The Epidemiology of Cerebral Palsy in Ontario, Canada: Patterns of Occurrence and Effects of Two Maternal Exposures

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Abstract

Cerebral palsy (CP) is a lifelong disorder of posture and movement and is the most common cause of physical disability in children. CP is caused by damage to the developing brain; however, the cause of the brain damage remains unknown for most children. Since there is no cure available for CP, understanding causal mechanisms is essential to develop effective primary prevention strategies. Whereas plenty of research has examined CP prevalence rates elsewhere, only a few Canadian studies have estimated these rates in selected health regions. Furthermore, evidence on secular trends of CP rates is inconsistent, and figures from North America are particularly scarce. Importantly, little is known about changes in CP rates by key sociodemographic characteristics over time. The goal of this doctoral research was to quantify the burden of CP in the Canadian context and better understand the underlying causal mechanisms of CP in pregnancy.

The aim of the **first manuscript** was to estimate the prevalence rate and temporal trends of CP in Ontario, Canada among children born in 2002–2017 both overall and by child, maternal and socioeconomic characteristics. I created a longitudinal retrospective cohort of over 2 million in-hospital births with maternal and their own health records by linking several individual- and area-level provincial administrative health datasets in Ontario, Canada. All children were followed from birth until the end of follow-up in 2018 to ascertain the study outcome. I estimated CP prevalence in children aged 0–16 years overall and by specific population characteristics. I used a non-linear Poisson model to examine temporal trends in CP rates—overall and stratified by characteristics—in young children (0–4 years) born in the same year (referred to as birth 'cohort') between 2002–2013 (n=1,587,087 live births) to allow for an equal follow-up time (4 years and 364 days) for all children. Overall CP prevalence among children aged 0–16 years was 2.52 (95% confidence interval (CI): 2.45, 2.59) per 1000 live births. CP rates in ages 0–4 increased through the 2007 cohort with 2.86 per 1000 live births but steadily declined afterward to 1.94 in the 2013 cohort. CP rates were consistently higher in boys, children born early, small, or with birth defects, and children of young (<20 years), old (≥40 years), primiparous or grand multiparous (≥4 previous live births) mothers, and those with

inadequate prenatal care; however, gaps by these characteristics have narrowed over time. Socioeconomic inequalities in CP persisted and remained stable over the study period.

Most literature on risk factors of CP has focused on preterm birth and low birth weight, with little emphasis on the role of preconception and prenatal modifiable factors that may lie early in the causal pathways that lead to CP. Maternal diabetes and unintentional injury during pregnancy are two such common exposures associated with several maternal and infant morbidities. Potential links between these exposures and offspring neurodevelopmental outcomes have been suggested, but the evidence on their association with CP in children is limited. In the **second manuscript**, therefore, I examined the effect of pre-gestational (PGDM) and gestational diabetes (GDM) on the risk of CP in offspring and the extent to which the effect is mediated through increased fetal size (large for gestational age (LGA)). Using the same birth cohort described above, I estimated crude and adjusted associations between maternal diabetes and CP using the Cox proportional hazards models to account for the unequal follow-up time in children. For the mediation analysis, I used marginal structural models to estimate the controlled direct effect of PGDM on the risk of CP not mediated by LGA. Children of mothers with PGDM showed an increased risk of CP in crude and adjusted models (Hazard ratio (HR) 1.84 (95% CI:1.59, 2.14) in the model adjusted for maternal sociodemographic and pre-existing factors). No associations were found between GDM and CP in both crude and adjusted analyses (adjusted HR 0.91 (95% CI: 0.77, 1.06)). The mediation analysis showed that the effects of PGDM on CP were not substantially mediated by LGA (LGA explained 12% of the effect).

The **third manuscript** aimed to assess the effects of exposure to maternal unintentional injury during pregnancy on the risk of CP and explore the role of different characteristics of injuries on the risk. Using the same data, I estimated crude and adjusted risk ratios using the Cox proportional hazards models for exposure to any injury and also stratified the exposed groups according to the severity of injury. Maternal unintentional injury was associated with a slightly higher risk of CP (HR 1.33 (95% CI: 1.18, 150), adjusted for maternal sociodemographic and lifestyle factors). Injuries that resulted in hospitalization and those followed by the delivery within a week conferred higher risks of CP (adjusted HR: 2.18 (95% CI: 1.29, 3.68) and 3.40 (95% CI: 1.93, 6.00), respectively).

In sum, the collective findings of this thesis not only lead to a better appreciation of the magnitude of the CP burden in Canada but also offer key insights on potential causal mechanisms of CP. Ultimately, this work will contribute to developing preventative strategies to reduce the risk of this disabling disorder in Canada and elsewhere.

Résumé

La paralysie cérébrale (PC) est un trouble permanent de la posture et du mouvement et est la cause la plus fréquente d'incapacité physique chez les enfants. PC est causée par des lésions au cerveau en phase de développement; cependant, la cause des lésions cérébrales reste inconnue pour la plupart des enfants. Puisqu'il n'y a pas de remède disponible pour la PC, il est essentiel de comprendre les mécanismes causaux pour développer des stratégies de prévention primaire efficaces. Bien que de nombreuses recherches aient examiné les taux de prévalence de la PC ailleurs, seules quelques études canadiennes ont estimé ces taux dans certaines régions sanitaires. De plus, les données sur les tendances séculaires des taux de PC sont incohérentes et les chiffres en Amérique du Nord sont particulièrement rares. Fait important, on sait peu de choses sur les changements dans les taux de PC selon les principales caractéristiques sociodémographiques au fil du temps. Le but de cette recherche doctorale était de quantifier le fardeau de la PC dans le contexte canadien et de mieux comprendre les mécanismes causaux sous-jacents de la PC pendant la grossesse.

L'objectif du **premier manuscrit** était d'estimer le taux de prévalence et les tendances temporelles de la PC en Ontario, au Canada, chez les enfants nés entre 2002 et 2017, à la fois globalement et par caractéristiques infantiles, maternelles et socioéconomiques. J'ai créé une cohorte rétrospective longitudinale de plus de 2 millions de naissances à l'hôpital avec la mère et ses propres dossiers de santé en reliant plusieurs ensembles de données administratives provinciales sur la santé au niveau individuel et régional en Ontario, au Canada. Tous les enfants ont été suivis de la naissance jusqu'à la fin du suivi en 2018 pour déterminer le résultat de l'étude. J'ai estimé la prévalence de la PC chez les enfants âgés de 0 à 16 ans dans l'ensemble et par caractéristiques spécifiques de la population. J'ai utilisé un modèle de Poisson non linéaire pour examiner les tendances temporelles des taux de PC (globalement et stratifiés par caractéristiques) chez les jeunes enfants (0 à 4 ans) nés la même année (appelée « cohorte » de naissance) entre 2002 et 2013 (n = 1 587 087 naissances vivantes) pour permettre un suivi égal (4 ans et 364 jours) pour tous les enfants. La prévalence globale de la PC chez les enfants âgés de 0 à 16 ans était de 2,52 (intervalle de confiance (IC) à 95 % : 2,45, 2,59) pour 1 000 naissances vivantes. Les taux de PC chez les 0 à 4 ans ont augmenté tout au long de la cohorte de 2007 avec 2,86

pour 1 000 naissances vivantes, mais ont régulièrement diminué par la suite pour atteindre 1,94 dans la cohorte de 2013. Les taux de PC étaient systématiquement plus élevés chez les garçons, les enfants nés prématurément, petits ou avec des malformations congénitales, et les enfants de mères jeunes (<20 ans), âgées (≥40 ans), primipares ou grand multipares (≥4 naissances vivantes précédentes), et ceux avec des soins prénataux inadéquats; cependant, les écarts selon ces caractéristiques se sont rétrécis au fil du temps. Les inégalités socio-économiques de PC ont persisté et sont restées stables au cours de la période d'étude.

La plupart des publications sur les facteurs de risque de PC se sont concentrées sur les naissances prématurées et le faible poids à la naissance, avec peu d'accent sur le rôle des facteurs modifiables avant la conception et prénataux qui peuvent se situer tôt dans les voies causales qui mènent à la PC. Le diabète maternel et les blessures non intentionnelles pendant la grossesse sont deux de ces expositions courantes associées à plusieurs morbidités maternelles et infantiles. Des liens potentiels entre ces expositions et les résultats neurodéveloppementaux de la progéniture ont été suggérés, mais les preuves de leur association avec la PC chez les enfants sont limitées. Dans le **deuxième manuscrit**, j'ai donc examiné l'effet du diabète pré-gestationnel (DPG) et gestationnel (DG) sur le risque de PC chez la progéniture et la mesure dans laquelle l'effet est médié par l'augmentation de la taille fœtale (un poids élevé pour l'âge gestationnel (PEAG)). En utilisant la même cohorte de naissance décrite ci-dessus, j'ai estimé les associations brutes et ajustées entre le diabète maternel et la PC en utilisant les modèles de risques proportionnels de Cox pour tenir compte du temps de suivi inégal chez les enfants. Pour l'analyse de médiation, j'ai utilisé des modèles structuraux marginaux pour estimer l'effet direct contrôlé du DPG sur le risque de PC non médié par PEAG. Les enfants de mères avec DPG ont montré un risque accru de PC dans les modèles bruts et ajustés (Rapport de risque (Hazard Ratio-HR) 1,84 (IC à 95 % : 1,59, 2,14) dans le modèle ajusté pour les facteurs sociodémographiques maternels et préexistants). Aucune association n'a été trouvée entre le DG et la PC dans les analyses brutes et ajustées (HR ajusté 0,91 (IC à 95 % : 0,77, 1,06)). L'analyse de médiation a montré que les effets de DPG sur PC n'étaient pas substantiellement médiés par PEAG (PEAG a expliqué 12% de l'effet).

Le **troisième manuscrit** visait à évaluer les effets de l'exposition à des blessures maternelles non intentionnelles pendant la grossesse sur le risque de PC et à explorer le rôle des différentes caractéristiques des blessures sur le risque. À l'aide des mêmes données, j'ai estimé les risques relatifs bruts et ajustés à l'aide des modèles de risques proportionnels de Cox pour l'exposition à toute blessure et j'ai également stratifié les groupes exposés en fonction de la gravité de la blessure. Les blessures maternelles non intentionnelles étaient associées à un risque légèrement plus élevé de PC (HR 1,33 (IC à 95 % : 1,18, 150), ajusté en fonction des facteurs sociodémographiques et liés au mode de vie maternel). Les blessures ayant entraîné une hospitalisation et celles suivies d'un accouchement dans la semaine conféraient des risques plus élevés de PC (HR ajusté : 2,18 (IC à 95 % : 1,29, 3,68) et 3,40 (IC à 95 % : 1,93, 6,00), respectivement).

En somme, les résultats collectifs de cette thèse conduisent non seulement à une meilleure appréciation de l'ampleur du fardeau de la PC au Canada, mais offrent également des informations clés sur les mécanismes causaux potentiels de la PC. Ultimement, ce travail contribuera à l'élaboration de stratégies préventives pour réduire le risque de ce trouble invalidant au Canada et ailleurs.

List of Abbreviations

CP — Cerebral Palsy

US — United States

GMFCS — The Gross Motor Function Classification System

CI — Confidence Interval

GA — Gestational Age

BW — Birth Weight

LBW — Low Birth Weight

PTB — Preterm Birth

SGA — Small for Gestational Age

LGA — Large for Gestational Age

PGDM — Pre-gestational Diabetes Mellitus

GDM — Gestational Diabetes Mellitus

OR — Odds Ratio

RR — Risk Ratio

MVA — Motor Vehicle Accidents

PA — Placental Abruption

ICES — Institute for Clinical Evaluative Sciences

MOMBABY — Mother and Baby Database

IKN — ICES Key Number

RPDB — Registered Persons Database

CIHI DAD — Canadian Institute for Health Information Discharge Abstract Database

ICD-10-CA — International Classification of Diseases, 10th Revision, Canada

OHIP — Ontario Health Insurance Plan

ICD-9 — International Classification of Diseases, 9th Revision

NACRS — National Ambulatory Care Reporting System

ODD — Ontario Diabetes Database

HYPER — Ontario Hypertension Database

ODB — Ontario Drug Benefit Claims

CENSUS — Ontario Census Area Profiles

ON-MARG — Ontario Marginalization Index

IDAVE — ICES Data and Analytic Virtual Environment

CCI — Canadian Classification of Health Interventions

RIO — Ontario Rurality Index

CSD — Census Subdivision

AIC — Akaike Information Criterion

CDE — Controlled Direct Effect

MSM — Marginal Structural Models

HR — Hazard Ratio

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Contribution of Authors

The three manuscripts that constitute this thesis are listed below. The data used in this thesis come from ICES (formerly known as the Institute for Clinical Evaluative Sciences), which houses multiple population health administrative databases for all residents eligible for the universal provincial healthcare system in Ontario, Canada. As the first author on all three manuscripts, I was responsible for drafting the protocol for the data request from ICES, developing the research objectives for each study, acquiring, managing, and cleaning the data, constructing the study cohort, analyzing the data, interpreting the findings, and writing the first draft of all manuscripts. I performed all of these tasks under the guidance and support of my Supervisor, Dr. Seungmi Yang. As my thesis supervisor and co-author, Dr. Yang assisted with all stages of the research process from the protocol development stage onward. She provided substantial guidance on research questions and study design, data analysis, and assisted with the interpretation of study results. Dr. Yang reviewed all of the manuscripts in detail and provided valuable feedback on the intellectual content of each of the manuscript drafts.

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Manuscript 1: **Ahmed, A**, Rosella, L, Oskoui, M, Watson, T, Yang, S. Trends of cerebral palsy occurrence in children born in 2002–2017: A population-based retrospective cohort study. Currently under review at *Developmental Medicine & Child Neurology*.

Manuscript 2: **Ahmed, A**, Rosella, L, Oskoui, M, Watson, T, Yang, S. In-Utero Exposure to Maternal Diabetes and the Risk of Cerebral Palsy. Currently being prepared for submission to *BMJ*.

Manuscript 3: **Ahmed, A**, Rosella, L, Oskoui, M, Watson, T, Yang, S. In-Utero Exposure to Maternal Unintentional Injury and the Risk of Cerebral Palsy: A Population-based Retrospective Cohort Study. Currently being prepared for submission to *JAMA.*

Statement of Originality

The research presented in this thesis constitutes an original contribution to the field of perinatal epidemiology. The three manuscripts presented in my thesis fill important gaps in the literature on the burden and etiology of cerebral palsy (CP) based on population-based data from ~2 million births. Specifically, **manuscript 1** examined the prevalence and temporal trends of cerebral palsy over 16 years, overall and by a wide range of child and maternal characteristics. Secular trends of overall CP prevalence in Canada have not been identified before; we also have a limited understanding of changes in CP rates across subgroups defined by key population characteristics, such as maternal demographics and socioeconomic factors. The work presented in **manuscript 2** enhances the existing knowledge of the effect of maternal diabetes on the risk of CP in children by 1) estimating effects of pre-gestational and gestational diabetes on CP separately; 2) considering the role of duration of pre-gestational diabetes; 3) examining the role of increased fetal size in the associations between maternal diabetes and CP. In **manuscript 3**, I present one of the first studies on the role of maternal injuries during pregnancy on long-term neurodevelopmental outcomes in children. I quantified the effect of in-utero exposure to maternal unintentional injury on CP and also explored the role of severity, timing, and mechanism of injury. In all three manuscripts, I used several methods to account for different sources of potential bias associated with using administrative data—including exposure and outcome misclassification and unmeasured confounding—by employing a range of sensitivity analyses, such as alternative exposure/outcome definitions and probabilistic bias analyses.

While I received indispensable support and guidance from my supervisor and thesis advisory committee members throughout the research process, I declare that the conception, execution, and drafting of this thesis manuscripts are of my own design motivated by important gaps in existing knowledge on the burden and determinants of cerebral palsy.

