenspace metrics, additionally adjusted for infant sex.

	HR (95% CI)
NDVI (per IQR = 0.1)	1.026 (0.979 - 1.075)
GVI (per IQR = 10.05%)	0.990 (0.946 - 1.037)
Park proximity (per IQR = 0.06)	0.937 (0.899 - 0.976)
ALE quintiles	
1 (lowest)	Ref.
2	1.073 (0.930 - 1.238)
3	1.001 (0.866 - 1.172)
4	0.883 (0.736 - 1.060)
5 (highest)	0.879 (0.704 - 1.098)

All the models were adjusted for maternal age at delivery, rurality, seasons of birth, birth year, birth weight, parity, residential instability, quintile groups of maternal deprivation, dependency (categorical), and ethnic concentration (categorical).
NDVI: Normalized Difference Vegetation Index
GVI: Green View Index
ALE: Active Living Environments

Supplementary Table S5. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between exposure to continuous greenspace metrics and CP stratified by rural/urban residence at birth.

Exposure	Rural		Urban		P-value
	Cohort size (cases)	HR (95% CI)	Cohort size (cases)	HR (95% CI)	
NDVI		1.113 (0.885 - 1.40)		1.029 (0.976 - 1.084)	0.07
GVI		1.010 (0.844 - 1.207)		0.989 (0.943 - 1.037)	0.93
Park proximity		0.981 (0.820 - 1.174)		0.936 (0.898 - 0.975)	0.57
ALE quintiles	59 023 (141)		1 370 206 (2 742)		
1 (lowest)		-		Ref.	
2		-		1.044 (0.895-1.218)	
3		-		0.986 (0.842-1.154)	-
4		-		0.863 (0.715-1.042)	
5 (highest)		-		0.861 (0.686-1.081)	

All the models were adjusted for maternal age at delivery, rurality, seasons of birth, birth year, birth weight, parity, residential instability, quintile groups of maternal deprivation, dependency (categorical), and ethnic concentration (categorical). P-values correspond to the multiplicative interaction term between the exposure and effect modifier (from a separate model).

Supplementary Table S6. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of CP per interquartile range (IQR) increase in continuous greenspace metrics, during the first 6 years of follow-up.

Exposure	Cohort size (cases)	HR (95% CI)
NDVI (per IQR = 0.09)		
Baseline model[1]		1.015 (0.899 - 1.146)
+ *Active living environments*[2]		1.003 (0.885 - 1.374)
+ *Air pollution*[3]		1.005 (0.884 - 1.142)
+ *Active living environments & Air pollution*[4]		0.991 (0.868 - 1.131)
GVI (per IQR = 10.19%)		
Baseline model[1]	294 436 (2 538)	0.989 (0.878 - 1.115)
+ *Active living environments*[2]		0.986 (0.874 - 1.112)
+ *Air pollution*[3]		0.989 (0.872 - 1.122)
+ *Active living environments & Air pollution*[4]		0.986 (0.868 - 1.119)
Park proximity (per IQR = 0.06)		
Baseline model[1]		0.966 (0.871 - 1.071)
+ *Active living environments*[2]		0.984 (0.879 - 1.101)
+ *Air pollution*[3]		0.973 (0.871 - 1.085)
+ *Active living environments & Air pollution*[4]		1.003 (0.891 - 1.128)

[1]Baseline model includes the following variables maternal age at delivery, rurality, seasons of birth, birth year, birth weight, parity, residential instability, quintile groups of maternal deprivation, dependency (categorical), and ethnic concentration (categorical).
[2]Includes the baseline model and additional adjustment for Active Living Environments
[3]Includes the baseline model and additional adjustment for air pollution
[4] Includes the baseline model and additional adjustment for Active Living Environments and air pollution
NDVI: Normalized Difference Vegetation Index
GVI: Greenview Index

Supplementary Table S7. Association between increasing quartiles of greenness and CP during gestation.

Greenspace measure		HR (CI %)	P-value for linear trend
NDVI	*Quartile 1 (NDVI: 0.09-0.65)*	Ref.	<0.0001
	Quartile 2 (NDVI: 0.66-0.71)	1.074 (0.970-1.189)	
	Quartile 3 (NDVI: 0.72-0.75)	1.091 (0.956-1.224)	
	Quartile 4 (NDVI: 0.76-1.0)	1.316 (0.977-1.671)	
GVI	*Quartile 1(GVI: 0.00-7.92)*	Ref.	<0.0001
	Quartile 2 (GVI: 7.93-12.18)	0.965 (0.869-1.071)	
	Quartile 3(GVI: 12.19-17.97)	0.966 (0.870-1.073)	
	Quartile 4 (GVI: 17.98-93.19)	0.998 (0.899-1.108)	

All the models were adjusted for maternal age at delivery, rurality, seasons of birth, birth year, birth weight, parity, residential instability, quintile groups of maternal deprivation, dependency (categorical), and ethnic concentration (categorical).
NDVI: Normalized Difference Vegetation Index
GVI: Green View Index

5.11 References

1. Appleton RE, Gupta R. Cerebral palsy: not always what it seems. *Arch Dis Child*. 2019;104(8):809-814. doi:10.1136/archdischild-2018-315633

2. Patel DR, Neelakantan M, Pandher K, Merrick J. Cerebral palsy in children: a clinical overview. *Transl Pediatr*. 2020;9(Suppl 1):S125-S12S135. doi:10.21037/tp.2020.01.01

3. Zhang Y, Hu Y, Talarico R, et al. Prenatal Exposure to Ambient Air Pollution and Cerebral Palsy. *JAMA Netw Open*. 2024;7(7):e2420717. doi:10.1001/jamanetworkopen.2024.20717

4. Yang BY, Zhao T, Hu LX, et al. Greenspace and human health: An umbrella review. *The Innovation*. 2021;2(4):100164. doi:10.1016/j.xinn.2021.100164

5. Slawsky ED, Hajat A, Rhew IC, et al. Neighborhood greenspace exposure as a protective factor in dementia risk among U.S. adults 75 years or older: a cohort study. *Environ Health*. 2022;21(1):14. doi:10.1186/s12940-022-00830-6

6. Pagalan L, Oberlander TF, Hanley GE, et al. The association between prenatal greenspace exposure and Autism spectrum disorder, and the potentially mediating role of air pollution reduction: A population-based birth cohort study. *Environ Int*. 2022;167:107445. doi:10.1016/j.envint.2022.107445

7. Juul V, Nordbø ECA. Examining activity-friendly neighborhoods in the Norwegian context: green space and walkability in relation to physical activity and the moderating role of perceived safety. *BMC Public Health*. 2023;23(1):259. doi:10.1186/s12889-023-15170-4

8. Tran I, Sabol O, Mote J. The Relationship Between Greenspace Exposure and Psychopathology Symptoms: A Systematic Review. *Biol Psychiatry Glob Open Sci*. 2022;2(3):206-222. doi:10.1016/j.bpsgos.2022.01.004

9. Diener A, Mudu P. How can vegetation protect us from air pollution? A critical review on green spaces' mitigation abilities for air-borne particles from a public health perspective - with implications for urban planning. *Sci Total Environ*. 2021;796:148605. doi:10.1016/j.scitotenv.2021.148605

10. Taylor L, Hochuli DF. Defining greenspace: Multiple uses across multiple disciplines. *Landsc Urban Plan*. 2017;158:25-38. doi:10.1016/j.landurbplan.2016.09.024

11. Kabisch N, Alonso L, Dadvand P, van den Bosch M. Urban natural environments and motor development in early life. *Environ Res*. 2019;179:108774. doi:10.1016/j.envres.2019.108774

12. Liao J, Zhang B, Xia W, et al. Residential exposure to green space and early childhood neurodevelopment. *Environ Int*. 2019;128:70-76. doi:10.1016/j.envint.2019.03.070

13. Hu CY, Yang XJ, Gui SY, et al. Residential greenness and birth outcomes: A systematic review and meta-analysis of observational studies. *Environ Res*. 2021;193:110599. doi:10.1016/j.envres.2020.110599

14. Gascon M, Cirach M, Martínez D, et al. Normalized difference vegetation index (NDVI) as a marker of surrounding greenness in epidemiological studies: The case of Barcelona city. *Urban For Urban Green*. 2016;19:88-94. doi:10.1016/j.ufug.2016.07.001