Chapter 1. Introduction

Cerebral palsy (CP) is a chronic lifelong disability of posture and movement that is caused by non-progressive damage to the developing brain. [1] It is an umbrella term that encompasses several clinical subtypes and is often associated with other disturbances, such as sensory (vision, hearing, speaking) deficits, disturbances of perception, cognition, and behavior, and epilepsy. [1] CP is currently affecting ~2 for every 1000 live births in developed countries, [2] with much higher estimates in low and middle-income countries. [3] CP is the most common cause of physical disability in children [1] and is associated with a significant economic burden to families, the health care system, and the general economy due to costs related to health expenditure, special education, social services, and lost economic opportunities. [4] Moreover, disturbingly high mortality rates among children with CP have been described—around a third of children with severe CP die between their third and 16th birthday. [5] The severity and significant burden of CP make it a public health priority to develop preventative strategies to alleviate the burden associated with this disabling disorder.

There is no cure for CP; thus, any primary prevention efforts require an understanding of the underlying causes of CP. [6] Cerebral palsy is caused by damage to the developing brain, but the cause of the brain damage remains unknown for most children. [1,6] Although earlier reports have suggested a major role of birth asphyxia in the etiology of CP, [1,7,8] it is now documented that the majority (~80%) of CP cases are attributed to prenatal factors, with birth asphyxia explaining <10% of cases. [6] Much research has been devoted to understanding the effects of prematurity and low birth weight, and much less has focused on maternal preconception and pregnancy factors. [1] Although gestational age at birth is strongly associated with CP, approximately two-thirds of CP cases are born at or near term, for whom we know very little about the cause of CP. [1,9] Moreover, timing and size at birth are themselves the result of pathological processes during pregnancy, and thus their risk factors could be the underlying causes of CP. [10] Therefore, there is still a need to understand the role of preconception and prenatal modifiable factors that may lie early in the causal pathways that lead to CP.

Several research gaps exist about the CP burden. Multiple studies have examined CP prevalence elsewhere; however, Canadian estimates were either outdated or restricted to certain health regions. [11-14] The evidence on secular trends is much limited. Whereas studies from Europe and Australia have mostly shown slight declines in CP rates in recent years, a few reports from the United States (US) have examined CP rates over time with conflicting findings. [15-25]
No similar research has been done in Canada. Furthermore, little is known about changes in CP rates by key sociodemographic characteristics over time.

The evidence on the effect of two maternal exposures—diabetes and unintentional injuries—on the risk of CP is also scarce. A limited number of population-based studies have examined these associations, but none have considered the role of exposure characteristics or plausible causal mechanisms. [26-28]

This thesis aimed to address these important knowledge gaps in the literature about the burden of CP in Canada and the role of two important and common maternal exposures in the etiology of CP—maternal diabetes and maternal unintentional injuries during pregnancy.

1.1. Research Objectives

The overarching goal of this thesis was to advance our knowledge about the recent trend in occurrence and the underlying causes of CP. The specific objectives were:
1) To examine the prevalence and temporal trends of CP rates in Ontario, Canada, among children born between 2002-2017 overall and by important sociodemographic characteristics (manuscript 1);
2) To estimate effects of maternal pre-gestational and gestational diabetes on the risk of CP in offspring and examine the role of increased fetal size as a potential mediator (manuscript 2); and
3) To assess effects of maternal unintentional injury during pregnancy on the risk of CP in offspring and understand variations of the effects by the severity of the injuries (manuscript 3).

1.2. Organization of the Thesis

This manuscript-based thesis begins with a discussion of the overall rationale for this work and research objectives in Chapter 1. In Chapter 2, I discuss background information on cerebral palsy burden and risk factors, together with other relevant contextual information for the specific research objectives of this thesis. Chapter 3 presents a brief overview of the data sources and analytical methods used to address each of the specific research objectives. In Chapter 4, I present a manuscript entitled "Trends of Cerebral Palsy Occurrence in Children Born in 2002–2017: A Population-Based Retrospective Cohort Study" that examines the prevalence and temporal trends of cerebral palsy—overall and by population characteristics—using data from all live births born in Ontario, Canada between 2002-2017. Chapter 5 presents a manuscript "In-Utero Exposure to Maternal Diabetes and the Risk of Cerebral Palsy" that examines effects of maternal diabetes on the risk of cerebral palsy in children using the same source of data. Chapter 6 presents a manuscript "In-Utero Exposure to Maternal Unintentional Injury and the Risk of Cerebral Palsy: A Population-based Retrospective Cohort Study" in which I examine effects of maternal unintentional injury on the risk of cerebral palsy. Finally, Chapter 7 includes an overall summary of the findings from the manuscripts contained in Chapters 4-6 and a discussion of the implications of this thesis work and concludes with possible directions for future research. References for manuscripts 1-3 are presented in their corresponding chapters (Chapters 4-6), and references for Chapters 1-3 and Chapter 7 are listed at the end of the thesis.

Chapter 2. Review of the Literature

2.1. Definition and Consequences of CP

2.1.1. Definition

CP is an umbrella term that includes several subtypes, multiple patterns of brain lesions on neuroimaging, and different phenotypes of motor impairment. [29] No test can provide a definitive diagnosis of CP, nor is there a particular cause, a brain pathology, or a specific clinical feature. [29] Instead, CP is diagnosed based on clinical and neurological signs, with or without neuroimaging findings. [30]

As early as the 18th century, researchers attempted to provide a specific definition of CP. In 1861, Little described CP as "[t]he condition of spastic rigidity of the limbs of newborn children." [1,8] Since then, CP definition has undergone several changes over time. [1] The newest CP definition, by Rosenbaum and colleagues in 2007, [31] recognized functional limitation and co-occurring impairments. They defined CP as "[a] group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy, and by secondary musculoskeletal problems." [31]

2.1.2. Subtypes

CP is classified according to the distribution of motor impairment and type of muscle tone abnormalities into four broad categories: spasticity (the most common, ~90%), dyskinesia, ataxia, and hypotonia. The spastic type is further classified based on the affected body region into hemiplegia (half the body), diplegia (lower limbs affected more than upper limbs), or quadriplegia (all 4 limbs and trunk). [30,32] Certain risk factors are associated with specific CP motor subtypes; for example, diplegia is mostly seen in preterm infants, whereas hemi and quadriplegia are more common in term-born babies. [33] It is, however, common for these motor impairments to co-exist, leading to significant variation in how these subtypes are defined. [34] Thus, classifications based on the motor type offered little help for prevention, management, or

prognosis due to the limited reliability to distinguish between these subtypes. [1,34] Consequently, there has been a recent shift in CP classification towards a new system that relies on the degree of functional limitation. [1] The Gross Motor Function Classification System (GMFCS) classifies children with CP into five groups based on the levels of functional limitations, ranging from GMFCS level 1 (able to walk, run, and jump with only reduced speed, balance, or coordination) to GMFCS level 5 (marked impairment in all areas of motor function with no ability to independently sit or stand, even with adaptive equipment). [35] Nevertheless, it is still unclear as to which classification would offer a greater insight into CP etiology. [1] Furthermore, dividing such a rare condition into narrower subcategories would make etiologic epidemiological research challenging owing to the smaller sample size in each subcategory. [1]

2.1.3. Comorbidities

CP is often accompanied by additional abnormalities to motor impairment. For example, three-quarters of children with CP suffer from pain, half has an intellectual disability, one-quarter has epilepsy, behavioral disorder, urinary incontinence, or speech abnormality, and many have sleep disorders, feeding difficulty, visual impairment, or hearing problems. [36] In addition, motor impairment usually results in secondary complications, such as muscle and joint contractures, scoliosis, and joint arthritis, deformities, or displacement. [4,36]

2.1.4. Impacts of CP on Children, Families, and Communities

CP causes significant limitations in activities of daily living in most affected children. [6] Furthermore, the complexity of caregiving duties for children with CP may significantly impact parents' physical and mental health. [37] The economic burden of CP is also huge; health care expenses in children with CP are approximately 10-26 times higher than those without CP because of more frequent visits to healthcare professionals, more surgical procedures, frequent and extended hospitalizations, and more comorbidities. [4,38] The economic burden of CP on families is also significant; it may include out-of-pocket medical expenses, reduced earnings due to caregiving responsibilities, and other expenses related to the functional limitations (e.g., hiring daily living assistants and house modifications). [4] Economic impacts on the government include expenses related to pensions, allowances, health equipment, and special educational needs. [4,39]

2.2. CP Prevalence

Oskoui and colleagues have systematically reviewed the literature for prevalence estimates of CP in developed countries and reported a pooled overall prevalence of 2.11 (95% confidence interval (CI): 1.98, 2.25) per 1000 live births. [2] The authors have noted the limited information on CP prevalence in North America. Global estimates of CP prevalence have been mostly drawn from high-income countries; [2,3] figures from low and middle-income countries are less clear but seem to be higher and with larger proportions of children with severe physical disabilities. [3]

Very few studies have examined the overall prevalence rates of CP in Canada. [11-14] Two studies have estimated prevalence rates of CP in Quebec [11] and Alberta [12] and showed a prevalence of 2.2 per 1000 9–11-year-old children born in 1999–2001 and 2.3 per 1000 5-year-old children born in 2008–2010, respectively. Both studies, however, used data from the Canadian Cerebral Palsy Registry, thus only included CP cases from rehabilitation centers in selected regions in each province (six out of the seventeen administrative health regions in Quebec and the northern part of Alberta). [40] These rates were comparable to old studies from Alberta (1985–1988) and British Columbia (1991–1995) that both used administrative data to ascertain CP cases. [13,14] A report from Ontario has examined the burden of neurological disorders in the province, including CP, using administrative databases. [41] Age and sex-adjusted prevalence of CP among children 5 years and younger was 2.6 per 1000 between 2004–2011 with a slight increase between 2004/2005 and 2010/2011 (from 2.8 to 3.1 per 1000). Corresponding figures for children 0–17 years was 4.5 per 1000. [41] These studies have focused, however, either on the overall prevalence of CP [11,41] or on rates of CP by gestational age (GA) [12] or birth weight (BW) only; [12-14] none have examined rates of CP by important sociodemographic characteristics.

Although reported CP prevalence was ~2 per 1000 live births in most developed countries, estimates from the US were consistently higher (~2.6–3.9 per 1000). [24,25,42-44] Some US studies have relied on parent-reported CP diagnoses and most have enumerated CP cases at a certain age (e.g., 2–17 years, or 8 years) and have used children at the same age as the denominator. [2,23-25] Several problems, however, could arise using these approaches. Aside from the issues related to self-reported diagnoses, biases could be introduced if migration patterns in or out of the region are related to physical disability, particularly prevalence estimates in specific geographic regions.

[45] For example, parents of children with CP might preferentially move to areas with an abundance of health care or educational services suitable for children with CP, which would inflate the numerator and lead to an overestimation of CP prevalence. [45,46] Other potential issues include in-migration of families from countries with high CP rates, or a higher chance of admitting refugee families with disabled children for humanitarian reasons. [46]

Several studies in Europe and Australia have explored trends of CP rates over time but showed inconsistent findings. [15-22] A study based on 20 European population-based CP registers showed decreasing prevalence rates of CP between 1980 to 2003. [15] Similarly, downward trends of CP rates were seen in Norway (1999–2010 births) [47], Denmark (1999–2007 births) [48], and Australia (since 1995). [22-25] However, reports from Sweden showed stable rates of CP between the 1980s and 2010 [16-18] and similarly, estimates from the United Kingdom have remained relatively unchanged since the 1970s. [19,20] Comparable evidence from North America is limited. Only a few studies in the US have explored CP rates over time with conflicting results. [23-25] Stable trends were reported by studies based on National Health Interview Survey in the US in children aged 3–17 between 2009–2017. [43,49] Conversely, declines in CP rates between 2006–2010 were documented based on population-based developmental disabilities surveillance programs for 8-year-olds in four states. [42]

The evidence on temporal trends of CP prevalence in Canada is even more limited. Three Canadian have studies explored temporal trends of CP only among preterm and/or low birth weight (LBW) survivors and have shown increasing rates of CP among preterm and LBW babies [50-52] Nonetheless, preterm infants not only constitute a small proportion (~11%) of all births but account for only about a third of CP cases. [6] To the best of our knowledge, no previous study has examined temporal changes in the overall prevalence rates of CP in Canada, and thus we have no information on whether overall CP prevalence has changed over time. Several factors may contribute to changes in the Canadian CP rates over time, such as the increasing number of older mothers, [53] immigrant mothers, [54] as well as the changing rates of multiple births, [55] preterm births (PTB), [56] and LBW babies. [57]

Whereas previous research has highlighted the higher rates of CP in certain population subgroups, such as multiples, [9,58] blacks, [59] and those born to adolescent or old mothers, [9,60] a paucity of research has examined rates of CP by sociodemographic characteristics over time. A report from the US has documented the persistence of racial disparities in CP rates over time (1985–2002), showing consistently high CP rates in non-Hispanic black, compared to non-Hispanic white children. [61] Data from the Australian CP Register (1993–2009) showed consistently higher rates of CP in male infants and multiples over time and reported improved rates of CP in multiples and across all maternal age groups except in mothers younger than 20 years whose rates were consistently higher than other groups. [9] No Canadian study so far has explored secular trends of CP rates in population subgroups defined by key sociodemographic factors.

2.3. Risk Factors of CP

Current evidence suggests that CP often results from several risk factors. [33] In this section, I give an overview of the known risk factors for CP and existing knowledge gaps.

2.3.1. Birth and Child Characteristics

Prematurity

PTB is an important risk factor of CP, with a prevalence inversely proportional to the GA; [1] CP prevalence in extremely preterm infants (<28 weeks) is as high as 50 times the prevalence in term-born babies. [16] However, only ~7–8% of all births in high-income countries are preterm, [62,63] making PTB a contributing factor in ~1/3 to 1/2 of CP cases in developed countries. [1,9] The proportion of CP cases attributed to prematurity is much lower in low-income countries because of high mortality rates of preterm infants in poor-resource settings. [64] The literature on risk factors for CP in preterm infants is extensive; researchers have identified several factors that predict CP in children born preterm, most notably white matter lesions (periventricular leukomalacia), intraventricular hemorrhage (grade 3 to 4), and postnatal steroid use. [1,65,66]
It should be noted that the underlying cause of PTB such as pre-eclampsia and chorioamnionitis could also cause—in addition to prematurity—CP in preterm born babies. [10,67]

Fetal Growth

Studies that examined birth weight for gestational age as a risk factor of CP have consistently reported positive associations between small for gestational age (SGA, birth weight for gestational age<10th percentile) and CP in singletons, [68] twins, [69] preterm [70] and term-born infants, [71] and across CP subtypes. [72,73] It is, however, less clear if SGA is a cause or a consequence of CP, or just a marker of an underlying pathology that leads to both SGA and CP. [74] Impaired fetal growth could possibly lead to brain damage either directly due to limited nutritional or oxygen supplies to the brain or indirectly via mechanisms such as neonatal hypoglycemia and perinatal asphyxia commonly seen in SGA babies. [74,75] On the other hand, severe damage to the brain in-utero may lead to fetal growth restriction due to disturbed control of growth. [76]

Studies have also reported a higher risk of CP in infants born with macrosomia (BW>4,000 grams) or with large for gestational age (LGA, birth weight for gestational age>90th percentile). [68,69] The mechanism of such an association is not clear though. [74,77] Many have argued that traumatic deliveries commonly occurring in larger babies could be the reason for increased risk of CP, but no empirical evidence has supported this hypothesis. [74] In fact, Jarvis and colleagues have found a higher risk of CP in LGA born preterm whose size is usually small relative to the delivery passage, [68] which further refutes the claim that traumatic deliveries explain these observations. Other possible mechanisms suggested are genetic causes or maternal hyperglycemia. [69]

Other aspects of fetal growth than BW have also been linked to CP. For example, researchers have documented higher risks of CP in children with low (asymmetric growth restriction) and high (large weight for height) Ponderal index, [78] low and high birth length, [79] low and high head circumference, [79] and low birth weight/ placenta weight ratio. [78]

Other Child Characteristics

Male infants had higher rates of CP in several reports. [73,80,81] A large European study has reported a 30% higher prevalence of CP in males than females. [73] Male infants seem to be more vulnerable to other perinatal morbidities, such as PTB and stillbirth, but the mechanisms of these

biological susceptibilities in males are still unclear. [80] High rates of CP have also been found in twins in several studies, with higher rates in higher-order multiples. [33,58,82] PTB and LBW commonly occur in twins play important role in explaining these associations. [1,33] Monozygotic twins and the death of one twin also seem to pose additional risks for CP. [33,83] The literature has also consistently reported higher rates of cerebral malformations in children with CP (structural brain malformations on neuroimaging are found in ~11% of CP cases). [6.33,84] Congenital malformations of other organs than the nervous system are also common in children with CP, including minor defects such as cleft lip or palate. [33,84] Intra-uterine infections (e.g., cytomegalovirus or toxoplasmosis), [85,86] as well as chorioamnionitis have also been associated with CP. [67,87]

Genetic causes of CP have received attention in the scientific literature only in recent years. [1,88] It has been estimated that 1–2% of CP could be linked to genetic factors. [33] Researchers have documented familial aggregation of CP cases and have also found genetic variants that are linked to CP. [89] In addition, genetic factors may play a role in the etiology of several risk factors of CP, such as PTB and preeclampsia. [33]

2.3.2. Perinatal Complications

Birth Asphyxia

In 1840, Little attempted to explain the underlying causes of CP and attributed nearly all CP cases to PTB or birth asphyxia. [8] This notion led to the widespread use of electronic fetal monitoring to detect birth asphyxia, assuming that timely intervention would prevent CP, a strategy that has later been proven ineffective in reducing the risk of CP. [90] It was not until the second half of the 20th century that evidence on the role of other factors in pregnancy and preconception started to emerge. [1] In 1986, Nelson and Ellenberg studied risk factors of CP in a sample of ~45,600 children (189 CP cases) born during 1959–1966 at 12 academic centers. [91] They concluded that preconception and pregnancy factors predominated in the etiology of CP, while factors around labor contributed very little. [91] The findings of this research made it clear that birth complications were not the leading cause of CP. [91] In fact, many children with CP have uneventful delivery, whereas children with birth asphyxia rarely develop CP. [33,91] Furthermore, signs of birth asphyxia, such as abnormal fetal heart rates, low Apgar scores, meconium staining,

or neurological depression, could all reflect a more chronic compromise caused by neurologic damage or maldevelopment in early pregnancy. [92]

Other Perinatal Factors

Perinatal stroke (stroke occurring between late gestation and 28 days after birth) is strongly linked to hemiplegic CP. [1,93] Most perinatal strokes are thrombotic, but their underlying causes are mostly unknown. [1] They have been linked to congenital health diseases, infections, placental thrombosis, preeclampsia, and fetal growth restriction. [1,93-95] Neonatal jaundice could also cause CP. High levels of unconjugated bilirubin could cross the blood-brain-barrier and cause neurological manifestations (known as Kernicterus). [1,96] Kernicterus has been linked to rare subtypes of CP (choreoathetosis or dystonic) but their occurrence is uncommon in high-income countries because of better management of neonatal jaundice. [1,96] Kernicterus is, however, still an important cause of CP in low-resource settings. [97] Studies have also associated Breech presentation at the time of delivery with CP, [98] but the method of breech delivery (vaginal vs cesarean section) did not affect the CP risk. [1,99] The mode of delivery also seems to be associated with CP. [100] A few reports have suggested higher CP risk is children delivered by instrumental deliveries. [100,101] A meta-analysis of the literature has linked emergency, but not elective, cesarean section to CP. [102] The increased risk after emergency cesarean sections, however, should be interpreted with caution, as many indications of the cesarean section have been linked to CP (e.g., pre-eclampsia, twin pregnancy). [10,33,58,82,102-104] Other perinatal factors of CP include neonatal seizures, hypoglycemia, infections, low Apgar score, and respiratory distress syndrome. [100,105]

2.3.3. Post-neonatal Factors

For a small minority of CP cases (~5%), CP could be attributed to post-neonatal causes (causes from 28 days after birth to age 1–2 years). [106] Common causes of post-neonatal CP are infections such as meningitis and encephalitis (~50%), vascular events such as complications of cardiac surgery and cerebrovascular accidents (~20%), and head injuries (account for ~12% of cases). [106]

2.3.4. Maternal Risk Factors

Sociodemographic Characteristics

Both advanced and young maternal age has been associated with increased risk of CP. [9,32,60] Maternal obstetric history has also been linked to CP, with high rates of CP in children of mothers with four or more previous live births and those with a history of previous stillbirth or neonatal death, or repeated miscarriages. [100] Differences in CP rates by mother's race have also been documented, with higher CP rates in children of black mothers than white mothers; differences in maternal education have not fully explained these racial disparities. [59] Researchers have also reported lower rates of CP in children of Asian mothers. [59,107] A Canadian study has found a reduced risk of CP in children of immigrant mothers, compared to non-immigrants, showing the lowest risk in children of mothers from East Asia and the Pacific and the Caribbean. [108] These increased risks were not fully explained by common risk factors for CP, such as maternal illness, and did not vary by duration of residence. [108] Socioeconomic disparity in CP based on both individual-level socioeconomic factors, such as family income and maternal education, and area-level factors (e.g., neighborhood income) has been reported, with more CP rates in socially disadvantaged children. [109-112] Several of these studies have attempted to examine these disparities in term and preterm infants separately and have consistently reported a lower risk of CP in preterm black infants compared to preterm white infants and in preterm babies born to mothers with low socioeconomic status relative to those born to women with high socioeconomic status. [59,111,112] These results, however, are likely biased by collider stratification bias, similar to the birth weight paradox. [113]

Maternal Illness

The link between maternal illnesses and CP has typically been studied in case-control studies that included selected CP cases and explored associations with a wide range of risk factors. [26,100,114] It was not until the last decade that population-based studies started to examine these associations. In 2013, Janik et al. have found a positive link between maternal in-hospital diagnosis of obesity and CP. [115] Since then, several others have reported positive associations between maternal overweight or obesity and CP, including dose-response associations with body mass index. [116-118] Likewise, multiple reports have described positive associations between pre-eclampsia and CP, with evidence that PTB and/or fetal growth restriction might explain most of

these associations. [10,103,104] Other maternal illnesses have received less attention in the literature. One study has examined thyroid disease and found links with thyroid diseases identified during pregnancy, but not with thyroid illness diagnosed before pregnancy. [119] A recent Norwegian study of ~ 1.4 million children has examined the associations of several maternal chronic conditions before and during pregnancy with CP and found positive associations for several maternal illnesses, most notably maternal type 2 diabetes and autoimmune diseases. [27]

2.4. Role of Maternal Diabetes

2.4.1. Definition and Prevalence

Diabetes is one of the most common chronic illnesses affecting women during pregnancy, and is a growing complication globally across racial/ethnic groups, [120] including Canada. [121] Maternal diabetes can either start before pregnancy (type 1 or 2), known as pre-gestational diabetes mellitus (PGDM), or during pregnancy (gestational diabetes mellitus (GDM)). Type 1 diabetes—also known as insulin-dependent diabetes—is an autoimmune disease characterized by the inability of the pancreas to produce insulin, and it typically starts at a young age (childhood or adolescence). [122] Type 2 diabetes is attributed to the inability of the body to utilize insulin (insulin resistance) or impaired insulin production; it usually starts during adulthood and is mostly linked to obesity. [123] GDM is an impairment in glucose tolerance with onset or recognition during pregnancy. [124] The majority of cases of diabetes in pregnancy are GDM (87.5 %), while pre-gestational type 1 and type 2 diabetes account for 7.5% and 5% of cases, respectively. [125] Epidemiological data suggests an alarming increase in rates of maternal diabetes. For example, rates of both PGDM and GDM have doubled in Ontario, Canada, between 1996 and 2010 (from 0.7 to 1.5% for PGDM and from 2.7 to 5.6% for GDM). [121]

2.4.2. Effects on Offspring

PGDM, especially if poorly controlled, is associated with an increased risk of spontaneous abortions (15–20%) and congenital malformations (5–10%), with neural tube defects and congenital heart malformation as the most common malformations. [124,126] It is also associated with a high risk of stillbirth, perinatal mortality, increased fetal size, and traumatic deliveries. [124,127] GDM is linked to higher rates of perinatal mortality, large fetal size, and traumatic deliveries. [124,128,129] Associations of PGDM and GDM with childhood adiposity and adverse

cardiometabolic outcomes have also been reported. [130] Maternal diabetes (both PGDM and GDM) have also been linked to poor neurodevelopmental outcomes in offspring, [131] including autism, [132,133] attention deficit hyperactivity disorder, [124] and cognitive impairment. [134]

2.4.3. Association with CP

The evidence on the relationship between maternal diabetes and CP is limited and inconclusive. Three case-control studies of risk factors of CP from Estonia, [135] Poland, [136] and Turkey [137] found no association between maternal diabetes and the risk of CP in children. These studies, however, were based on a small number of CP cases (~100–200 cases), did not adjust for important confounders, and some included only hospital-based CP cases born at term. [136,137] To the best of our knowledge, only two population-based studies in Sweden and Norway have examined the link between maternal diabetes and CP; both studies have reported positive associations between PGDM and CP and no associations for GDM. [26,27] The Swedish case-control study included 2303 cases of CP [26] and found that children exposed to type 1 diabetes were twice as likely to have CP compared to those who were not exposed (Odds Ratio (OR) 2.09 (95% CI: 1.41, 3.09)); [26] no association was found for GDM (OR 1.13 (95% CI: 0.62, 2.05)). However, this study restricted CP cases to those admitted to hospitals and examined these associations in crude analyses only. [26] The Norwegian study has included 1,360,149 children, including 3575 with CP, and found positive associations between maternal type 1 and 2 diabetes and CP (adjusted risk ratios (RR) 2.2 (95% CI: 1.4, 3.4) for type 1 and 3.2 (95% CI: 1.8, 5.4) for type 2 diabetes). [27] Corresponding figure for GDM was 1.1 (95% CI: 0.8, 1.5). Neither study has examined the role of PGDM duration in these associations. It is plausible that vascular dysfunctions associated with a longer duration of diabetes might lead to placental changes or cause maternal hypertension and chronic kidney diseases; [138] both are linked to CP. [27] Furthermore, although these authors speculated a role of increased fetal size in explaining the increased risk of CP in infants of diabetic mothers, no study so far has explored these plausible causal pathways. [27]

2.4.4. Potential Contribution to Brain Damage

Maternal diabetes is one of the most important causes of increased fetal size. [128,139-141] In mothers with diabetes, prolonged periods of hyperglycemia, coupled with increased levels of transfer of gluconeogenic branch chain amino acids, could induce hyperplasia of the fetus's pancreatic beta

cells, resulting in fetal hyperinsulinemia. [142] High levels of fetal insulin stimulate the growth of tissues sensitive to insulin, such as muscles, connective tissues, and adipose tissue, which would increase fetal size. [142] Increased levels of insulin-like growth factors and leptin may also play a role in enhancing growth in fetuses exposed to maternal diabetes. [124] Previous studies have documented an increased risk of CP in children with excessive intrauterine growth both in term and preterm babies. [68,69] The increased adiposity, particularly in the intrascapular area and around shoulders, could lead to shoulder dystocia and traumatic deliveries, [142] which are linked to birth asphyxia, hypoxic-ischemic brain injury, and subsequent neurological injuries, including CP. [143,144]

Fetal hyperinsulinemia could also lead to impaired surfactant production that is important for lung maturation, putting the infant at increased risk of neonatal respiratory distress syndrome. [142] The enhanced fetal growth may also cause increased metabolic demand that may lead to intrauterine tissue hypoxia due to increased oxygen consumption and metabolism, [142] which may, in turn, impair brain development. [142] This hypermetabolic state requires increasing oxygen supply to the tissue, which may trigger increased production of red blood cells and increased demand for iron, resulting in reduced iron stores in vital organs, including the brain. [142,145,146]

Exposure to maternal hyperglycemia could also increase the circulating levels of reactive oxygen species and reduce antioxidants, which may cause oxidative stress and impair brain development. [124,147] In-utero exposure to high levels of glucose during critical periods of organ development, coupled with exposures to high levels of ketones, free oxygen radicals, and oxidative stress, may lead to congenital malformations [124,142] that are frequently seen in children with CP. [33,84] Maternal diabetes may also increase the levels of cytokine interleukin-6 and other proinflammatory cytokines that could cross the placenta and disrupt brain development, as observed in animal studies. [148-150] Increased levels of inflammatory cytokines have been linked to white matter brain injuries and CP. [142] The evidence is also suggestive that altered fetal epigenome in fetuses exposed to maternal diabetes may affect gene expression and consequently long-term offspring outcomes. [124,151] Thus, epigenetic modification, such as DNA methylation, could mediate the effect of maternal diabetes on long-term children outcomes, including

neurodevelopment. [124] Despite the plausible mechanisms described above, the role of fetal epigenome modification in CP etiology remains unclear. [130]

2.5. Role of Maternal Injury

2.5.1. Definition and Prevalence

Exposure to injury during pregnancy is relatively common; between 5–8% of pregnancies are affected by traumatic injuries. [152,153] Injury is the most common cause of non-obstetric death, accounting for ~20% of maternal deaths in the US. [154,155] Fetal mortality could reach as high as 60% in major trauma, but estimates from the literature typically range between 1.3–19%. [154,156,157] Most injuries in pregnancy are unintentional (~95%), with motor vehicle accidents and falls as the two most frequent sources of injuries. [152,153,158] Risk factors of injuries in pregnancy include young maternal age, low socioeconomic status, and belonging to certain racial/ethnic groups (Black and Hispanic). [154,159] Risk factors for maternal and/or fetal complications include high severity of injury, multiple gestations, or development of vaginal bleeding or uterine contractions after injuries. [160] As many as one in three pregnant women hospitalized for injury would deliver during the hospitalization, and they have more adverse maternal and fetal outcomes than women who deliver after being discharged. [158,161]

Motor vehicle accidents (MVA) are the most life-threatening mechanism of injury and are associated with the highest rates of maternal morbidities and poor fetal outcomes. [160] Almost all pregnant women involved in MVA (~90%) seek medical attention, and most are admitted if GA>20 weeks. [162] Outcomes are particularly poor for women who experience accidents of high force impact, with improper or lack of use of seat belts, or illicit drugs or alcohol involved. [160] Unfortunately, not wearing a seatbelt is common in pregnant women, and it has been linked to as high as 50% of fetal deaths after MVA. [163] Alcohol or drug use is also common in pregnant women involved in MVA (up to 45%). [159]

Approximately a quarter of pregnant women experience a fall, at least once during pregnancy, most commonly in the 2nd and 3rd trimesters due to the increased weight and changes in the center of gravity as a result of anatomical changes in pregnancy. [160,164,165] Most falls occur from standing height (slipping, tripping, or stumbling, ~35%) or involve stairs (~16%). [160,164]

Although the majority of falls are minor, they have been linked to fetal complications, such as stillbirth. [164]

2.5.2. Effects on Offspring

Unintentional injury during pregnancy is associated with a range of serious complications in both the mother and the baby. [158,162,166] Maternal complications include uterine rupture, preterm delivery, premature rupture of membranes, placental abruption (PA), and caesarean section delivery. [158,162,166] It is also associated with various fetal and neonatal complications, such as fetal hypoxia, fetal asphyxia, and neonatal respiratory distress syndrome. [158,166] Fetal complications can be immediate or delayed and may occur without direct injury to the uterus. [28,167] Moreover, the degree of fetal compromise is not highly correlated with the severity of injury, as severe complications (e.g., fetal death, PA, and PTB) have been reported after a minor injury. [28,167,168] In addition, the harmful effects of maternal injuries seem to extend well beyond the time of injury. For instance, researchers have found that women who do not deliver immediately after the trauma continue to be at increased risk of PA, PTB, having a LBW infant, and perinatal mortality, [161,169] despite normal fetal monitoring and obstetric evaluation at the time of injury. [166]