15. Kumakoshi Y, Chan SY, Koizumi H, Li X, Yoshimura Y. Standardized Green View Index and Quantification of Different Metrics of Urban Green Vegetation. *Sustainability*. 2020;12(18):7434. doi:10.3390/su12187434

16. Tobin M, Hajna S, Orychock K, et al. Rethinking walkability and developing a conceptual definition of active living environments to guide research and practice. *BMC Public Health*. 2022;22(1):450. doi:10.1186/s12889-022-12747-3

17. ICES. ICES | Our Organization | Mission, Vision & Values. ICES. Accessed April 26, 2023. https://www.ices.on.ca/our-organization/mission-and-vision/

18. Murphy MSQ, Fell DB, Sprague AE, et al. Data Resource Profile: Better Outcomes Registry & Network (BORN) Ontario. *Int J Epidemiol*. 2021;50(5):1416-1425. doi:10.1093/ije/dyab033

19. Brook JR, Setton EM, Seed E, et al. The Canadian Urban Environmental Health Research Consortium – a protocol for building a national environmental exposure data platform for integrated analyses of urban form and health. *BMC Public Health*. 2018;18(1):114. doi:10.1186/s12889-017-5001-5

20. Gandhi GM, Parthiban S, Thummalu N, Christy A. Ndvi: Vegetation Change Detection Using Remote Sensing and Gis – A Case Study of Vellore District. *Procedia Comput Sci*. 2015;57:1199-1210. doi:10.1016/j.procs.2015.07.415

21. Gorelick N, Hancher M, Dixon M, Ilyushchenko S, Thau D, Moore R. Google Earth Engine: Planetary-scale geospatial analysis for everyone. *Remote Sens Environ*. 2017;202:18-27. doi:10.1016/j.rse.2017.06.031

22. Lavigne E, Shin H, Murphy M, Abdulaziz K, Wen SW. Early Life Exposure to Greenspace and Autism Spectrum Disorder and the Mediating Effects of Air Pollution in Ontario, Canada. *ISEE Conf Abstr*. Published online September 18, 2022. doi:10.1289/isee.2022.O-OP-207

23. Ross N, Wasfi R, Herrmann T, Gleckner W. Canadian Active Living Environments Database (Can-ALE) User Manual. Published online 2018.

24. Elten M, Benchimol EI, Fell DB, et al. Residential Greenspace in Childhood Reduces Risk of Pediatric Inflammatory Bowel Disease: A Population-Based Cohort Study. *Off J Am Coll Gastroenterol ACG*. 2021;116(2):347. doi:10.14309/ajg.0000000000000990

25. Markevych I, Schoierer J, Hartig T, et al. Exploring pathways linking greenspace to health: Theoretical and methodological guidance. *Environ Res*. 2017;158:301-317. doi:10.1016/j.envres.2017.06.028

26. Akpinar A, Barbosa-Leiker C, Brooks KR. Does green space matter? Exploring relationships between green space type and health indicators. *Urban For Urban Green*. 2016;20:407-418. doi:10.1016/j.ufug.2016.10.013

27. Dzhambov AM, Browning MHEM, Markevych I, Hartig T, Lercher P. Analytical approaches to testing pathways linking greenspace to health: A scoping review of the empirical literature. *Environ Res*. 2020;186:109613. doi:10.1016/j.envres.2020.109613

28. Sun Y, Sheridan P, Laurent O, et al. Associations between green space and preterm birth: windows of susceptibility and interaction with air pollution. *Environ Int*. 2020;142:105804. doi:10.1016/j.envint.2020.105804

29. Esih K, Trunk T, Osredkar D, et al. The impact of birthweight on the development of cerebral palsy: A population-based matched case-control study. *Early Hum Dev*. 2022;165:105533. doi:10.1016/j.earlhumdev.2021.105533

30. Klompmaker JO, Laden F, Browning MHEM, et al. Associations of Greenness, Parks, and Blue Space With Neurodegenerative Disease Hospitalizations Among Older US Adults. *JAMA Netw Open*. 2022;5(12):e2247664. doi:10.1001/jamanetworkopen.2022.47664

31. Yu H, Zhou Y, Wang R, et al. Associations between trees and grass presence with childhood asthma prevalence using deep learning image segmentation and a novel green view index. *Environ Pollut*. 2021;286:117582. doi:10.1016/j.envpol.2021.117582

32. Lavigne É, Abdulaziz KE, Murphy MSQ, et al. Associations of neighborhood greenspace, and active living environments with autism spectrum disorders: A matched case-control study in Ontario, Canada. *Environ Res*. 2024;252:118828. doi:10.1016/j.envres.2024.118828

33. Taliento C, Piccolotti I, Sabattini A, et al. Effect of Physical Activity during Pregnancy on the Risk of Hypertension Disorders and Gestational Diabetes: Evidence Generated by New RCTs and Systematic Reviews. *J Clin Med*. 2024;13(8):2198. doi:10.3390/jcm13082198

34. Witvrouwen I, Mannaerts D, Van Berendoncks AM, Jacquemyn Y, Van Craenenbroeck EM. The Effect of Exercise Training During Pregnancy to Improve Maternal Vascular Health: Focus on Gestational Hypertensive Disorders. *Front Physiol*. 2020;11. doi:10.3389/fphys.2020.00450

35. van den Heuvel MI. From the Womb into the World: Protecting the Fetal Brain from Maternal Stress During Pregnancy. *Policy Insights Behav Brain Sci*. 2022;9(1):96-103. doi:10.1177/23727322211068024

36. Xing Y, Brimblecombe P. Urban park layout and exposure to traffic-derived air pollutants. *Landsc Urban Plan*. 2020;194:103682. doi:10.1016/j.landurbplan.2019.103682

37. Dadvand P, de Nazelle A, Triguero-Mas M, et al. Surrounding Greenness and Exposure to Air Pollution During Pregnancy: An Analysis of Personal Monitoring Data. *Environ Health Perspect*. 2012;120(9):1286-1290. doi:10.1289/ehp.1104609

38. Hazlehurst MF, Carroll KN, Loftus CT, et al. Maternal exposure to PM2.5 during pregnancy and asthma risk in early childhood. *Environ Epidemiol*. 2021;5(2):e130. doi:10.1097/EE9.0000000000000130

39. Salam MT, Millstein J, Li YF, Lurmann FW, Margolis HG, Gilliland FD. Birth Outcomes and Prenatal Exposure to Ozone, Carbon Monoxide, and Particulate Matter: Results from the

Children's Health Study. *Environ Health Perspect*. 2005;113(11):1638-1644. doi:10.1289/ehp.8111

40. Klompmaker JO, Hoek G, Bloemsma LD, et al. Associations of combined exposures to surrounding green, air pollution and traffic noise on mental health. *Environ Int*. 2019;129:525-537. doi:10.1016/j.envint.2019.05.040

Ch. 6 Discussion

6.1 Summary of thesis objectives and scope

CP is a complex neurological disorder with various proposed etiological factors, including genetic predispositions, prenatal and perinatal complications. In the context of environmental epidemiology, the role of environmental factors, such as air pollution, greenspace, and ALE exposures, have not been extensively studied in the etiology of CP. While several epidemiological studies have explored the relationship between environmental exposures and neurological disorders, such as ASD and ADHD, the specific context of CP remains highly under-researched.

This thesis aimed to fill this gap by investigating the relationship between prenatal exposure to various environmental factors—including $PM_{2.5}$ mass, specific $PM_{2.5}$ components (SO_4, NH_4, NO_3, SS, BC, dust, OM), O_3, NO_2, NDVI, GVI, park proximity, and Can-ALE—and the risk of CP as reflected in birth outcomes. By focusing on both air pollution and greenspace, this research provides a comprehensive analysis of how these environmental factors may contribute to the multifactorial development of CP, offering novel insights into potential pathways and mechanisms. The integration of both harmful and protective environmental exposures provides a balanced perspective on the environmental determinants of CP, offering a more holistic understanding of the factors that may influence its development. This research is particularly timely, given the increasing global concern about the impact of environmental factors on public health, and it contributes valuable data to the limited but growing body of literature on the environmental determinants of neurological disorders. Gestational exposures to air pollutants and CP risk were explored in Chapter 4, while gestational exposures to greenspaces, ALEs and CP risk were investigated in Chapter 5.