2.5.3. Association with CP

There is a paucity of research that examined the long-term effects of maternal injury on offspring's neurodevelopment. Few case reports have described an increased risk of several neurological abnormalities (e.g., hemi or quadriplegia and epilepsy) following the in-utero exposure to injury. [170-172] In a case series, Hayes and colleagues described ten cases of cerebral palsy that followed maternal trauma in pregnancy. [172] All ten cases were delivered uneventfully at term with no sign of perinatal asphyxia, but all showed neuroimaging findings consistent with prenatal brain damage. [172] A report based on the Australian CP Register found that pregnant women exposed to trauma requiring hospitalization had 1.4 times (95% CI: 0.34, 5.77) the risk of having a child with CP than those unexposed to trauma. [173] Estimates from this study, however, were highly imprecise owing to the small number of exposed cases (only two). [173] To the best of our knowledge, only one population-based study has examined the association between maternal unintentional injury and the risk of CP in children. [28] This Canadian study showed a possible increase in the risk of CP in children whose mothers experienced a motor

vehicle accident (RR 1.29 (95% CI: 0.84, 2.10)), most apparent in preterm infants (RR 1.89 (95% CI: 1.07, 3.66)). [28] This study, however, has considered injuries related to motor vehicle crashes only that affected ~8,000 pregnancies (18 exposed cases) in the study population, resulting in imprecise effect estimates. [28]

2.5.4. Potential Contribution to Brain Damage

As discussed above, unintentional injuries could lead to fetal hypoxia, fetal respiratory distress, LBW, PTB, and PA, which all have been linked to CP [100,158,162,166] Uterine contractions are the most common complication of maternal injury, [154] and they may progress to preterm labor, particularly with a severe injury and injuries occurring at earlier GA or after PA. [169] Injury may lead to a shearing effect at the uteroplacental interface owing to differences in tissue characteristics between the uterus and the placenta, which may cause partial or complete PA (occur in 5-50% after maternal injury). [154,169] PA most commonly follows severe injuries but could also occur after minor injuries.[174] PA usually develops 2–6 hours after injury but could be delayed for up to 24 hours. [154] Subclinical PA is also possible, which may progress to acute PA, PTB, or could lead to chronic placental insufficiency, resulting in fetal growth restriction and oligohydramnios. [160] Other potential mechanisms include direct injuries involving the fetus, placenta, or uterus, [154,175] or placental under-perfusion as a result of maternal physiological changes related to fluid loss and shock. [174] Severe traumatic events could also trigger maternal stress, which is linked to several negative effects on the fetus. [176] Diagnostic and treatment interventions for the mother, such as vasopressors and excessive radiation exposure due to imaging, may also negatively affect the developing fetus. [160]

2.6. Summary

CP is the most common cause of physical disability in children; [1] thus, it is important to estimate the disease burden and understand how it has changed over time for proper service planning and provision. The few such Canadian studies are either old or based on selected health regions. CP prevalence in Ontario, the most populated Canadian province, is also scarcely known. Moreover, no study has examined time trends in CP prevalence in Canada. Importantly, studies on temporal trends of CP rates in other developed countries have not systematically quantified CP rates by important population characteristics over time. Examining these trends would identify population

subgroups with persistently high CP rates, which would shed a light on possible determinants and may help inform preventative strategies.

Current evidence suggests that the majority of CP cases are attributed to prenatal factors. Thus, it is important to understand the role of underlying maternal illnesses in CP etiology in order to develop effective preventative strategies. However, great attention in the literature has been devoted to the roles of PTB and LBW, with much less focus on pre-conception and pregnancy factors. Furthermore, studies that examined associations between maternal factors and CP have commonly stratified infants according to GA or BW, making these results prone to collider stratification bias. [113] The role of maternal diabetes and unintentional injury in CP etiology is still unclear, as most evidence is from case reports or small unrepresentative samples, with little emphasis on underlying mechanisms. Because the effects of both exposures on brain development might potentially be preventable, the findings of this thesis would help inform future preventative efforts. In summary, the work presented in this thesis would provide novel contributions to our understanding of the burden and causes of CP, an otherwise scarce area of research.

Chapter 3. Overview of Data and Methods

3.1. Study Population

I formed a population-based retrospective birth cohort using administrative databases housed at ICES (formerly known as Institute for Clinical Evaluative Sciences) that contain health and demographic information of all users of the publicly funded health care system in Ontario, Canada. [28,108] The study cohort was created from the Mother and Baby Database (MOMBABY) that links maternal hospital delivery and birth records. [108] I included all births with at least 20 weeks of gestation born at an Ontario hospital between April/2002–March/2017, yielding 2,227,286 births. I excluded the following: 98,303 births for missing or invalid mother ICES Key Number (IKN); 3,332 for missing or invalid baby IKN; 6,987 because of MOMBABY linkage warning (suspicious matches, e.g., mothers IKN equals to baby IKN, or baby IKN shows up in more than one record); 17 for missing or invalid mother's age (< 10 or > 55 years); 143 for missing or invalid sex of the mother; 107 for missing or invalid sex of the baby; 301 for the death of mother on or before the delivery date; 3,317 for the death of the baby on or before the delivery date, based on the Registered Persons Database (RPDB); 1,425 of non-Ontario mother residents; 733 for missing gestational age; 78 for missing birth weight; 995 for implausible birth weight-gestational age combinations identified using the Alexander method; [177] and 1,371 stillbirths. After these exclusions, our final cohort included 2,110,177 live births. All children were followed from birth until their death (n=6,721, 0.3%) or end of the follow-up period. The study period was extended until March 31, 2018, to allow for a minimum of 1 year of follow-up for each child.

3.2. Data Sources

I linked ten ICES datasets to define study variables. I present a brief overview of each of these datasets, and further details are explained in manuscripts 1–3.

The Mother and Baby Database (MOMBABY)

This database links inpatient admission records of all mothers who deliver an alive or stillborn baby at an Ontario hospital with their newborn baby records. Maternal and newborn records are deterministically linked with reported linkage rates consistently above 98%. [178] This dataset

contains maternal demographic information (e.g., age, parity) and birth characteristics (e.g., birth weight and gestational age). MOMBABY database covers hospital deliveries but does not capture deliveries at other settings; however, most births in Ontario occur in hospitals, and only ~2% occur in other settings, such as at home under midwifery care. [179]

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

This dataset records clinical information for all hospital admissions in the province since 1988. [180] The database contains information on admission and discharge date and a list of up to 25 diagnoses according to the International Classification of Diseases, 10th Revision, Canada (ICD-10-CA), coding system. [181]

Ontario Health Insurance Plan Claims Database (OHIP)

The OHIP includes all fee-for-service payment claims for Ontario physicians and other healthcare providers for services insured by the province's insurance plan. Information recorded includes the provider information, patient identifier, visit date, and diagnostic codes. [180] Physicians paid via models other than fee-for-service (e.g., capitation-based models) are required to provide a "shadow bill" or "information only" claims to ensure the availability of comparable data across payment models. [182] OHIP diagnostic codes were only limited to major disease categories (i.e., the first three numbers of the International Classification of Diseases, 9th Revision (ICD-9) codes) rather than specific diagnoses. [180] In addition, OHIP does not contain information on services provided by Community Health Centers and Health Service Organizations that provide primary health services and health promotion programs for individuals with or without health insurance. [183]

National Ambulatory Care Reporting System (NACRS)

NACRS provides data on hospital and community-based ambulatory care using ICD-10-CA codes. Although this database is available from July 2000, [180] we only included data from 2002 to ensure consistency of diagnostic codes. Also, the data was incomplete in the year 2000/2001 due to non-participation of some facilities, mostly in Ottawa and Hamilton. [180]

Ontario Diabetes Database (ODD)

ODD is an annually updated data-driven registry of all patients in Ontario diagnosed with non-gestational diabetes (type 1 or 2), maintained and updated by ICES. [180,184] It includes prevalent cases of diabetes since 1991and incident cases since 1994. [184] Diabetes diagnoses included in this cohort were defined as individuals with one in-hospital diagnosis of diabetes from CIHI-DAD or two or more outpatient physician diagnoses over a 2-year period. [184]

Ontario Hypertension Database (HYPER)

HYPER is a registry of all patients in Ontario diagnosed with hypertension since 1988; it is annually updated and maintained by ICES. [180]

The Ontario Drug Benefit (ODB)

ODB database contains claims for prescription drugs received under the Ontario Drug Benefit program. Most people receiving these benefits are people 65 years or older. [180] Other eligible groups include residents of long-term care facilities/homes for special care; children and youth age 24 and under who are not covered by private plans; people receiving services under the home care program; trillium drug program recipients; people receiving social assistance; and people eligible for the special drugs program (e.g., certain medications for patients with cystic fibrosis or thalassemia). [180,185]

Ontario Census Area Profiles (CENSUS)

Each mother's postal code at index delivery was linked to data from the closest Canadian census, obtained from Statistics Canada's Census of Canada (years 2001, 2006). [180] CENSUS contains sociodemographic data by six levels of geographic regions with dissemination area as the smallest. [180]

The Ontario Marginalization Index (ON-MARG)

ON-MARG is comprised of four indices developed to capture different aspects of marginalization. ON-MARG was created at ICES using census data and calculated at the dissemination area level. [186] ON-MARG data were available for the years 2001 and 2006 for the study participants. [180]

Registered Persons Database (RPDB)

RPDB collects personal information (including mortality) of each individual eligible for Ontario health benefits and contains records since 1990. [180]

3.3. Data Access and Linkage

Access to the datasets housed at ICES was obtained following the ICES's standard data access procedures. The initial data request form with the intended research description was submitted and approved. I developed, with an ICES analyst, the data creation plan specific to this research including details related to the cohort creation, such as the list of datasets, diagnostic codes, and observation windows. The ICES analyst then extracted all the requested data for all study participants (mothers and children) from ICES central databases. The extracted data were moved to the ICES Data and Analytic Virtual Environment (IDAVE) for virtual access. Using the unique, anonymous identifier (IKN) assigned to each individual in all ICES databases, I then carried out all data linkage. All data management and analyses were done virtually through a secure virtual desktop infrastructure. Once all analyses were completed and results were ready, manuscript-ready outputs were then requested and were later accessed after assessment for re-identification risk.

3.4. Measures

In this section, I provide a brief overview of the variables used in the thesis to supplement the information included in manuscripts 1–3. Further details about these measures are presented in Table 3.1.

3.4.1. Cerebral Palsy

I followed each child from birth until the end of the follow-up period to ascertain the outcome. A diagnosis of CP was defined as having 1) a single inpatient diagnosis (CIHI-DAD) or 2) at least two outpatient diagnoses (OHIP) at least two weeks apart.

3.4.2. Child and Birth Characteristics

Information about child sex (male/female), birth plurality (singleton/multiple), birth weight in grams, and gestational age at birth in completed weeks was obtained from the MOMBABY

database. Preterm birth categories, birth weight categories, and birth weight for gestational age categories were then defined according to the birth weight and gestational age at birth. Congenital malformations were ascertained between the child's birth and the age of six years and were defined as having any inpatient or outpatient diagnosis of major or minor congenital malformations using ICD-9 codes for OHIP "outpatient" diagnoses or ICD-10-CA codes for CIHI-DAD "inpatient" diagnoses.

3.4.3. Maternal Characteristics

Maternal Demographic Characteristics

Maternal age in years at the index delivery date was available in the MOMBABY dataset as a continuous variable except for those <15 or >47 years, which were available as categories owing to privacy concerns over small numbers in each stratum. In this thesis, maternal age was categorized as <20, 20–24, 25–29, 30–34, 35–39, or ≥40 years. Parity (number of previous live births) was also obtained from the MOMBABY dataset as a continuous variable and was categorized as 0, 1, 2, 3, or ≥4 previous live births.

Pregnancy and Delivery Characteristics

Pregnancy-related maternal disorders (gestational diabetes and pregnancy-induced hypertension) were ascertained based on the presence of inpatient or outpatient diagnoses made up to 294 days before the index delivery date. [187] Maternal unintentional injury was ascertained based on inpatient or emergency department diagnoses during the 294 days before the index delivery date. Type of delivery was ascertained from CIHI-DAD using the Canadian Classification of Health Interventions (CCI) codes and was categorized as unassisted vaginal delivery, operative vaginal delivery, or caesarean section delivery. Quality of prenatal care was assessed by counting the number of visits to a health care professional (including midwives, primary care physicians, and specialists) during the pregnancy period (from conception, calculated based on gestational age, to delivery date). The start of prenatal care was calculated based on the gestational age in completed weeks when the first visit to a health care professional occurred. Delayed onset of prenatal care was defined as having the first prenatal care visit after 13 weeks of gestation. The quality of prenatal care was considered inadequate if the first visit occurred after 13 weeks' gestation or the total number of prenatal visits was <13. [188]

Pre-pregnancy Maternal Disorders

Maternal PGDM and pre-gestational hypertension were ascertained from their respective disease registries that collect data on all incident and prevalent cases in the province as described above. Maternal substance use disorder (including smoking, alcohol, drugs) and obesity were ascertained for the period of pregnancy and the year before (660 days before index delivery date). [189]

Socioeconomic Factors

Rural residence was defined according to the Ontario Rurality Index (RIO). RIO incorporates data on population density and time travel to the nearest basic and advanced referral center. The original RIO was developed in 1999/2000 and then updated in 2004 (RIO2004) and 2007 (RIO2008). RIO was calculated at the Census Subdivision (CSD) level (municipalities) using the version of RIO closest to the year of birth (RIO-2004 for 2002–2006 births and RIO-2008 for 2007–2017 births).[190] I defined rural residence as RIO>45, similar to how rural areas are defined for the purposes of physicians' incentives and reimbursement. [191]

Quintiles of the four ON-MARG indices—residential instability, material deprivation, economic dependency, and ethnic concentration—and neighborhood income were used to measure area-based socioeconomic status. These measures were based on Statistics Canada Census data and available at the dissemination area level—the smallest geographical area in the Canadian Census with a population of approximately 400–700 people. [192] Data from the census year closest to the birth year were used (i.e., 2001 census for 2002–2003 births and 2006 census for 2004–2017 births).[192] I did not use data from the 2011 census due to differences in methodology and data collection methods from the traditional long-form questionnaire used in earlier years. [180] Further details of these measures are provided in manuscripts 1–3. I used the mother's eligibility to receive the provincial drug coverage during pregnancy as a proxy for individual-level socioeconomic status. Most eligible individuals under the age of 65 are also receiving welfare benefits. [185]

3.5 Analyses

3.5.1 Primary Analyses

The statistical analyses used to answer each objective are explained in detail in the corresponding chapter (manuscripts 1–3). In brief, for the first objective (manuscript 1), I estimated the overall prevalence of CP during the study period as $\frac{Number\ of\ children\ born\ between\ 2002-2017\ with\ CP}{Number\ of\ live\ births\ born\ between\ 2002-2017}$. The CP prevalence was then estimated separately for each subgroup defined by population characteristics. For temporal trends of CP over time, I restricted the analytical sample to those born between 2002–2013 to allow for an equal follow-up time for all children (n=1,587,087). I followed each child from birth through four years of age (i.e., 4th birthday plus 364 days) for any CP diagnosis. I chose this age cut-off because previous studies have shown that >90% of children with CP are diagnosed before age five years. [9,193] This was also confirmed in our cohort that ~88% of CP cases were diagnosed by that age. I used the Poisson regression analyses to estimate temporal trends of CP prevalence over time and used the number of live births as the offset variable. I examined and found no evidence of over-dispersion in the data (both the mean and variance of the outcome = 0.002; the over-dispersion parameter=0 with *p*-value=1.00; the Poisson goodness-of-fit chi-square test *p*-value=1.00); thus the Poisson regression was deemed appropriate. I tested for non-linear temporal trends using restricted cubic splines and compared models with different numbers of knots amongst each other and relative to a linear model using the Likelihood-ratio X^2 test and the Akaike information criterion (AIC). [194,195] A model with 3 knots at years 2003, 2008, and 2012 showed the best fit as it had the lowest AIC, and the *p*-value for the Likelihood-ratio X^2 test comparing this model to a linear model was 0.001. I then fitted a separate Poisson model for each subgroup defined by population characteristics and checked whether a non-linear model would better fit the data and found that the non-linear model described above had the best fit for the data.

For objectives 2 and 3, I used the Cox proportional hazards models to examine the associations between maternal diabetes (PGDM or GDM) or maternal unintentional injury and CP. For each child, the time of birth indicated the start of follow-up time (time 0), and their follow-up time ended at the time of death, first CP diagnosis, or the end of follow-up period on March 31, 2018, whichever came first. I chose to use the Cox model to account for unequal follow-up time. The Cox model would also be suitable to estimate risk ratios when the outcome is rare, as is the case

of CP. I adjusted for *a priori* identified potential confounders for each exposure. For objective 2 (manuscript 2), I tested for associations for PGDM and GDM separately and also examined associations according to PGDM duration. I also estimated controlled direct effect (CDE) of PGDM on CP not mediated by large for gestational age using marginal structural models (MSM). I chose to use MSM, rather than traditional regression-based mediation analysis because of concerns about the presence of mediator-outcome confounders affected by the exposure (e.g., preeclampsia and the presence of congenital malformations) that would bias CDE estimates based on regression-based techniques.[196,197] In manuscript 3, I examined associations by injury severity, timing, and mechanism of injury.

3.5.2 Sensitivity Analyses

I used a wide range of sensitivity analyses to test the robustness of the findings. In manuscript 1, I re-estimated CP prevalence and temporal trends using an alternative definition of the outcome. I also repeated the analyses using neonatal survivors as the denominator to enhance the comparability of our findings to other reports that used neonatal survivors as the denominator. I also used this denominator to examine if CP rates would be higher in categories with high neonatal mortality (e.g., the extremely preterm and extremely low birth weight categories).

In manuscripts 2 and 3, I re-examined associations with CP using Poisson regression with follow-up time as the offset variable (rate ratios) and log-binomial regressions (risk ratios). I did these analyses because the age of CP diagnosis would not accurately reflect the disease incidence, as most CP cases develop before birth or shortly after. Thus, the results of the Cox model may potentially be influenced by factors that affect how soon a child is diagnosed with CP. In manuscripts 2 and 3, I also conducted record-level probabilistic bias analyses to test the robustness of estimated effects against the presence of misclassifications (outcome or exposure) and unmeasured confounding. I also re-estimated CDE in the presence of moderate to severe unmeasured mediator-outcome confounding in manuscript 2. The associations were also examined under alternative definitions of exposures. For example, we excluded GDM diagnosed after 28 weeks to account for the fact that children born preterm were less likely to be classified as exposed. Finally, associations for maternal unintentional injuries (manuscript 3) were also

examined separately for preterm and term-born infants to deal with the problem that pregnancies that ended early had a lower chance to be exposed to injuries than those carried to term.

Table 3.1 Variables Definitions, Diagnostic Codes, and Relevant Data Sources

Variable	Datasets	ICD-10-CA	OHIP code	CCI codes	Period of assessment	Variable definition
Cerebral palsy	CIHI-DAD & OHIP	G80	343	-	From birth to death or end of follow-up	CP if 1 inpatient diagnosis or 2 or more outpatient diagnoses at least 2 weeks apart
Birth characteristics (BW, GA, infant's sex, birth plurality)	MOMBABY	-	-	-	Index delivery admission	BW in grams, GA in completed weeks, infant's sex (male/female), birth plurality (singleton/multiple)
Maternal age and parity	MOMBABY	-	-	-	Index delivery admission	Maternal age was categorized as <20, 20–24, 25–29, 30–34, 35–39, or ≥40 years. Parity was categorized as 0, 1, 2, 3, or ≥4 previous live births
Area-based socioeconomic characteristics	CENSUS & ON-MARG	-	-	-	Index delivery admission	Rural residence (yes/no), and quintiles of neighborhood income, residential instability, material deprivation, economic dependency, and ethnic concentration
Maternal eligibility for ODB	ODB	-	-	-	From conception to index delivery date	Eligible (yes/no)
Quality of prenatal care	OHIP	-	-	-	From conception to index delivery date	Delayed onset if first visit >13 weeks; inadequate if first visit >13 weeks or number of visits <13 [188]
Type of delivery	CIHI-DAD	-	-	5MD51, 5MD52,	Index delivery date +/- 7 days	Unassisted vaginal delivery, Operative vaginal delivery, or Caesarean section delivery

				5MD53, 5MD54, 5MD55, 5MD56, 5MD60		
Child's mortality	RPDP	-	-	-	From birth to end of follow-up	Age at death in years
Congenital malformations	CIHI-DAD & OHIP	Q00–Q99	740-759	-	From birth to age 6 years	Any congenital malformation (yes/no) and by type of malformation
Maternal pre-gestational diabetes	ODD	-	-	-	All cases since 1992	Maternal pre-gestational diabetes (yes/no) and by duration of diabetes
Maternal pre-gestational hypertension	HYPER	-	-	-	All cases since 1988	Maternal pre-gestational hypertension (yes/no)
Maternal substance use disorder	CIHI-DAD & OHIP	F10–F19	303-305	-	660 days before the index delivery date	Maternal substance use disorder (yes/no)
Maternal obesity	CIHI-DAD & OHIP	E66	278	-	660 days before the index delivery date	Maternal obesity (yes/no)
Maternal unintentional injury	CIHI-DAD & NACRS	V01–X59	-	-	294 days before the index delivery date	Maternal unintentional injury (yes/no) and by mechanism of injury
Gestational diabetes	CIHI-DAD & OHIP	E10, E11, E12, E13, E14, O24	250	-	294 days before the index delivery date	Gestational diabetes if 1 inpatient diagnosis or 2 or more outpatient diagnoses not on the same day

Gestational hypertensive disorders	CIHI-DAD & OHIP	O10, O11, O13, O14, O15, O16	642	-	294 days before the index delivery date	Gestational hypertensive disorders if 1 inpatient or outpatient diagnosis

Chapter 4. Manuscript 1-Trends of cerebral palsy occurrence in children born in 2002–2017: A population-based retrospective cohort study.

4.1. Preface

For life-long disabling conditions such as CP, having an accurate estimate and description of the disease burden is key to deliver optimal health care and educational services that meet the needs of the affected children and their families. The literature on the burden of CP is limited, particularly in Canada, in several ways. First, only a few Canadian studies have estimated CP prevalence and were limited to specific regional health authorities. Secular changes in CP rates over time in Canada are currently unknown. Furthermore, whereas studies in other developed countries have examined temporal trends of overall CP rates, no study so far has assessed these trends across population subgroups defined by key characteristics. Therefore, I conducted a population-based study to examine the prevalence and temporal trends of CP in Canada—both overall and by key population characteristics—over a 16-years period. This manuscript entitled "Trends of cerebral palsy occurrence in children born in 2002–2017: A population-based retrospective cohort study" is currently under review at *Developmental Medicine & Child Neurology*, manuscript ID: DMCN-OA-21-10-0659.

4.2. Manuscript 1

Prevalence and temporal trends of cerebral palsy in children born in 2002–2017: A population-based retrospective cohort study

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Short title: Prevalence and Temporal Trends of Cerebral Palsy

ABSTRACT

Aim: To examine the prevalence and temporal trends of cerebral palsy (CP) overall and by population characteristics.

Method: We identified 2,110,177 live births born in the province of Ontario, Canada, between 2002–2017, and estimated CP prevalence in children aged 0–16 years overall and by specific population characteristics. We also examined temporal trends in CP rates—overall and by characteristics—in young children (0–4 years) by their year of birth between 2002–2013 (n=1,587,087 live births).

Results: Overall CP prevalence among children aged 0–16 years was 2.52 (95% confidence interval: 2.45, 2.59) per 1000 live births. CP rates in ages 0–4 peaked at 2.86 in 2007 births but steadily declined afterward to 1.94 per 1000 live births in 2013. CP rates were higher in children born preterm, small-for-gestational-age, boys, multiples, children with congenital malformations, and in children of young (<20 years), old (≥40 years), primiparous, or grand multiparous (≥4) mothers, or those with inadequate prenatal care or who delivered by caesarean section. While differences by these characteristics decreased over time, the magnitudes of socioeconomic disparities in CP rates remained unchanged over the study period.

Interpretation: Despite the decreasing trend of CP rates overall, CP rates varied by the child and maternal characteristics over time.

Abbreviations:

CP — Cerebral Palsy

OHIP — Ontario Health Insurance Plan

GA — Gestational Age

SGA — Small for Gestational Age

AGA — Appropriate for Gestational Age

LGA — Large for Gestational Age

BW — Birth Weight

RIO — Rurality Index of Ontario

ON-Marg — Ontario Marginalisation Index

RII — Relative Index of Inequality

SII — Slope Index of Inequality

HIE — Hypoxic Ischemic Encephalopathy

What this study add

- The overall CP prevalence was 2.5 per 1000 live births among children born in 2002-2017.
- CP prevalence peaked in children born in 2007 and then steadily decreased between 2007-2013.
- Changes in CP rates varied over time by child and maternal characteristics.
- Socioeconomic inequalities in CP persisted and remained stable over the study period.

Cerebral palsy (CP) is a lifelong disorder of posture and movement caused by damage to the developing brain, and is the most common cause of physical disability in children. [1] The most recent meta-analysis of CP prevalence has reported an overall rate of 2.11 (95% confidence interval (CI): 1.98–2.25) per 1000 live births; [2] however, the authors noted the limited information on secular trends of CP rate in the existing literature. Studies from European countries have mostly shown slight declines in more recent years, though the results are inconsistent. [3-6] For instance, rates in Sweden have remained stable since 1999 with a slight decline in 2007–2010 births, [3] while Norway (1999–2010 births) [4] and Denmark (1999–2007 births) [5] have seen declining trends, as did a multi-site European study of earlier birth cohorts (1980–2003). [6] Australian studies have also reported declining trends in multiple states since 1995. [7-9]

Evidence on prevalence rates of CP from population studies in North America is more limited. Two Canadian studies have estimated CP prevalence in selected health regions and showed a prevalence of ~2.2 per 1000 children born in 1999-2001 [10] and 2008-2010, [11] which were comparable to older studies (1985–1988, and 1991–1995). [12,13] Canadian studies that explored temporal trends of CP have been limited to preterm and/or low birth weight survivors. [14,15] Only a few studies from the US have examined CP rates over time and have shown conflicting findings. [16-18] Studies that used data from the National Health Interview Survey in the US have reported stable trends in parent-reported CP diagnoses among children aged 3–17 between 2009–2017,[16,17] while a study based on population-based developmental disabilities surveillance programs for 8-year-olds in four states have documented declining rates between 2006–2010.[18]

Differences in years covered, data sources and CP ascertainment across studies make drawing a conclusion in temporal trend of CP occurrence difficult. Moreover, CP rates over time by important population characteristics are further limited and inconsistent in results between studies. Higher rates of CP in preterm and low birth weight infants are well-documented; [2] however, studies have reported stable,[5] decreasing, [9] and increasing [14 19] rates in extremely preterm infants (<28 weeks) over time. Higher rates of CP have also been observed in multiples, male infants,[3,20] infants with congenital malformations,[21] and in children born to adolescent or

old mothers [7,8] and mothers with low socioeconomic status.[22] However, we know little about temporal changes in CP rates across these key sociodemographic characteristics.

Using data from over two million births, this study aims to estimate the prevalence rate and temporal trends of CP in Ontario, Canada among children born in 2002–2017 both overall and by child, maternal and sociodemographic characteristics.

METHODS

Study Design

We created a population-based longitudinal cohort using seven existing datasets from the ICES (formerly known as the Institute for Clinical Evaluative Sciences) in Ontario, Canada. Details about ICES are available elsewhere.[23,24] Briefly, ICES houses multiple population health administrative databases that contain sociodemographic and health data of all residents eligible for the universal provincial healthcare system, the Ontario Health Insurance Plan (OHIP). These datasets were linked using unique encoded identifiers and analyzed at ICES, and eTable 1 shows details of data sources used to define our study variables. Ethics approval was received from the Institutional Review Board of the Faculty of Medicine and Health Sciences at McGill University.

Participants

We included all in-hospital deliveries >20 gestational weeks in the province between April 1, 2002, and March 31, 2017, identified from the Mother-Baby database (MOMBABY) that links maternal delivery and infant birth records with 98% completeness of all births in Ontario.[24] Of 2,227,286 identified births, we excluded those with missing or invalid maternal or child records, those with missing or invalid birth characteristics, and stillbirths, yielding a total of 2,110,177 live births in the study cohort (eFigure 1). We followed each child until death or the end of follow-up on March 31, 2018, when the data for this study was extracted. For temporal analyses, we restricted our sample to children born between April 2002 and March 2013 to allow for an equal follow-up time (up to four years) for all children (n=1,587,087 live births). We chose the age 0–4 because studies have shown >90% of CP cases are diagnosed by the age of four years.[7,25]

The outcome

The outcome was cerebral palsy diagnosis in the child defined as (1) any inpatient hospitalization diagnosis, using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision diagnostic codes (ICD-10-CA codes: G80), or (2) two or more outpatient diagnoses of CP on physician billings claims at least two weeks apart (code: 343).[23,24]

Child characteristics

Gestational age at birth (GA) was categorized as a binary preterm birth variable (GA < 37 weeks) and also as a multi-category variable (eMethods). Birth weight for sex and gestation using a Canadian reference[26] was categorized into small for gestational age (SGA, <the 10th percentile for gestational age and sex) appropriate for gestational age (AGA, the 10th–90th percentiles), and large for gestational age (LGA, > the 90th percentile).[26] We also examined rates by birth weight categories (eMethods). Other child characteristics included the child's sex (male/female), the birth plurality (singleton/multiple), and the presence (yes/no) and type of any congenital malformations (details in eTable 2).

Maternal Characteristics

Maternal age and parity (number of previous live births) were categorized as <20, 20-24, 25-29, 30-34, 35-39, or ≥40 years, and 0, 1, 2, 3, or ≥4, respectively. For temporal analyses, some categories were collapsed owing to similar CP rates. Type of delivery was categorized as unassisted vaginal delivery, operative vaginal delivery, or caesarean section delivery (eTable 2). The quality of prenatal care was created based on the timing and number of prenatal care visits obtained from the physician billings claims and considered adequate if the first visit was between 0–13 weeks' gestation and the total number of prenatal visits was >12.[27]

Socioeconomic Characteristics

Rural residence was defined according to the Rurality Index of Ontario (RIO, rural if RIO>45),[28] which is a widely used measure of rurality in the Ontario health system. We used quintiles of small-area based income and the four Ontario Marginalization (ON-Marg) indices—residential

instability (proportion of individuals at risk of family and housing instability), material deprivation (proportion of people with low material resources), economic dependency (proportion of people with no income from employment), and ethnic concentration (proportion of recent immigrants and of visible minorities).[29] We also used the mother's eligibility for the provincial drug program benefits as an individual-level socioeconomic indicator.[30] Details of these measures are in eMethods and eTable 3.

Statistical Analysis

We first estimated the overall prevalence of CP per 1000 live births in children at 0–16 years of age and then the rates according to the child, maternal, and socioeconomic characteristics, using Poisson regression. The Poisson regression was deemed appropriate to model the rates as there was no evidence of over-dispersion in the data (eMethods). To examine changes in CP rates over time, we estimated the rate of CP diagnosed at 0–4 years for children born in the same year (henceforth birth 'cohort') between 2002–2013 using the number of live births as the offset variable. A non-linear Poisson model with three knots (year 2003, 2008, and 2012) showed the best fit for the data. We fitted separate Poisson models for subgroups defined by population characteristics. To account for multiple births to some mothers during the study period (n=1,021,086 births to 450,929 mothers), we adjusted standard errors in all models using clustered sandwich estimators. Socioeconomic inequalities over time were examined using the Relative Index of Inequality (RII) and the Slope Index of Inequality (SII) [31] (eMethods).