6.2 Summary of thesis findings

6.2.1 Objective 1: Air Pollution and CP

The first objective, explored in chapter 4, examined the association between CP risk and gestational exposure to both total $PM_{2.5}$ mass and its individual component composition (SO_4, NH_4, NO_3, SS, BC, dust, OM). Additional gestational exposure to air pollutants, such as NO_2 and O_3, were also assessed for their potential associations with CP risk. To account for potential confounding, both single-pollutant and $PM_{2.5}$ residual-adjusted models were employed in the analyses. From the analysis, we found a consistent association between SO_4 exposure during the early gestational period and increased CP risk across all models. While slight increased associations were found for gestational exposure to mineral dust, these associations were found to be inconsistent between models, and thus could not be confidently interpreted as robust or significant findings. Additionally, no significant associations were found between overall pregnancy exposure to $PM_{2.5}$, NO_2 and O_3.

6.2.2 Objective 2: Greenspaces, active living environments, and CP

The second objective, explored in chapter 5, examined the association between greenspaces (measured by NDVI and GVI at birth as a proxy of prenatal exposures), ALEs (measured by park proximity and Can-ALE at birth as a proxy of prenatal exposures), and the risk of CP. In this study, a slight protective effect was observed for residential proximity to parks at birth, suggesting that living closer to parks may be associated with reduced CP risk. However, no significant associations were found between gestational exposure to greenspace metrics in either continuous or categorical analyses, nor for indicators of Can-ALE.

6.3 Integrative synthesis of findings

6.3.1 Existing literature on air pollution and CP risk

Currently, very limited research exists on the associations between environmental factors and the risk of CP during the gestational period. Only one recent study by Zhang et al. was found

looking at the association between air pollution measures during gestation and CP risk.[1] This was a retrospective cohort study conducted from the years 2002 to 2017, looking at the associations between $PM_{2.5}$, NO_2, and O_3, in an Ontarian population. Overall, a cohort of 1 587 935 was obtained, of which 3 170 (0.2%) were diagnosed with CP during the follow-up period. The researchers found an association of 1.12 (95% CI: 1.03-1.21) per IQR (2.7 $\mu g/m^3$) increase in prenatal ambient $PM_{2.5}$ concentration and CP, suggesting that $PM_{2.5}$ may play a significant role in influencing neurodevelopment and increasing the likelihood of CP. Overall, no significant associations were found with NO_2 and O_3. Results from this paper were contradicting to the findings in chapter 4, which found null associations between overall prenatal $PM_{2.5}$ exposure and CP risk (HR: 1.015, 95% CI: 0.936-1.102). These differences may be attributed to variations in study design, such as differences in cohort characteristics, time periods of exposure assessment, and the covariates controlled for in each analysis. Changes in air pollution levels over time or differences in the underlying health profiles of the populations studied could further explain these discrepancies. Despite these methodological differences however, the conflicting results highlight the complexity of understanding the impact of air pollution on neurodevelopmental disorders like CP and the need for further research in this area. While the significance of overall $PM_{2.5}$ and CP risk HRs were contradicting between the Zhang et al. paper and the findings of this thesis, no sensitive windows were found in both studies when assessing the weekly associated HRs and Cis for gestational $PM_{2.5}$.

Another similarity with the Zhang et al. paper were the non-significant associations found between NO_2, O_3, and CP risk across models in chapter 4. While no other studies exist on the associations between NO_2, O_3, and CP risk, this finding contradicts the broader literature, where NO_2 and O_3 have been found to be significantly associated with neurodevelopmental disorders.

Several studies have demonstrated links between prenatal NO_2 exposure and conditions such as ASD, cognitive impairment, and motor delays. For instance, a meta-analysis found that prenatal exposure to NO_2 increased the risk of ASD, highlighting that traffic-related air pollutants could have detrimental effects on neurodevelopment.[2] Additionally, a study conducted on a cohort in Southern California showed that exposure to NO_2 was associated with motor function impairments in infants, especially among males.[3] Similarly, one study found that prenatal exposure to higher O_3 concentrations during the later pregnancy period was linked to an increased risk of ASD, but not for girls.[4] Another investigation into the effects of O_3 on cognitive development showed reduced cognitive function in children exposed to higher levels of O_3 during pregnancy.[5,6] Despite these findings in the literature, both analyses in the Zhang et al. paper and chapter 4 did not find significant associations with CP risk, which may be attributed to differences in levels of air pollutant exposures between the study regions, limited statistical power in our studies due to the number of CP cases, or the differing confounders that were adjusted for.

Furthermore, when stratifying the analysis by infant sex, exposure to $PM_{2.5}$ concentrations for boys (HR_{boys}: 1.14, 95% CI: 1.03-1.26) were found to have slightly increased CP risk compared to girls (HR_{girls}: 1.08, 95% CI: 0.96-1.22) in the Zhang et al. paper. The findings from the infant-sex stratified analysis in chapter 4 followed a similar pattern for overall $PM_{2.5}$ exposure (HR_{boys}: 1.038, 95% CI: 0.931-1.155, and HR_{girls}: 0.994, 95% CI: 0.874-1.13), though the associations were not found to be significant. These findings are consistent with the literature that reports higher rates of CP diagnoses in boys.[7] These sex differences can be explained by several biological and environmental factors. One suggested theory may be that male fetuses are more vulnerable to adverse prenatal conditions, such as hypoxia or inflammation, due to their slower brain maturation and higher metabolic rates compared to females.[8,9] This developmental delay may leave male

fetuses less equipped to handle neurodevelopmental stressors, making them more susceptible to CP. Additionally, differences in sex hormones, particularly estrogen, may provide neuroprotective benefits to female fetuses, further contributing to the higher incidence of CP among boys.[10]

Overall, a notable finding in this thesis was the association between early gestational SO_4 exposure and CP risk. To date, there is limited literature that directly investigates the relationship between SO_4 exposure during pregnancy and the risk of CP, thus comparing the findings to existing studies is challenging and warrants caution in interpretation. However, the relationship between SO_4 and neurodevelopmental disorders has been studied and may be able to explain the findings in this thesis. One study by Chiu et al. investigating prenatal ambient air pollutant mixture exposure and neurodevelopment in a cohort of children living in urban settings in the United States, found that after assessing all seven components in the air pollution mixture, the pollutants that were linked to traffic, such as NO_2, organic carbon (OC), elemental carbon (EC), and SO_4, were most associated with reduced memory function and inattentiveness in the cohort.[11] Another cross-sectional study found short term SO_4 exposure to be associated with epigenetic modifications of mitogen-activated protein kinase (MAPK) pathway genes.[12] The MAPK pathway is crucial for processes such as cellular signaling, cell growth, differentiation, and apoptosis.[13,14] This pathway plays a crucial role in responding to environmental stressors, including exposure to air pollutants like SO_4. These epigenetic modifications, can then lead to altered gene expression, potentially impacting how cells respond to environmental exposures during critical periods of development, increasing susceptibility to neurodevelopmental disorders, such as CP. Furthermore, a systematic review investigating various air pollutants found SO_4 to be associated with both adverse cardiovascular health and respiratory health outcomes, indicating its broad impact on multiple organ systems. These findings suggest that SO_4 may contribute to increased oxidative stress and

inflammation, which are central mechanisms in the development of cardiovascular diseases, such as hypertension and heart disease, as well as respiratory conditions, such as asthma and chronic obstructive pulmonary disease (COPD).[15–18]

Overall, while the findings in chapter 4 were both novel and, at times, inconsistent with existing literature, further research is crucial to deepen our understanding of the relationship between air pollutants—particularly SO_4—and human health. Additional studies are needed to clarify these associations, replicate the results, and explore the underlying mechanisms by which SO_4 exposure may contribute to a range of adverse health outcomes, including CP risk.