Due to potential misclassification in the administrative data-based CP diagnosis, we re-analyzed the data using an alternative definition of CP (*any* inpatient or outpatient CP diagnosis). [32] We also examined rates after restricting our sample to neonatal survivors to enhance comparability and examine if CP rates would be higher in categories with high neonatal mortality (e.g., the extremely preterm and extremely low birth weight categories).. All statistical analyses were conducted using Stata version 16.1 (StataCorp, College Station, TX, USA).

RESULTS

Overall CP Prevalence Rate

Among the 2,110,177 live births eligible for the study, 5,317 children were diagnosed with CP, corresponding to the overall prevalence rate of 2.52 (95% (CI): 2.45, 2.59) per 1000 live births among children at ages 0–16. The median age at CP diagnosis was 1.66 years (interquartile range: 0.94-3.03); more than half (58.5%) were diagnosed before 2 years of age, and 87.9% between 0-4 years (eTable 4).

Figure 4.1 presents rates of CP diagnosed in ages 0–4 years per 1000 live births for each birth cohort between 2002 and 2013. The rate increased from 2.58 (2.39, 2.78) in the 2002 birth cohort to 2.86 (2.73, 2.95) in 2007 births, followed by a steady decline, reaching a low of 1.94 (1.78, 2.11) in those born in 2013.

Prevalence Rates by Child Characteristics

Rates of CP per 1000 live birth among children born preterm (<37 weeks) were more than six times those born at term or later (11.89 (11.38, 12.43) vs 1.72 (1.67, 1.78)) (Table 4.1). Consistent with the overall pattern, rates of CP in preterm children were stable in 2002–2007 birth cohorts and steadily decreased afterward; however, they remained consistently higher than those born at term or post-term (Figure 4.2-a). CP rates in children born at term or post-term slightly increased from 1.66 (1.51, 1.83) per 1,000 in 2002 births to 1.89 (1.87, 2.00) in 2007 births and then steadily declined to 1.29 (1.16, 1.44) in 2013 births. The highest rates of CP were seen in children born extremely preterm (<28 weeks) (66.93 (61.55, 72.74)) and in those with birth weight < 1000g (59.53 (54.43, 65.06)) (eTable 5); temporal trends across categories of GA and BW were stable in 2002–2007 birth cohorts followed by a slow decline (eFigure 2). CP rates in children born SGA were almost double those born AGA, while the rates of children born LGA and AGA were similar (Table 4.1). These patterns remained unchanged throughout the study period (Figure 4.2-b).

Overall rates of CP were higher in boys than girls (2.87 (2.77, 2.97) vs 2.16 (2.07, 2.25)) and in multiple births, approximately three times those in singletons (Table 4.1). CP rates were also higher in children with any congenital malformations (13.87 (13.41, 14.35) vs 1.08 (1.03, 1.13)).

Rates were highest in children with malformations of the nervous system (87.18 (82.2, 92.42)) and lowest in children with congenital malformations of the digestive system (8.40 (7.47, 9.45)) (eTable 6). CP rates by sex, birth plurality, and presence of congenital malformations increased until 2007 and decreased afterward, and the gaps narrowed in more recent years (Figure 4.2-c, d, and e).

Prevalence Rates by Maternal Characteristics

CP rates were higher in children of mothers aged < 20 years and ≥40 years and of primiparous mothers and mothers with ≥4 previous live births (Table 4.1). Rates of CP for children delivered by caesarean section were close to double those born by unassisted vaginal delivery (3.78 (3.63, 3.94) vs 2.01 (1.93, 2.08)). Temporal trends by these characteristics showed similar patterns to the overall trend with a peak rate in the 2007 birth cohort followed by a gradual decrease in 2007–2013 births, but the decrease was greater in children of women ≥40 years and ≥4 previous live births (Figure 4.3 and eFigure 3). CP rates were higher in women with inadequate prenatal care than women with adequate prenatal care (Table 4.1), but these gaps decreased in recent birth cohorts (Figure 4.3-d).

Prevalence Rates by Socioeconomic Characteristics

Socioeconomic gradients in CP rates were observed across quintiles of neighborhood income and the Ontario marginalization indices, except for ethnic concentration showing higher rates in children residing in areas with low ethnic-diversity (~2.71 per 1000 in quintiles 1 and 2 vs. 2.36 in quintile 5) (Table 4.1). Socioeconomic disparities were also evident in both relative and absolute scales as estimated in RII and SII, respectively (eTable 7). For example, CP rates among children of women living in the most materially deprived areas were 1.40 (1.27, 1.54) times relative to those living in the least deprived areas. Rates of CP among children whose mothers received the provincial drug benefit during their pregnancy were also higher than those of mothers who did not (Table 4.1).

Socioeconomic differences had remained relatively stable over time for neighborhood income, residential instability, and material deprivations, while the disparities tended to decrease for the economic dependency and ethnic concentration indices and maternal receipt of the drug benefit

in recent birth cohorts (eFigure 4). However, RII and SII over time showed that the inequalities remained relatively unchanged for all indicators (eFigure 5), and formal testing of interaction terms between period and cumulative rank scores were statistically insignificant (all *p*-values>0.1).

Additional analyses results

As expected, the overall CP prevalence was higher when we used the alternative definition of the outcome (4.18 (4.09, 4.26) per 1000 live births) but the rates over time and by characteristics were similar to our main results, as were figures in neonatal survivors (eFigures 6, 7 and eTables 8, 9).

DISCUSSION

This population-based study examined CP prevalence rates overall and stratified by important population characteristics using a large cohort of live births over a 16-year period, providing the most recent and comprehensive Canadian data on CP rates and the first on temporal trends. Our overall prevalence estimate of 2.52 (95% CI: 2.45, 2.59) per 1000 live births was comparable with those reported in Europe [3-6] and Australia [7-9] but considerably lower than those from the US (3-4 per 1000 children 3–17 years).[16,17] Direct comparison of results from different studies should be made with caution because of variation in methodology and definitions. For example, US studies have used parent reports of "ever" CP diagnoses to ascertain CP, which may have misclassified some unconfirmed cases. Furthermore, rates would vary by the choice of the denominator (e.g., live births vs. surviving children at certain ages) that would be affected by migration and survival patterns. [33]

Consistent with other studies, [3,9,11] CP rates were considerably higher in preterm infants but showed a declining trend in more recent births. This trend suggests that the improved survival of preterm infants in Canada [34] has not resulted in increased CP rates in preterm children. Several advances in neonatal care of preterm infants that are known to reduce the risk of CP (e.g., antenatal steroids, postnatal surfactant, caffeine therapy for apnea) may have contributed to the declining trend in preterm children. [35]

We also observed a rise in CP rates among children born at term until 2007 and a steady decline afterward. Use of therapeutic hypothermia for hypoxic-ischemic encephalopathy (HIE) has been shown to decrease both the risk of death and CP in term-born infants, and its use has increased since 2005. [36] Nevertheless, therapeutic hypothermia would account for a small portion of the decline as HIE lesions arise in <20% of term-born children with CP. [6,37]

Only a few studies have examined CP rates by maternal and socioeconomic characteristics in the literature, and the evidence on CP rates by these characteristics over time is particularly scarce. Consistent with data from Australia, [8] we found higher rates in children of young (<20 years), old (≥40 years), primiparous, and grand multiparous (≥4) mothers that are associated with known predictors of CP, such as preterm birth, SGA, and birth defects. [38] Despite the gradual increase in maternal age over time, [39] it is reassuring that CP rates in this group have decreased over time. We observed that CP rates were higher in women with inadequate prenatal care, comparable to a study from California, [40] and that these differences in CP rates by prenatal care adequacy have decreased over time. Given the decreased gap was mostly driven by lowered CP rates in the inadequate prenatal care group, we speculate that the decrease of preterm births in women with inadequate prenatal care (from ~12% to 10% between 2007–2013 in our data) would in part explain the narrowing gap over time. We also observed socioeconomic disparities in CP rates using several small-area-based socioeconomic indicators and the disparities mostly remained stable over the study period. Several important risk factors of CP, such as preterm birth and low birth weight, are also associated with low socioeconomic status, but these factors are unlikely to fully explain the inequalities in CP prevalence. [22]

Strengths and limitations

Our study used all live births within a single-payer health system identified by the validated data linkage of maternal and child records with high linkage rates. [24,41] This would reduce the risk of selection bias and improve the generalizability of our results. We included over 2 million births with data spanning over 16 years to estimate not only the overall patterns in CP rates but population-specific estimates across a wide range of child, maternal and sociodemographic characteristics and their changing patterns over time.

Administrative databases may have diagnostic code entry errors and thus prone to misclassification. However, CP diagnostic codes in administrative health data have been validated and have shown a sensitivity of 65.5% and a specificity of 99.9%. [32] Our CP definition of at least a single inpatient diagnosis or two or more outpatient diagnoses at least two weeks apart—assuming that inpatient diagnoses are more accurate as they are mostly made by pediatric specialists—was developed in consultation with experienced researchers and clinicians. This definition was also used by other researchers who used ICES data with CP as the outcome. [23,24] Additionally, we have used an alternative definition for CP and found similar results to our primary findings. Under-ascertainment of CP may have occurred due to the short follow-up time for children born in the most recent years. To mitigate the impact of differential follow-up window for outcome ascertainment, our analyses to examine temporal trends were restricted to children born up to 2013. This age cut-off of 4 years was arbitrary and may not include all CP cases, particularly children with a milder phenotype that may only be diagnosed at a later age.[25] However, ~90% of CP cases were diagnosed before the age of 5 years in our data, consistent with other studies. [7,25]

Some children with CP may have moved out of the province before getting a CP diagnosis in Ontario and thus were not included in our study. However, migration rates from Ontario to other Canadian provinces were minimal during the study period (<0.5%) [42] and it would be nondifferential with respect to study outcome given the availability of good-quality health and educational services in Ontario for children with disabilities. [43] We did not have access to other potentially important individual-level characteristics (e.g., maternal race/ethnicity, immigration status, and education), which have shown to be associated with CP, [22,24] and to the severity or functional status of CP cases. Furthermore, we could not examine CP prevalence and temporal trends by CP subtype as diagnostic codes in outpatient databases were limited to the main disease categories rather than specific subtypes.

Conclusion

This study provides comprehensive prevalence estimates of cerebral palsy in recent years in Canada. Declines in CP rates in more recent births and across gestational age and birth weight categories are encouraging and might reflect potential positive impacts of advances in perinatal

care and neuroprotective strategies. Our results highlight the need for continued population-based surveillance of the rates of CP to determine if these trends continue. Future studies that describe temporal trends by CP subtype and functional status will better guide services planning and provision. The persistence of socioeconomic disparities in CP over time warrants further investigation. Future work should also focus on recognizing factors that may explain the changes in CP rates over time in relation to simultaneous changes in CP risk factors in the population.

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Conflict of Interest Disclosures (includes financial disclosures): None declared.

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Table 4.1 Cerebral palsy prevalence rates (95% CI) per 1000 live births among children aged 0–16 born between 2002–2017 in Ontario, Canada by maternal and sociodemographic characteristics (n=2,110,177)

Characteristics	Number of CP cases	Number of live births (%)	CP rate per 1000 live birth (95% CI)
Child's sex			
Female	2,218	1,028,540 (49%)	2.16 (2.07, 2.25)
Male	3,099	1,081,637 (51%)	2.87 (2.77, 2.97)
Pregnancy plurality			
Single	4,793	2,038,089 (97%)	2.35 (2.29, 2.42)
Multiple	524	72,088 (3%)	7.27 (6.67, 7.92)
Preterm birth			
No	3,352	1,944,932 (92%)	1.72 (1.67, 1.78)
Yes	1,965	165,245 (8%)	11.89 (11.38, 12.43)
Birth weight for gestational age			
Appropriate for gestational age	3,936	1,691,472 (80%)	2.33 (2.26, 2.40)
Small for gestational age	865	201,164 (10%)	4.30 (4.02, 4.59)
Large for gestational age	516	217,541 (10%)	2.37 (2.18, 2.58)
Any congenital malformation			
No	2,018	1,872,311 (89%)	1.08 (1.03, 1.13)
Yes	3,299	237,866 (11%)	13.87 (13.41, 14.35)
Maternal age			
<20 years	265	66,364 (3%)	3.99 (3.54, 4.50)
20–24 years	755	262,940 (13%)	2.87 (2.67, 3.08)
25–29 years	1,400	585,570 (28%)	2.39 (2.27, 2.52)
30–34 years	1,732	736,102 (35%)	2.35 (2.24, 2.47)
35–39 years	927	378,474 (18%)	2.45 (2.30, 2.61)
≥40 years	238	80,727 (4%)	2.95 (2.60, 3.35)
Parity			
0	2,648	944,887 (45%)	2.80 (2.70, 2.91)
1	1,655	748,127 (36%)	2.21 (2.11, 2.32)
2	648	275,799 (13%)	2.35 (2.18, 2.54)
3	187	84,056 (4%)	2.22 (1.93, 2.57)
4+	179	57,308 (3%)	3.12 (2.70, 3.62)

Characteristics	Number of CP cases	Number of live births (%)	CP rate per 1000 live birth (95% CI)
Type of delivery			
Unassisted vaginal delivery	2,605	1,299,054 (62%)	2.01 (1.93, 2.08)
Operative vaginal delivery	444	211,025 (10%)	2.10 (1.92, 2.31)
Caesarean section	2,268	600,098 (28%)	3.78 (3.63, 3.94)
Quality of prenatal care [a]			
Adequate	3,290	1,444,385 (68%)	2.28 (2.20, 2.36)
Inadequate	2,027	665,792 (32%)	3.04 (2.92, 3.18)
Living in rural area [b]			
No	4,755	1,897,003 (90%)	2.51 (2.44, 2.58)
Yes	560	212,379 (10%)	2.64 (2.43, 2.86)
Recipient of Ontario Drug Benefit			
No	4,670	1,932,615 (92%)	2.42 (2.35, 2.49)
Yes	647	177,562 (8%)	3.64 (3.37, 3.94)
Neighborhood income quintile [c]			
Q1 (highest)	756	347,321 (17%)	2.18 (2.03, 2.34)
Q2	1,069	435,226 (21%)	2.46 (2.31, 2.61)
Q3	1,111	429,620 (20%)	2.59 (2.44, 2.74)
Q4	1,049	420,658 (20%)	2.49 (2.35, 2.65)
Q5 (lowest)	1,309	469,691 (22%)	2.79 (2.64, 2.94)
ON-Marg residential instability quintile [d, e]			
Q1 (least marginalized)	909	415,409 (20%)	2.19 (2.05, 2.34)
Q2	1,041	417,061 (20%)	2.50 (2.35, 2.65)
Q3	997	374,155 (18%)	2.66 (2.50, 2.84)
Q4	1,038	398,022 (19%)	2.61 (2.45, 2.77)
Q5 (most marginalized)	1,244	469,399 (23%)	2.65 (2.51, 2.80)
ON-Marg material deprivation quintile [d, e]			
Q1 (least marginalized)	1,087	502,692 (24%)	2.16 (2.04, 2.29)
Q2	888	382,315 (18%)	2.32 (2.18, 2.48)
Q3	981	375,275 (18%)	2.61 (2.46, 2.78)
Q4	994	367,034 (18%)	2.71 (2.55, 2.88)
Q5 (most marginalized)	1,279	446,730 (22%)	2.86 (2.71, 3.02)

Characteristics	Number of CP cases	Number of live births (%)	CP rate per 1000 live birth (95% CI)
ON-Marg economic dependency quintile [d, e]			
Q1 (least marginalized)	1,530	637,090 (31%)	2.40 (2.28, 2.52)
Q2	1,190	474,534 (23%)	2.51 (2.37, 2.65)
Q3	938	373,369 (18%)	2.51 (2.36, 2.68)
Q4	842	316,221 (15%)	2.66 (2.49, 2.85)
Q5 (most marginalized)	729	272,832 (13%)	2.67 (2.49, 2.87)
ON-Marg ethnic concentration quintile [d, e]			
Q1 (least marginalized)	711	262,584 (13%)	2.71 (2.52, 2.91)
Q2	832	302,901 (15%)	2.75 (2.57, 2.94)
Q3	896	348,636 (17%)	2.57 (2.41, 2.74)
Q4	1,127	456,665 (22%)	2.47 (2.33, 2.62)
Q5 (most marginalized)	1,663	703,260 (34%)	2.36 (2.25, 2.48)