6.3.2 Existing literature on greenspaces and CP risk

No published studies were found looking at the association between exposure to greenspaces or ALEs during gestation and CP risk, thus the findings in chapter 5 are novel and should be interpreted with caution. While there is no direct literature on CP, existing studies have explored the relationship between greenspace exposure and various other birth outcomes and neurodevelopmental disorders, such as ASD, ADHD, and cognitive development.[19–21] These studies generally suggest that increased exposure to greenspaces during pregnancy can have protective effects on neurodevelopment, likely due to factors such as reduced pollution, increased physical activity, and lower maternal stress.[22]

While the analyses in chapter 5 did not find any significant associations between greenspace measures (NDVI and GVI), previous studies have shown that higher NDVI values, which represent greater vegetation density, are associated with improved cognitive development, lower risk of behavioral problems, and better mental health in children.[23,24] One national cohort study assessing the risk of prenatal NDVI exposure and risk of ASD and ADHD in children found a positive and significant association for ASD (HR: 1.07, 95% CI: 1.03-1.14) per IQR (0.121) increase, but not

for ADHD.[25] Interestingly, most greenspace studies in the literature use NDVI for their greenspace metric, limiting findings that might be uncovered with the use of GVI. While NDVI provides a useful measure of overall vegetation density and health across broad areas, it may not fully capture the nuanced ways in which individuals interact with and perceive greenspace. GVI has been found to be linked with childhood asthma in a study by Yu et al., which found an increase in odds for asthma diagnosed by a doctor (OR: 1.04, 95% CI: 1.00-1.08), and current asthma (OR: 1.08, 95% CI: 1.02-1.14) per IQR increase in GVI_{800m} for grass.[26] In contrast, a matched case-control study done in Ontario, Canada investigating the associations between greenspaces and ASD did not find significant associations between GVI and ASD risk (OR: 1.015, 95% CI: 0.948-1.082, per 9.45%), similar to results from chapter 5.[27]

Overall, differences between the non-significant findings for NDVI and GVI in this thesis compared to the literature may be attributed to several factors such as, variations in study design, including differences in sample size, geographic location, and data collection methods. Additionally, the context-specific characteristics of the study area, such as local environmental conditions or socio-economic factors, could play a role in moderating the relationship between greenspace metrics and health outcomes. The differing time frames may also impact the significance of the findings.

Chapter 5 also explored novel associations between active living environments and CP risk. The literature on active living environments and health outcomes generally focuses on factors such as physical activity, mental health, and stress reduction, however other health outcomes have also been studied. One study by Mah et al. found a decreased risk of cardiometabolic causes in women who were in higher ALE quintiles (HR: 0.78, 95% CI: 0.63-0.97).[28] Interestingly, the previously mentioned matched case-control study by Lavigne et al. found significant increased risk for ASD

when compared to a reference (quintile 1) in a baseline model, with an OR of 1.386 in quintile 2 (95% CI: 1.017-1.890), 1.843 in quintile 3 (95% CI: 1.372-2.476), and 3.165 in quintile 4 (95% CI: 2.347-4.270). In contrast, the highest quintile (quintile 5) had a lowered risk compared to the previous quintile, with an odds of 1.881 (95% CI: 1.343-2.634).[27] This differs from the results in chapter 5 which followed a linear decreasing risk pattern with each increasing ALE quintile, however these associations were not significant.

While no significant associations between Can-ALE and CP risk were found in chapter 5, a potential protective association with park proximity was observed. In the literature, park proximity is associated with multiple positive health outcomes, such as improved mental health, enhanced physical activity, and reduced stress levels.[29–31] One study done by Reuben at al. in 2020 found children who did not have parks in the neighborhood were less likely to be active (OR: 1.36, 95% CI: 1.24-1.48), have increased screen-time (OR: 1.19, 95% CI: 1.14-1.25), and have inadequate sleep (OR: 1.23, 95% CI: 1.18-1.29). In addition to behavioural effects, this lack of park presence was also associated with childhood obesity (OR: 1.32, 95% CI:1.21-1.43) and a being diagnosed with ADHD (OR: 1.20, 95% CI: 1.12-1.29).[32] When assessing the prenatal period, one study found increased distances to parks to be associated with an increase in preterm birth risk and a decrease in GA, both of which are contributors to CP risk.[33,34] However, it is important to note the findings on park proximity and CP risk in chapter 5 are novel and should be interpreted with caution as well. The measure of park proximity in various studies, including Chapter 5, does not take into consideration actual use of the park by residents, and thus might not accurately depict greenspace exposures and active lifestyles. Future research should consider incorporating more detailed measures of park usage, accessibility, and the perceived quality of parks to better understand the relationship between greenspace exposure and health outcomes, including those related to CP risk.

This can be done through mixed research methods, combining quantitative and qualitative approaches to provide a more comprehensive understanding of greenspace exposure and its impact on health. For instance, quantitative methods such as geographic information system mapping and distance measures for park proximity can be complemented by surveys or interviews that assess park usage, perceived safety, and accessibility. Additionally, direct observational studies or the use of wearable technology (e.g., GPS trackers or activity monitors) could capture accurate greenspace interaction and physical activity levels. Incorporating community input through participatory research could also help identify barriers to park use and provide valuable context on how different populations experience and benefit from greenspaces.

6.3.3 Dual role of environmental exposures

Overall, both the literature and this thesis have reinforced the dual role that environmental factors play in shaping human health. These findings highlight how environmental exposures can act as both risk factors and protective elements, depending on their nature and context. On one hand, harmful exposures such as air pollution, which includes $PM_{2.5}$ and SO_4, may be linked to adverse pregnancy outcomes and risk factors which may influence CP risk. On the other hand, protective environmental factors, such as access to greenspace, may offer a buffering effect. The presence of nearby parks or natural areas might help mitigate some of the risks associated with urban living and pollution exposure. However, the interaction between these harmful and protective factors is complex. For instance, while greenspace might offer benefits, it may not fully counteract the detrimental effects of severe air pollution. Understanding this dual role—where environmental exposures can simultaneously pose risks and offer protection—is crucial for developing more effective interventions to reduce CP risk and improve maternal and child health outcomes.

6.3.4 Potential biological mechanisms

Based on existing research and the literature, several potential biological mechanisms could explain how environmental exposures influence CP risk and the overall findings of this thesis.

As mentioned previously, one of the primary pathways in which air pollutants are suspected to influence health, including the risk of CP, is through inflammation and oxidative stress. Pollutants such as $PM_{2.5}$ and SO_4, can enter the maternal bloodstream through inhalation into the lungs, triggering a systemic inflammatory response.[35] This response not only causes inflammation but also leads to the production of reactive oxygen species (ROS), which may lead to increased oxidative stress.[36,37] These oxidative molecules can damage cells and tissues, particularly in sensitive areas such as the placenta and the developing fetal brain.[38] Inflammation and oxidative stress can impair placental function, reducing the supply of oxygen and nutrients to the fetus, which may potentially lead to fetal hypoxia.[39,40] This reduction in oxygen, especially during critical periods of neurodevelopment, can result in white matter damage or other brain injuries that are strongly linked to CP.[41] Endocrine disruption may also play a role, as some pollutants may have the ability to interfere with hormone regulation during pregnancy.[42,43] This disruption could affect brain development and neurogenesis, particularly during early gestation when critical brain structures are forming. Another mechanism involves vascular dysfunction, where environmental toxins can negatively impact blood flow in both the mother and fetus.[44] Compromised blood flow to the developing brain may increase the risk of hemorrhagic events or damage to brain regions responsible for motor control, further elevating the likelihood of CP.[45] Additionally, environmental exposures may induce epigenetic modifications which can potentially alter gene expression patterns. These epigenetic changes, such as DNA methylation or histone

modification, could affect genes responsible for brain development, potentially predisposing the fetus to neurodevelopmental disorders like CP.[46–48] Overall, the mechanisms through which air pollution impacts CP risk are complex, involving various biological processes that may disrupt fetal development and increase vulnerability to adverse outcomes.

Similarly, the protective effects of greenspaces may also be explained by various biological mechanisms. While air pollutants may induce stress and inflammation, one potential mechanism of greenspaces is the reduction in stress and inflammation. Greenspaces and parks have been shown to lower stress levels by providing a calming environment and opportunities for relaxation.[49] Reduced stress can decrease the production of stress hormones such as cortisol, which, when elevated, can lead to systemic inflammation.[50,51] Lower systemic inflammation and stress can improve maternal health and placental function, potentially reducing the risk of adverse pregnancy outcomes that are associated with CP.[52] Additionally, regular exposure to greenspaces can enhance mental well-being by alleviating symptoms of anxiety and depression.[53] Often parks are seen as places of socialization and community. These calming effects of natural environments are linked to improved mood and cognitive function.[54] Subsequently, better maternal mental health is associated with healthier pregnancy outcomes, which may lower the risk of neurodevelopmental disorders in the fetus, including CP.[55] Furthermore, greenspaces and ALEs also help by encouraging physical activities such as walking, jogging, or recreational sports. Increased physical activity is beneficial for maintaining a healthy weight, managing blood pressure, and improving overall cardiovascular health.[56] In the literature, physical activity during pregnancy has been linked with positive aspects of fetal development and can reduce the likelihood of complications such as preterm birth or low birth weight, which are risk factors for CP.[57] Interestingly, one notable mechanism through which the protective effects of greenspaces may be explained is through the

improvement of air quality. The literature has shown that greenspaces can contribute to better air quality by reducing urban heat island effects and filtering air pollutants through vegetation.[58,59] The urban heat island effect exacerbates temperatures in cities, leading to increased energy consumption for cooling and heightened air pollution levels. These elevated temperatures can worsen heat-related health issues, such as heat exhaustion and heat stroke, and may contribute to adverse health effects.[60] In general, cleaner air reduces exposure to harmful air pollutants that can negatively affect maternal and fetal health, which can mitigate some of the risks associated with pollution-related inflammation and oxidative stress, potentially lowering the risk of CP.

Overall, the biological mechanisms linking environmental exposures to CP involve a complex interplay of inflammation, oxidative stress, neurodevelopmental disruption, and systemic factors. Understanding these mechanisms highlights the importance of addressing both environmental risks and benefits to improve prenatal health outcomes and reduce the risk of CP.

6.4 Generalizability of findings

The generalizability of the findings from this thesis is an important consideration. Given the use of large, population-based administrative cohorts and an extensive study period, the results may be representative of similar populations. Since the studies in chapter 4 and 5 were conducted in Ontario, Canada, the findings may be generalizable to similar Canadian populations. However, the specific demographic, environmental, and healthcare characteristics of Ontario may limit the applicability of the results to other regions and countries. Exposure to air pollutants and greenspaces may differ in countries due to variations in industrial activities, transportation systems, urban planning, and environmental policies. Similarly, the availability and quality of greenspaces are influenced by urban design, green infrastructure investments, and regional policies

that promote or restrict access to parks and recreational areas. Thus, due to these differences, caution should be exercised when interpreting these findings in the context of other populations.

6.5 Strengths

This thesis significantly contributes to the field of environmental epidemiology by helping fill in the gap in the existing literature of environmental influences on the risk of CP. By building upon and validating prior research, this thesis adds a valuable layer to this novel area of study. The various strengths in this thesis will be highlighted in this section.

One major strength of this thesis was the use of large population-based administrative cohorts. By leveraging data from ICES, we were able to access comprehensive, high coverage, and high-quality data on patient-level health outcomes, demographics, and diagnoses. With a source cohort of over 2 million mother-infant pairs, the statistical power to detect associations between environmental exposure and CP was enhanced, even for relatively rare cases. The richness of the ICES health administrative data allowed for detailed control of important confounders, such as socioeconomic indicators, maternal health conditions, and birth characteristics, which allowed for robust analysis. In addition, the longitudinal nature of the data also made it possible to track health outcomes over time, ensuring that exposure assessments and health diagnoses over the follow-up period were accurately aligned within the study period, which are critical for understanding the development of CP.

Another major strength of this thesis was the use of a large study period. Spanning retrospectively over almost two decades, this extended timeframe allowed us to analyze extensive air quality and greenspace data regarding CP risk, that may not be feasible in studies with shorter timeframes. This may help strengthen the consistency and reliability of the findings, further supporting the generalizability of the research to other settings and contexts.

In addition to the lengthy study period, the use of time-varying air pollution data in chapter 4 added a significant strength to this thesis. By incorporating weekly and bi-weekly air pollution exposure measures that change over time, rather than relying on static or cross-sectional data, we were able to more accurately capture participants' real-world exposure across different stages of pregnancy. This approach allows for a more dynamic understanding of how fluctuations in air pollution levels, influenced by factors such as seasonal variations, policy changes, and shifts in industrial activity, could impact maternal and fetal health. Time-varying data also enhances the precision of exposure assessments, particularly in identifying critical windows of vulnerability, such as specific trimesters or gestational weeks where the fetus may be more sensitive to environmental stressors. This method strengthens the ability to draw meaningful conclusions about the relationship between air pollution and CP risk while accounting for both short- and long-term exposure effects in this thesis.

The use of different greenspace metrics in chapter 5 of this thesis was another notable strength, as it allowed for a more nuanced assessment of the relationship between natural environments and CP risk. By incorporating multiple measures—such as the NDVI, GVI, Can-ALE, and park proximity—we captured diverse aspects of greenspace and active living exposures. Each metric offers a unique perspective on how individuals may experience and interact with greenspace in their daily lives. Most greenspace studies in the literature rely heavily on NDVI as their primary measure of greenspace exposure, and rarely consider ALEs. NDVI is widely used because it is easily accessible and provides a broad, satellite-based estimate of overall vegetation density in a given area. However, NDVI has limitations as it does not capture the quality, accessibility, or visibility of greenspace from a ground-level perspective. It simply reflects the presence of vegetation, without considering how individuals actually interact with or benefit from

it. This reliance on NDVI can overlook other important dimensions of greenspace, such as park proximity or the amount of greenery visible in everyday environments, which might play a crucial role in health outcomes. By focusing primarily on NDVI, many studies may miss potential nuances in the relationship between greenspace and health that could be uncovered by using alternative metrics, like GVI. Using these complementary metrics provided a more comprehensive understanding of how different types of greenspaces may influence maternal health and fetal development. This multi-faceted approach enhances the robustness of the findings in chapter 5, as it considers a holistic approach to the protective effects of greenspaces on health and potential pathways for mitigating CP risk.

Finally, the robust analysis techniques employed in this thesis, including the use of cox proportional hazards models and DLNMs, significantly enhance the rigor and depth of the findings. The application of DLNMs in chapter 4 enabled the exploration of complex, non-linear relationships between environmental exposures and CP, accounting for potential delayed effects and interactions over time. By modeling the cumulative effects of exposures across different gestational periods, DLNMs provided insights into how varying levels of environmental stressors at different stages of pregnancy influence CP risk. This approach allowed for a more precise identification of critical windows, which are key to understanding the timing and duration of exposure that could be most detrimental or protective, thereby enhancing the overall interpretation of the relationship between environmental factors and CP risk.

In summary, the strengths of this thesis lie in its ability to contribute to existing and novel knowledge, the inclusion of a substantial study population, its consideration of time-varying data, its innovative exploration of greenspace exposures, and the application of robust statistical techniques, collectively enhancing the strength and significance of the research findings.

6.6 Limitations

While various strengths of this thesis have been highlighted, several limitations in the thesis also exist which must be considered when interpreting the findings. As such, it is important to note that the findings of this thesis should be cautiously interpreted and validated through further studies. The various limitations in this thesis will be highlighted in this section.

A key limitation in this thesis is the uncertainty surrounding the accuracy of the code algorithm used to identify CP cases from the administrative data. While the algorithm has been employed in prior research, the sensitivity and specificity of the CP coding have not been thoroughly validated. This raises important questions about its performance, such as how accurately it identifies true CP cases (sensitivity) and how many false positives it may generate (specificity). Additionally, there is a concern about how many true CP cases are missed due to misclassification or coding errors. Since CP is often misdiagnosed in clinical practice, these coding inaccuracies could introduce significant bias into the study's results, potentially impacting the reliability of the findings. Given the reliance on administrative data, future research should explore ways to validate the CP code algorithm and assess its accuracy to ensure more precise identification of cases and stronger interpretations of the study outcomes.

In addition, this thesis did not differentiate between the various types of CP in the analyses, and instead focused on CP as an overall outcome. As mentioned in chapter 1, CP is a heterogeneous condition with multiple subtypes, including spastic, dyskinetic, ataxic, and mixed types, each of which may have different etiologies, risk factors, and clinical presentations. By grouping all types of CP together, the thesis may have missed important nuances in the relationship between environmental exposures and specific CP subtypes. For example, some environmental factors may be more strongly associated with certain types of CP, while having little or no impact on others.

Failing to assess the distinct types of CP limits the ability to explore potential differential effects and may lead to an underestimation or overestimation of certain associations. Future research could benefit from a more granular analysis that distinguishes between CP subtypes, offering a clearer understanding of how specific environmental exposures influence different forms of the disorder.

Another notable limitation for this thesis is the potential for exposure misclassification in the data. Environmental exposures, such as air pollution and greenspaces, were estimated using geographic proxies and satellite-derived metrics, which may not accurately reflect the true exposure levels experienced by individuals.