Notes

[a] Adequate prenatal care if the first visit is between 0–13 weeks' gestation and the total number of prenatal visits is >12

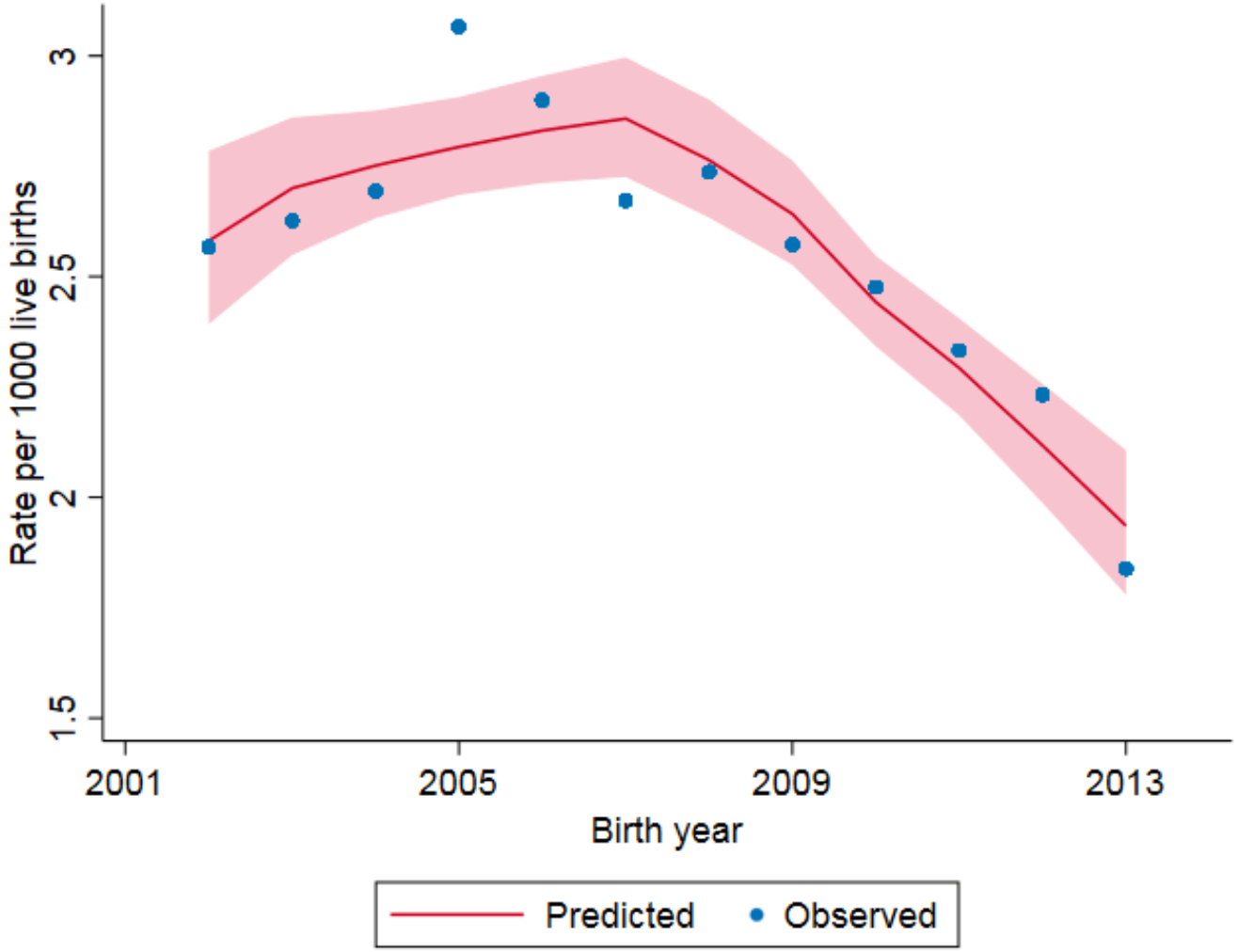
[b] n=795 had missing information on rural residence status

[c] n=7,661 had missing information on neighborhood income

[d] ON-Marg – Ontario Marginalization Index

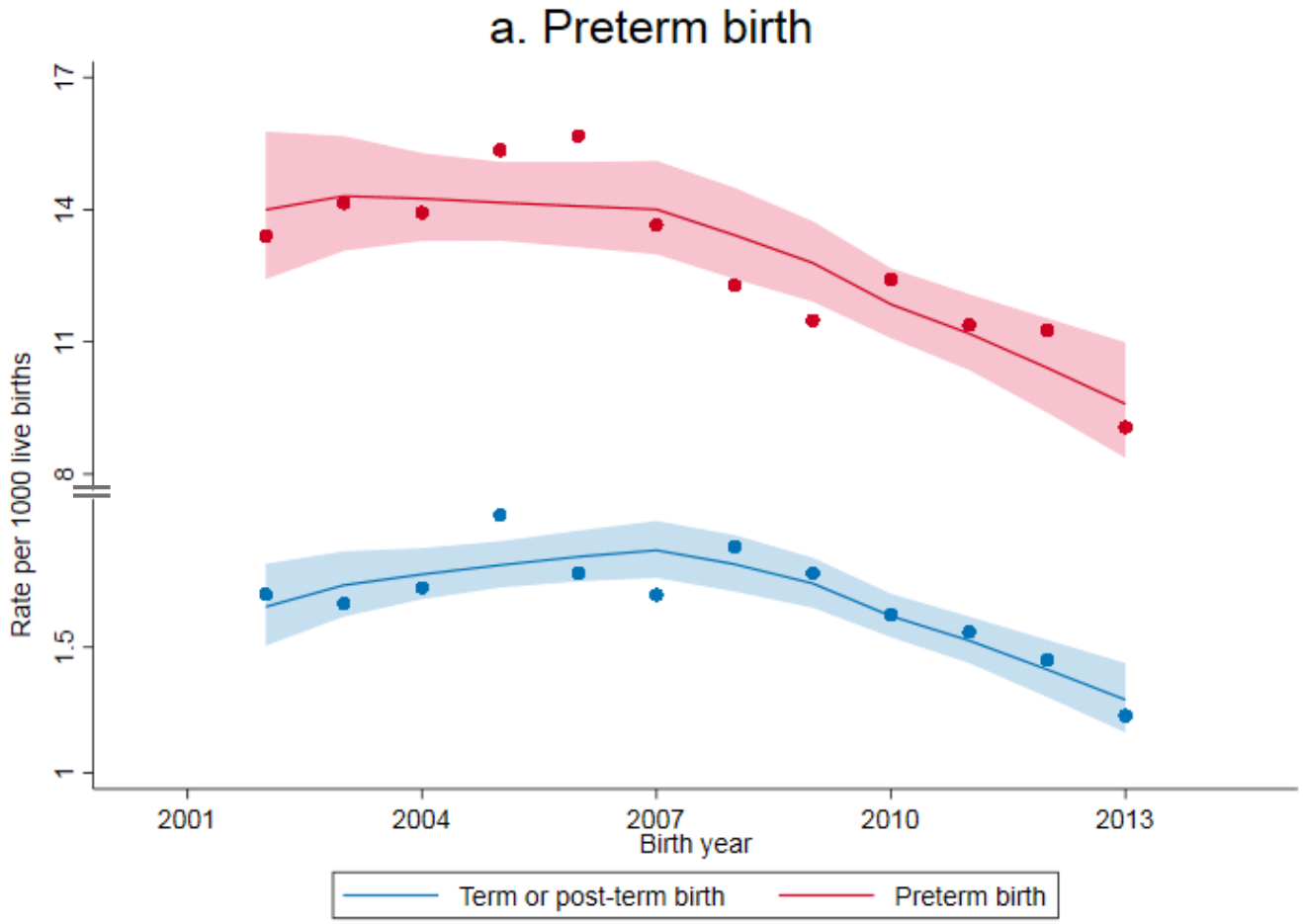
[e] n=36,131 had missing information on ON-Marg indices

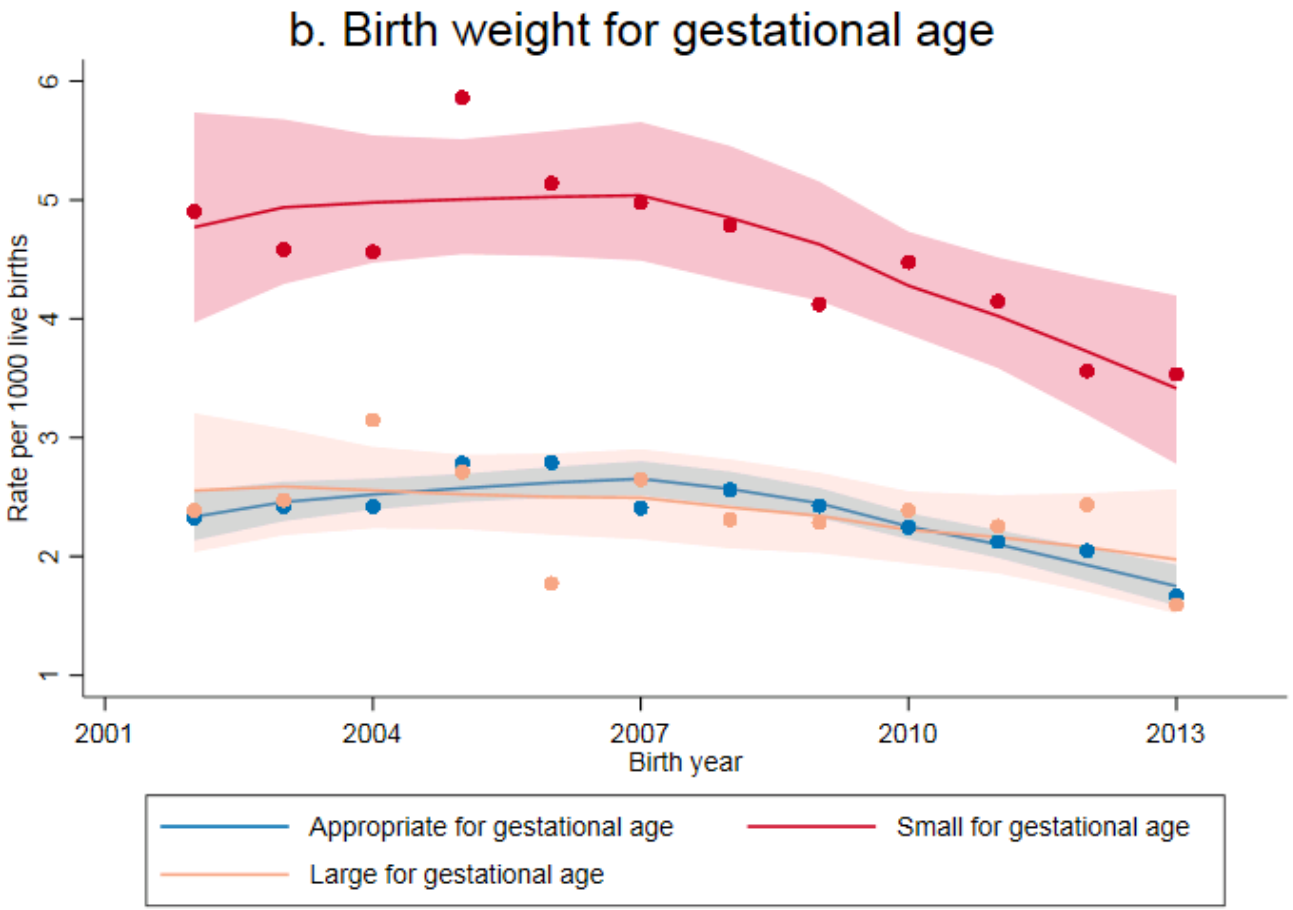
Figure 4.1. Cerebral palsy rates (95% CI) per 1000 live births by year of birth among children aged 0–4 years (N=1,587,087) in Ontario, Canada