For example, this thesis assigned exposures to mother-infant pairs based on residential postal codes, meaning that only exposures occurring at the home address were considered for air pollution, greenspace, and ALEs. This approach does not capture potential exposures that individuals may experience outside their immediate residential area, such as at their place of employment, school, or during daily commutes. As a result, any time spent in environments with differing levels of pollution or greenspace, such as traffic-heavy areas or industrial zones, is not accounted for. This limitation could lead to exposure misclassification, as the true environmental exposure experienced by the mother-infant pair may differ from what was estimated based on the home postal code alone. Additionally, the reliance on postal codes also ignores intra-neighborhood variations, where pollution or greenspace access can vary significantly even within small geographic areas. This geographic resolution may miss localized environmental conditions, leading to potential bias.

In addition, the greenspace metrics used in this study were not perfect, as they primarily relied on satellite-derived measurements, such as NDVI, which capture the presence of vegetation but

do not account for the quality, accessibility, or actual use of these spaces. Metrics like NDVI measure greenness at a broad scale but fail to differentiate between types of vegetation or assess whether these areas are accessible or suitable for recreational use. Moreover, NDVI and similar measures do not account for the social or physical barriers that may limit individuals' ability to engage with nearby greenspaces, such as busy roads, lack of safety, or poor infrastructure. This limitation could lead to overestimation of the actual greenspace exposure and its potential benefits, as mere proximity to greenery does not guarantee meaningful interaction with or use of these spaces. GVI, while offering a more human-centered perspective by capturing the visible greenery from street-level images, also does not consider the overall quality, accessibility, or usability of these spaces. It provides a measure of visual greenness but overlooks whether individuals have physical access to these green areas or how often they interact with them. Furthermore, GVI is limited by the availability of imagery, which may not consistently cover all regions, particularly in more rural or underdeveloped areas, potentially leading to gaps in exposure measurement. Similarly, park proximity, which measures the distance to the nearest park, fails to account for important factors like the condition, safety, or amenities of the park, or whether residents feel comfortable or are able to use it. Proximity does not necessarily translate to park use or interaction with greenspace, as various barriers such as social, economic, or physical factors may prevent individuals from utilizing nearby parks. These limitations suggest that while these greenspace metrics offer valuable insights, they do not fully capture the complexity of how greenspaces interact with human health, and future research could benefit from more nuanced and comprehensive measures.

Furthermore, the findings in this thesis may have been influenced by the COVID-19 pandemic, which occurred toward the end of the study period. The pandemic led to significant changes in

daily life, including widespread lockdowns, reduced mobility, shifts in healthcare access, and alterations in environmental exposures such as air pollution levels due to decreased traffic and industrial activity.[61–64] These factors could have impacted both the exposure data and health outcomes assessed in the study. For example, reduced outdoor activities and changes in greenspace use during the pandemic may have affected the way people interacted with their environments, while alterations in healthcare utilization may have influenced the timing or accuracy of CP diagnoses. As a result, the pandemic introduces an additional layer of complexity, potentially confounding the relationships explored in this thesis. Future research may need to account for these disruptions to better isolate the true effects of environmental exposures on health outcomes during this period.

The utilization of administrative databases for research purposes, while common, also comes with potential limitations. One key concern is the reliance on pre-existing data that was not originally collected for research purposes but for administrative, billing, or operational functions. As a result, important variables related to clinical detail, health behaviors, and environmental exposures may be missing or incompletely recorded, leading to potential misclassification or measurement error.

In addition, this thesis is constrained by the availability of only those covariates present in administrative databases. This limitation might result in an incomplete characterization of potential confounding variables or influential factors not captured within the dataset. For example, while increased maternal BMI was reported as a risk factor for CP, the studies were not able to include this variable as a confounder in models, due to a lack of data. Thus, the reliance on administrative data, not originally designed for research purposes, necessitates cautious interpretation due to potential data limitations.

Finally, another key limitation for this thesis is the approach used for analyzing the mixture effects of multiple air pollutants in chapter 4. While single-pollutant and residual adjusted models were utilized, these models do not fully account for the complex interactions between pollutants that could influence health outcomes. Future research could benefit from more advanced mixture effect analyses, such as quantile g-computation or Bayesian kernel machine regression techniques.[65–67] These methods may offer more robust ways of addressing the correlated nature of environmental exposures by evaluating their joint effects rather than isolating each pollutant, especially for exposures with high correlations. Overall, incorporating these approaches could provide a more robust understanding of how air pollution mixtures affect health outcomes, leading to more accurate risk assessments.

In summary, the identified limitations for this thesis include challenges related to the absence of case validation for CP, potential exposure and outcome misclassification, the unintended use of administrative data for research, constraints imposed by lack of availability for covariates in administrative databases and the absence of mixture effects analysis. Therefore, while the study offers valuable insights, its findings should be viewed with these limitations in mind, and further research is needed to address these gaps and refine the understanding of environmental influences on CP risk.

6.7 Recommendations for clinical practice

The findings of this thesis may have important implications for clinical practice, particularly in the realm of prenatal care and maternal health counseling. Healthcare providers can play a crucial role in mitigating the risks associated with environmental exposures by educating pregnant women about the potential impacts of air pollution on fetal development and the associated risk of CP. Utilizing tools like the Air Quality Health Index (AQHI) can help clinicians

convey real-time air quality data to patients, allowing for more informed decisions regarding outdoor activities. The AQHI is presented as a numerical scale designed to inform the public about the health risks associated with outdoor air pollution, primarily focusing on three key pollutants: O_3, PM, and NO_2. The index ranges from 1 to 10+, with lower values indicating good air quality and minimal health risk, while higher values signify increasing health risks.[68] By incorporating AQHI data into prenatal care protocols, healthcare providers can better educate patients about the potential impacts of air quality on fetal development and guide them in taking proactive measures to mitigate exposure to harmful pollutants.

Based on these epidemiological findings and future studies, clinicians can advise patients on practical steps to reduce exposure to harmful pollutants, such as avoiding high-traffic areas, particularly during peak pollution times, and considering the use of air purifiers at home. Additionally, the potential protective effects of greenspace exposure suggest that encouraging pregnant women to spend time in natural environments could be beneficial, not only for physical health but also for reducing stress, which is known to impact fetal development. Integrating these considerations into routine prenatal care could help to optimize fetal health outcomes and reduce the risk of CP. Furthermore, the findings highlight the importance of incorporating environmental risk assessments into prenatal care protocols, advocating for a more holistic approach that considers both the physical and environmental well-being of the mother and fetus.

6.8 Implications for future research and public health

This thesis was one of the first to examine the specific components of $PM_{2.5}$, greenspaces, and ALEs in relation to CP. As mentioned previously, while broad-level research has been conducted on these topics, this project helped refine and specify findings related to CP and environmental factors. The detailed analysis of $PM_{2.5}$ components, and the exploration of multiple

greenspace and ALE measures provide new insights into the multifaceted ways in which environmental exposures during pregnancy can influence the risk of CP. The findings highlight the need for more targeted research in this area, particularly studies that can further delineate the specific components of air pollution that are most harmful and the types of greenspaces that offer the greatest protective benefits. In addition, future studies could benefit from considering the effects of additional influences, such as existing maternal comorbidities. While this thesis only adjusted for maternal comorbidities in the models, future studies should comprehensively assess how these conditions interact with environmental exposures, influencing both health outcomes and clinical implications.

At the governmental level, the findings of this thesis can be instrumental in developing and implementing policy changes and programs aimed at mitigating and reducing the concentrations of specific pollutants. Such measures can have significant population-level impacts and contribute to the overall improvement of public health. Given that the studies in this thesis were funded by Health Canada, the evidence generated can directly support risk management strategies and be utilized by various governmental sectors, including the Air Quality Assessment Section (AQAS), Canadian Ambient Air Quality Standards (CAAQS), and Air Sectors Health Assessment Section (ASHAS). These findings also provide a scientific basis for advocating for urban planning and public health policies that prioritize the reduction of harmful exposures, and the enhancement of greenspace availability and ALEs, especially in areas with vulnerable populations.

Furthermore, this research not only strengthens the existing literature but also lays the groundwork for future studies to better understand how maternal health and exposure to different environmental agents affect fetal development. By highlighting the importance of both harmful and protective environmental factors, this thesis advocates for a more holistic approach to prenatal

care and public health interventions. Ultimately, the work presented here paves the way for more comprehensive research that could lead to improved health outcomes for future generations, particularly in reducing the burden of CP and other neurodevelopmental disorders.

6.9 References

1. Zhang Y, Hu Y, Talarico R, et al. Prenatal Exposure to Ambient Air Pollution and Cerebral Palsy. *JAMA Netw Open*. 2024;7(7):e2420717. doi:10.1001/jamanetworkopen.2024.20717

2. Shang L, Yang L, Yang W, et al. Effects of prenatal exposure to NO2 on children's neurodevelopment: a systematic review and meta-analysis. *Environ Sci Pollut Res*. 2020;27(20):24786-24798. doi:10.1007/s11356-020-08832-y

3. Morgan ZEM, Bailey MJ, Trifonova DI, et al. Prenatal exposure to ambient air pollution is associated with neurodevelopmental outcomes at 2 years of age. *Environ Health*. 2023;22(1):11. doi:10.1186/s12940-022-00951-y

4. Rahman MM, Shu YH, Chow T, et al. Prenatal Exposure to Air Pollution and Autism Spectrum Disorder: Sensitive Windows of Exposure and Sex Differences. *Environ Health Perspect*. 130(1):017008. doi:10.1289/EHP9509

5. Zou ML, Jiang CB, Chen YH, et al. Effects of air pollution, land-use type, and maternal mental health on child development in the first two years of life in the Greater Taipei area. *Environ Res*. 2021;197:111168. doi:10.1016/j.envres.2021.111168

6. Ha S, Yeung E, Bell E, et al. Prenatal and early life exposures to ambient air pollution and development. *Environ Res*. 2019;174:170-175. doi:10.1016/j.envres.2019.03.064

7. Tegegne KT. Determinants of cerebral palsy in children: systematic review. *Sudan J Paediatr*. 2023;23(2):126-144. doi:10.24911/SJP.106-1670589241

8. Johnston MV, Hagberg H. Sex and the pathogenesis of cerebral palsy. *Dev Med Child Neurol*. 2007;49(1):74-78. doi:10.1017/S0012162207000199.x

9. Dipietro JA, Voegtline KM. The gestational foundation of sex differences in development and vulnerability. *Neuroscience*. 2017;342:4-20. doi:10.1016/j.neuroscience.2015.07.068

10. Bustamante-Barrientos FA, Méndez-Ruette M, Ortloff A, et al. The Impact of Estrogen and Estrogen-Like Molecules in Neurogenesis and Neurodegeneration: Beneficial or Harmful? *Front Cell Neurosci*. 2021;15. doi:10.3389/fncel.2021.636176

11. Chiu YHM, Wilson A, Hsu HHL, et al. Prenatal ambient air pollutant mixture exposure and neurodevelopment in urban children in the Northeastern United States. *Environ Res*. 2023;233:116394. doi:10.1016/j.envres.2023.116394

12. Carmona JJ, Sofer T, Hutchinson J, et al. Short-term airborne particulate matter exposure alters the epigenetic landscape of human genes associated with the mitogen-activated protein kinase network: a cross-sectional study. *Environ Health*. 2014;13(1):94. doi:10.1186/1476-069X-13-94

13. Yue J, López JM. Understanding MAPK Signaling Pathways in Apoptosis. *Int J Mol Sci*. 2020;21(7):2346. doi:10.3390/ijms21072346

14. Cargnello M, Roux PP. Activation and Function of the MAPKs and Their Substrates, the MAPK-Activated Protein Kinases. *Microbiol Mol Biol Rev MMBR*. 2011;75(1):50-83. doi:10.1128/MMBR.00031-10

15. Guzik TJ, Nosalski R, Maffia P, Drummond GR. Immune and inflammatory mechanisms in hypertension. *Nat Rev Cardiol*. 2024;21(6):396-416. doi:10.1038/s41569-023-00964-1

16. Donia T, Khamis A. Management of oxidative stress and inflammation in cardiovascular diseases: mechanisms and challenges. *Environ Sci Pollut Res*. 2021;28(26):34121-34153. doi:10.1007/s11356-021-14109-9

17. Gillissen A, Paparoupa M. Inflammation and infections in asthma. *Clin Respir J*. 2015;9(3):257-269. doi:10.1111/crj.12135

18. Barnes PJ. Oxidative Stress in Chronic Obstructive Pulmonary Disease. *Antioxidants*. 2022;11(5):965. doi:10.3390/antiox11050965

19. Pagalan L, Oberlander TF, Hanley GE, et al. The association between prenatal greenspace exposure and Autism spectrum disorder, and the potentially mediating role of air pollution reduction: A population-based birth cohort study. *Environ Int*. 2022;167:107445. doi:10.1016/j.envint.2022.107445

20. Thygesen M, Engemann K, Holst GJ, et al. The Association between Residential Green Space in Childhood and Development of Attention Deficit Hyperactivity Disorder: A Population-Based Cohort Study. *Environ Health Perspect*. 2020;128(12):127011. doi:10.1289/EHP6729

21. Zare Sakhvidi MJ, Knobel P, Bauwelinck M, et al. Greenspace exposure and children behavior: A systematic review. *Sci Total Environ*. 2022;824:153608. doi:10.1016/j.scitotenv.2022.153608

22. Dadvand P, de Nazelle A, Figueras F, et al. Green space, health inequality and pregnancy. *Environ Int*. 2012;40:110-115. doi:10.1016/j.envint.2011.07.004

23. Bezold CP, Banay RF, Coull BA, et al. The relationship between surrounding greenness in childhood and adolescence and depressive symptoms in adolescence and early adulthood. *Ann Epidemiol*. 2018;28(4):213-219. doi:10.1016/j.annepidem.2018.01.009

24. Engemann K, Pedersen CB, Arge L, Tsirogiannis C, Mortensen PB, Svenning JC. Residential green space in childhood is associated with lower risk of psychiatric disorders from adolescence into adulthood. *Proc Natl Acad Sci U S A*. 2019;116(11):5188-5193. doi:10.1073/pnas.1807504116

25. Choi HM, Huybrechts K, Diaz SH, et al. Prenatal exposure to greenspace and risk of children's neurodevelopmental disease: a national cohort study of Medicaid recipients. *ISEE Conf Abstr*. 2024;2024(1). doi:10.1289/isee.2024.1549

26. Yu H, Zhou Y, Wang R, et al. Associations between trees and grass presence with childhood asthma prevalence using deep learning image segmentation and a novel green view index. *Environ Pollut*. 2021;286:117582. doi:10.1016/j.envpol.2021.117582

27. Lavigne É, Abdulaziz KE, Murphy MSQ, et al. Associations of neighborhood greenspace, and active living environments with autism spectrum disorders: A matched case-control study in Ontario, Canada. *Environ Res*. 2024;252:118828. doi:10.1016/j.envres.2024.118828

28. Mah SM, Sanmartin C, Riva M, Dasgupta K, Ross NA. Active living environments, physical activity and premature cardiometabolic mortality in Canada: a nationwide cohort study. *BMJ Open*. 2020;10(11):e035942. doi:10.1136/bmjopen-2019-035942

29. Orstad SL, Szuhany K, Tamura K, Thorpe LE, Jay M. Park Proximity and Use for Physical Activity among Urban Residents: Associations with Mental Health. *Int J Environ Res Public Health*. 2020;17(13):4885. doi:10.3390/ijerph17134885

30. Schipperijn J, Cerin E, Adams MA, et al. Access to parks and physical activity: An eight country comparison. *Urban For Urban Green*. 2017;27:253-263. doi:10.1016/j.ufug.2017.08.010

31. Sturm R, Cohen D. Proximity to Urban Parks and Mental Health. *J Ment Health Policy Econ*. 2014;17(1):19-24.

32. Reuben A, Rutherford GW, James J, Razani N. Association of neighborhood parks with child health in the United States. *Prev Med*. 2020;141:106265. doi:10.1016/j.ypmed.2020.106265

33. Grazuleviciene R, Danileviciute A, Dedele A, et al. Surrounding greenness, proximity to city parks and pregnancy outcomes in Kaunas cohort study. *Int J Hyg Environ Health*. 2015;218(3):358-365. doi:10.1016/j.ijheh.2015.02.004

34. Stavsky M, Mor O, Mastrolia SA, Greenbaum S, Than NG, Erez O. Cerebral Palsy—Trends in Epidemiology and Recent Development in Prenatal Mechanisms of Disease, Treatment, and Prevention. *Front Pediatr*. 2017;5:21. doi:10.3389/fped.2017.00021

35. Chiarello DI, Ustáriz J, Marín R, et al. Cellular mechanisms linking to outdoor and indoor air pollution damage during pregnancy. *Front Endocrinol*. 2023;14:1084986. doi:10.3389/fendo.2023.1084986

36. Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive Oxygen Species in Inflammation and Tissue Injury. *Antioxid Redox Signal*. 2014;20(7):1126-1167. doi:10.1089/ars.2012.5149

37. Pizzino G, Irrera N, Cucinotta M, et al. Oxidative Stress: Harms and Benefits for Human Health. *Oxid Med Cell Longev*. 2017;2017:8416763. doi:10.1155/2017/8416763

38. Marseglia L, D'Angelo G, Manti S, et al. Oxidative Stress-Mediated Aging during the Fetal and Perinatal Periods. *Oxid Med Cell Longev*. 2014;2014:358375. doi:10.1155/2014/358375

39. Baker BC, Heazell AEP, Sibley C, et al. Hypoxia and oxidative stress induce sterile placental inflammation in vitro. *Sci Rep*. 2021;11:7281. doi:10.1038/s41598-021-86268-1

40. Silvestro S, Calcaterra V, Pelizzo G, Bramanti P, Mazzon E. Prenatal Hypoxia and Placental Oxidative Stress: Insights from Animal Models to Clinical Evidences. *Antioxidants*. 2020;9(5):414. doi:10.3390/antiox9050414

41. Jiang H, Li X, Jin C, et al. Early Diagnosis of Spastic Cerebral Palsy in Infants with Periventricular White Matter Injury Using Diffusion Tensor Imaging. *AJNR Am J Neuroradiol*. 2019;40(1):162-168. doi:10.3174/ajnr.A5914

42. Colicino E, Cowell W, Pedretti NF, et al. Maternal steroids during pregnancy and their associations with ambient air pollution and temperature during preconception and early gestational periods. *Environ Int*. 2022;165:107320. doi:10.1016/j.envint.2022.107320

43. Saleem A, Awan T, Akhtar MF. A comprehensive review on endocrine toxicity of gaseous components and particulate matter in smog. *Front Endocrinol*. 2024;15. doi:10.3389/fendo.2024.1294205

44. Finch J, Conklin DJ. Air Pollution-Induced Vascular Dysfunction: Potential Role of Endothelin-1 (ET-1) System. *Cardiovasc Toxicol*. 2016;16(3):260-275. doi:10.1007/s12012-015-9334-y

45. Babcock MA, Kostova FV, Ferriero DM, et al. Injury to the Preterm Brain and Cerebral Palsy: Clinical Aspects, Molecular Mechanisms, Unanswered Questions, and Future Research Directions. *J Child Neurol*. 2009;24(9):1064-1084. doi:10.1177/0883073809338957

46. Baccarelli A, Bollati V. Epigenetics and environmental chemicals. *Curr Opin Pediatr*. 2009;21(2):243-251.

47. Lossi L, Castagna C, Merighi A. An Overview of the Epigenetic Modifications in the Brain under Normal and Pathological Conditions. *Int J Mol Sci*. 2024;25(7):3881. doi:10.3390/ijms25073881

48. Mallick R, Duttaroy AK. Epigenetic modification impacting brain functions: Effects of physical activity, micronutrients, caffeine, toxins, and addictive substances. *Neurochem Int*. 2023;171:105627. doi:10.1016/j.neuint.2023.105627

49. Ewert A, Chang Y. Levels of Nature and Stress Response. *Behav Sci*. 2018;8(5):49. doi:10.3390/bs8050049

50. Knight EL, Jiang Y, Rodriguez-Stanley J, Almeida DM, Engeland CG, Zilioli S. Perceived stress is linked to heightened biomarkers of inflammation via diurnal cortisol in a national sample of adults. *Brain Behav Immun*. 2021;93:206-213. doi:10.1016/j.bbi.2021.01.015

51. Jones R, Tarter R, Ross AM. Greenspace Interventions, Stress and Cortisol: A Scoping Review. *Int J Environ Res Public Health*. 2021;18(6):2802. doi:10.3390/ijerph18062802

52. Hantsoo L, Kornfield S, Anguera MC, Epperson CN. Inflammation: A Proposed Intermediary Between Maternal Stress and Offspring Neuropsychiatric Risk. *Biol Psychiatry*. 2019;85(2):97-106. doi:10.1016/j.biopsych.2018.08.018

53. Patwary MM, Bardhan M, İnan HE, et al. Exposure to urban green spaces and mental health during the COVID-19 pandemic: evidence from two low and lower-middle-income countries. *Front Public Health*. 2024;12:1334425. doi:10.3389/fpubh.2024.1334425

54. Jimenez MP, DeVille NV, Elliott EG, et al. Associations between Nature Exposure and Health: A Review of the Evidence. *Int J Environ Res Public Health*. 2021;18(9):4790. doi:10.3390/ijerph18094790

55. Howard LM, Khalifeh H. Perinatal mental health: a review of progress and challenges. *World Psychiatry*. 2020;19(3):313-327. doi:10.1002/wps.20769

56. Ghodeshwar GK, Dube A, Khobragade D. Impact of Lifestyle Modifications on Cardiovascular Health: A Narrative Review. *Cureus*. 15(7):e42616. doi:10.7759/cureus.42616

57. Bauer I, Hartkopf J, Kullmann S, et al. Spotlight on the fetus: how physical activity during pregnancy influences fetal health: a narrative review. *BMJ Open Sport — Exerc Med*. 2020;6(1):e000658. doi:10.1136/bmjsem-2019-000658

58. Paudel S, States SL. Urban green spaces and sustainability: Exploring the ecosystem services and disservices of grassy lawns versus floral meadows. *Urban For Urban Green*. 2023;84:127932. doi:10.1016/j.ufug.2023.127932

59. Venter ZS, Hassani A, Stange E, Schneider P, Castell N. Reassessing the role of urban green space in air pollution control. *Proc Natl Acad Sci U S A*. 121(6):e2306200121. doi:10.1073/pnas.2306200121

60. Santamouris M. Recent progress on urban overheating and heat island research. Integrated assessment of the energy, environmental, vulnerability and health impact. Synergies with the global climate change. *Energy Build*. 2020;207:109482. doi:10.1016/j.enbuild.2019.109482

61. Bhat SA, Bashir O, Bilal M, et al. Impact of COVID-related lockdowns on environmental and climate change scenarios. *Environ Res*. 2021;195:110839. doi:10.1016/j.envres.2021.110839

62. Health Canada. Health Impacts of Air Pollution in Canada 2021 Report. March 15, 2021. Accessed September 18, 2024. https://www.canada.ca/en/health-canada/services/publications/healthy-living/health-impacts-air-pollution-2021.html

63. Onyeaka H, Anumudu CK, Al-Sharify ZT, Egele-Godswill E, Mbaegbu P. COVID-19 pandemic: A review of the global lockdown and its far-reaching effects. *Sci Prog*. 2021;104(2):00368504211019854. doi:10.1177/00368504211019854

64. Latif MT, Purhanudin N, Afandi NZM, et al. In-depth analysis of ambient air pollution changes due to the COVID-19 pandemic in the Asian Monsoon region. *Sci Total Environ*. 2024;941:173145. doi:10.1016/j.scitotenv.2024.173145

65. Wen F, Xie Y, Li B, et al. Combined effects of ambient air pollution and PM2.5 components on renal function and the potential mediation effects of metabolic risk factors in China. *Ecotoxicol Environ Saf*. 2023;259:115039. doi:10.1016/j.ecoenv.2023.115039

66. Keil AP, Buckley JP, O'Brien KM, Ferguson KK, Zhao S, White AJ. A Quantile-Based g-Computation Approach to Addressing the Effects of Exposure Mixtures. *Environ Health Perspect*. 2020;128(4):047004. doi:10.1289/EHP5838

67. Bobb JF, Claus Henn B, Valeri L, Coull BA. Statistical software for analyzing the health effects of multiple concurrent exposures via Bayesian kernel machine regression. *Environ Health*. 2018;17(1):67. doi:10.1186/s12940-018-0413-y

68. Environment and Climate Change Canada. About the Air Quality Health Index. September 10, 2007. Accessed October 5, 2024. https://www.canada.ca/en/environment-climate-change/services/air-quality-health-index/about.html