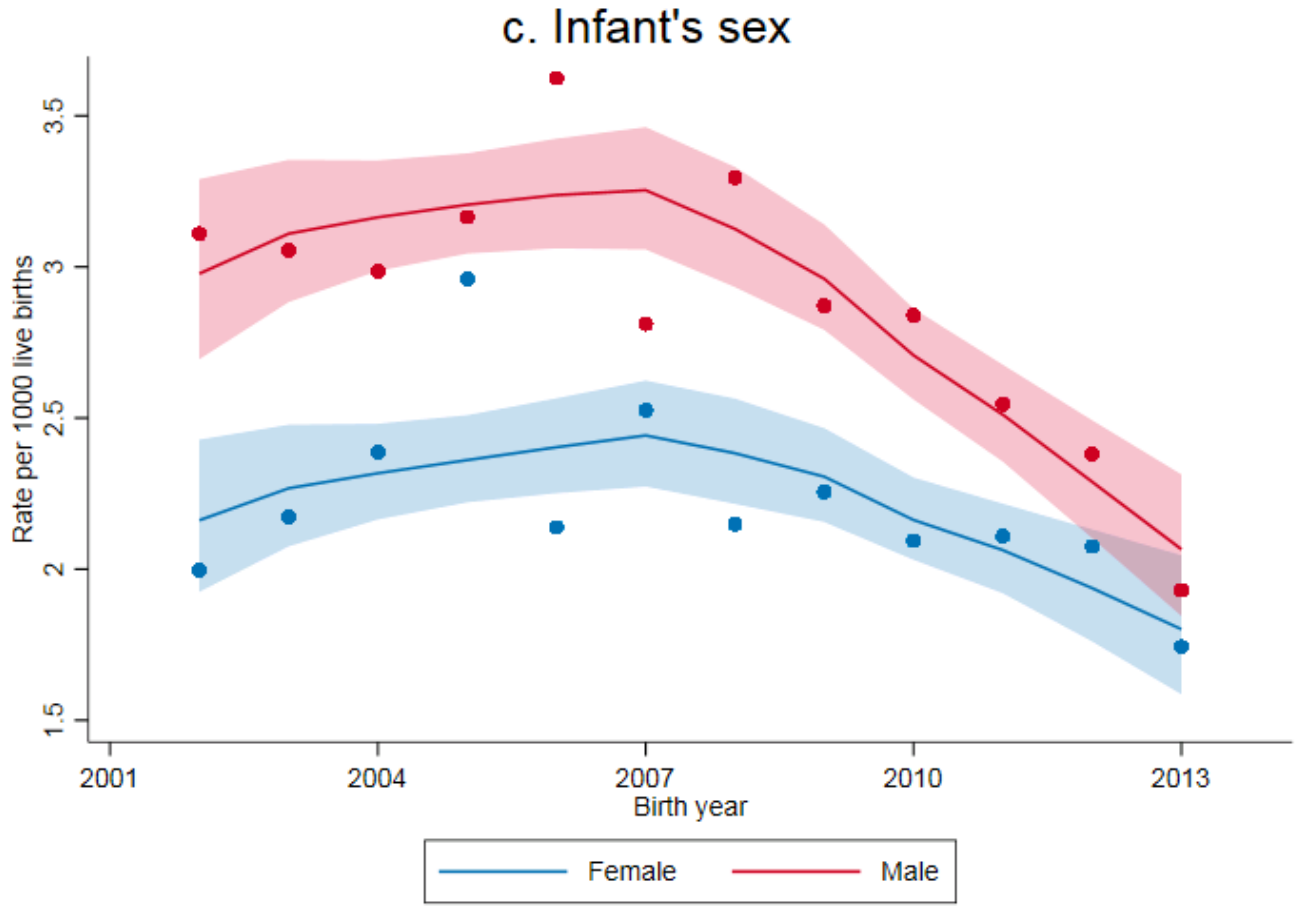


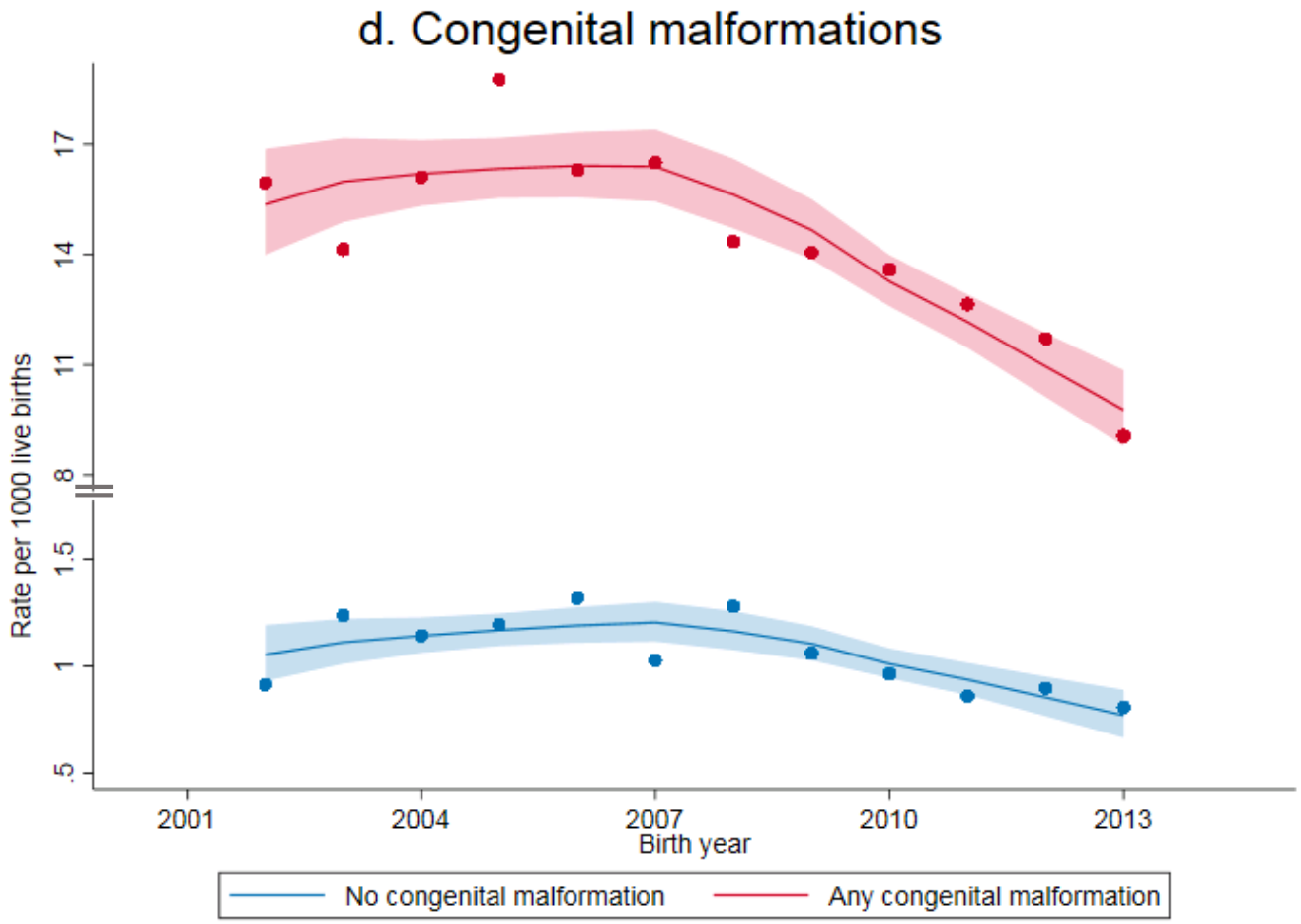
Note: Predicted estimates are based on a Poisson model with time trend modeled using restricted cubic splines with 3 knots at 2003, 2008, and 2012

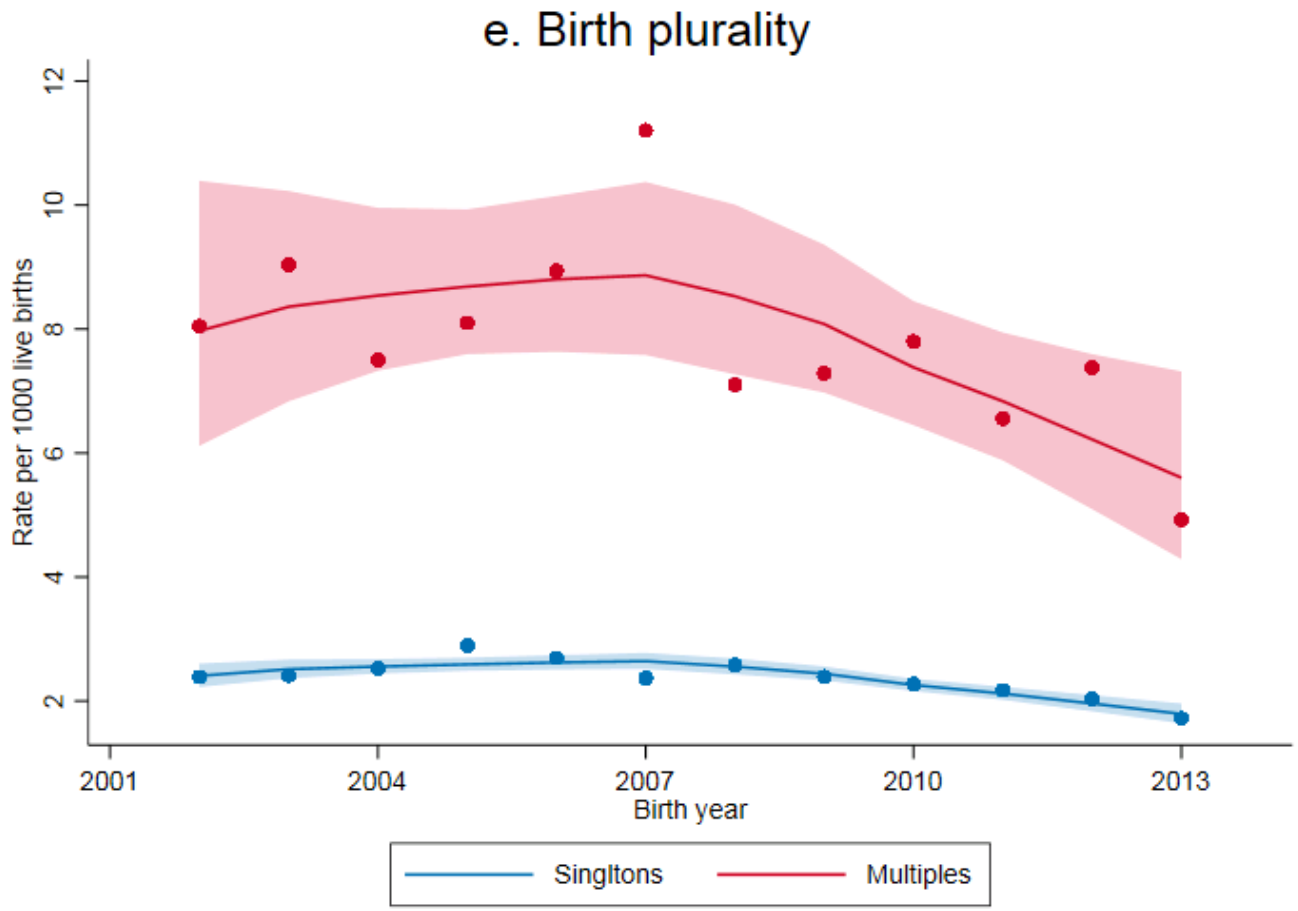
Figure 4.2. Cerebral palsy rates (95% CI) per 1000 live births by year of birth among children aged 0–4 years (N=1,587,087) in Ontario, Canada according to child characteristics over time: (a) preterm birth status, (b) birth weight for gestational age categories, (c) infants' sex, (d) the presence of congenital malformation and (e) birth plurality




b. Birth weight for gestational age
Rate per 1000 live births
1
2
3
4
5
6
2001
2004
2007
2010
2013
Birth year
Appropriate for gestational age
Small for gestational age
Large for gestational age

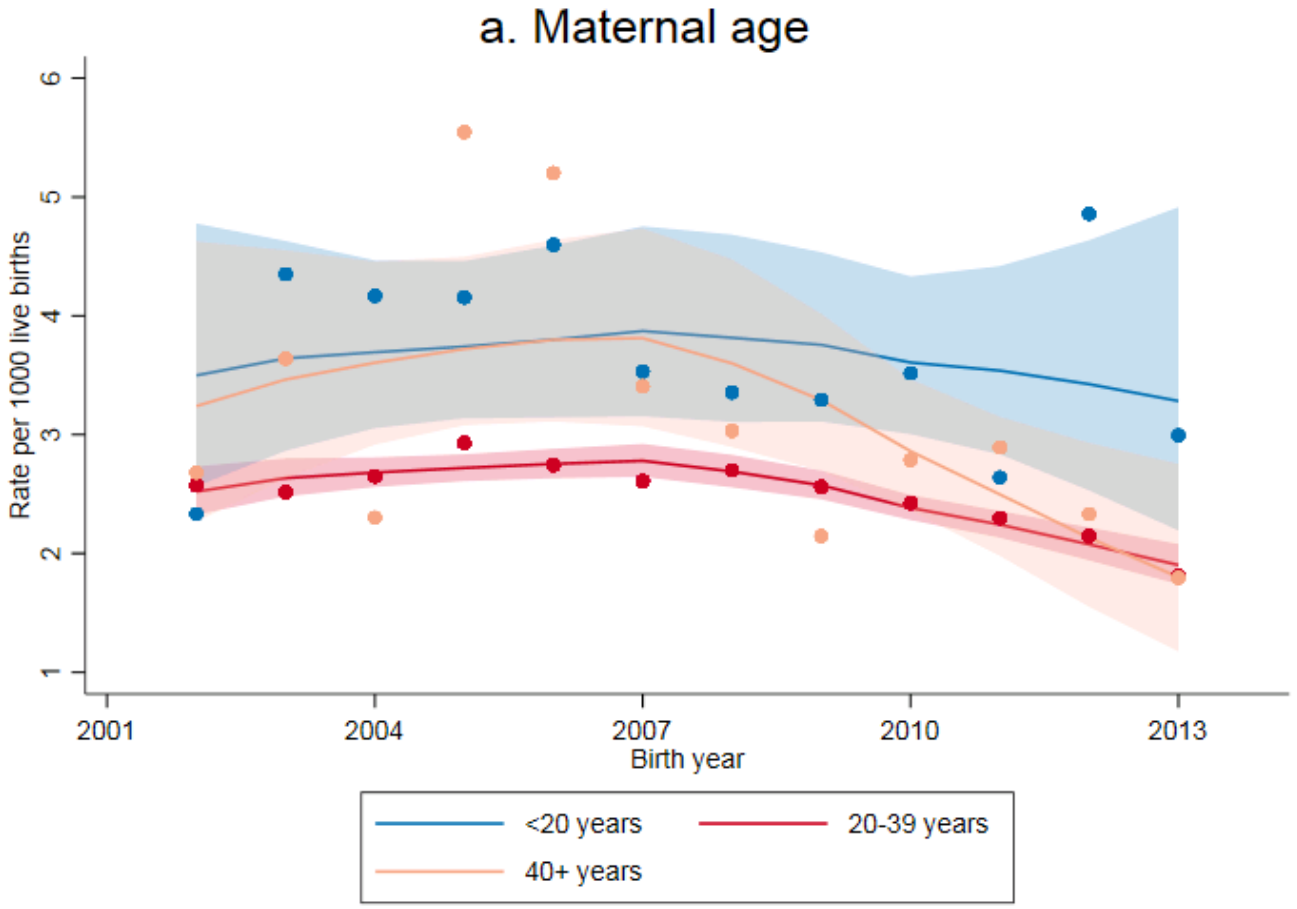

c. Infant's sex
Rate per 1000 live births
1.5
2
2.5
3
3.5
2001
2004
2007
2010
2013
Birth year
Female
Male

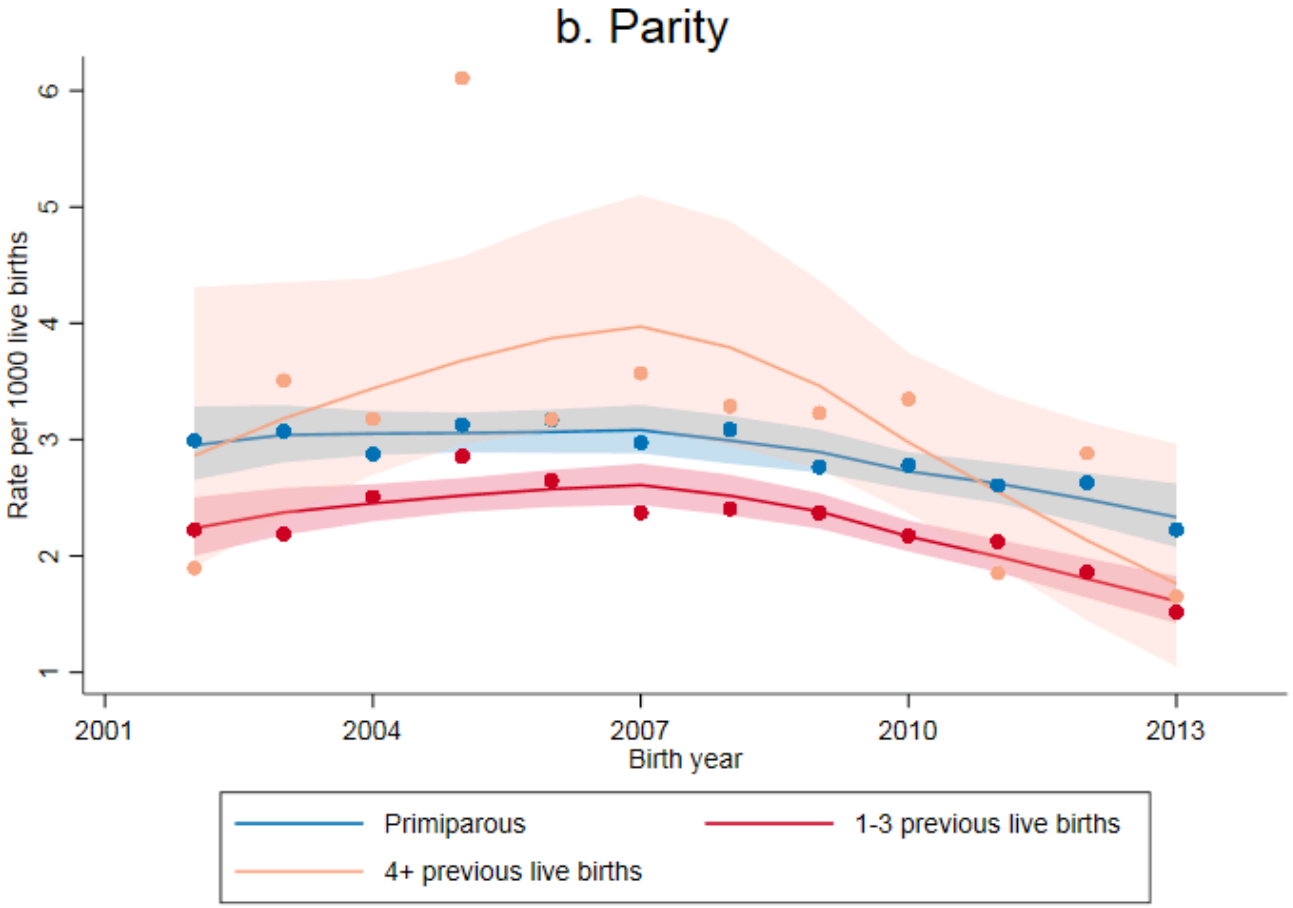

d. Congenital malformations
Rate per 1000 live births
.5
1
1.5
8
11
14
17
2001
2004
2007
2010
2013
Birth year
No congenital malformation
Any congenital malformation

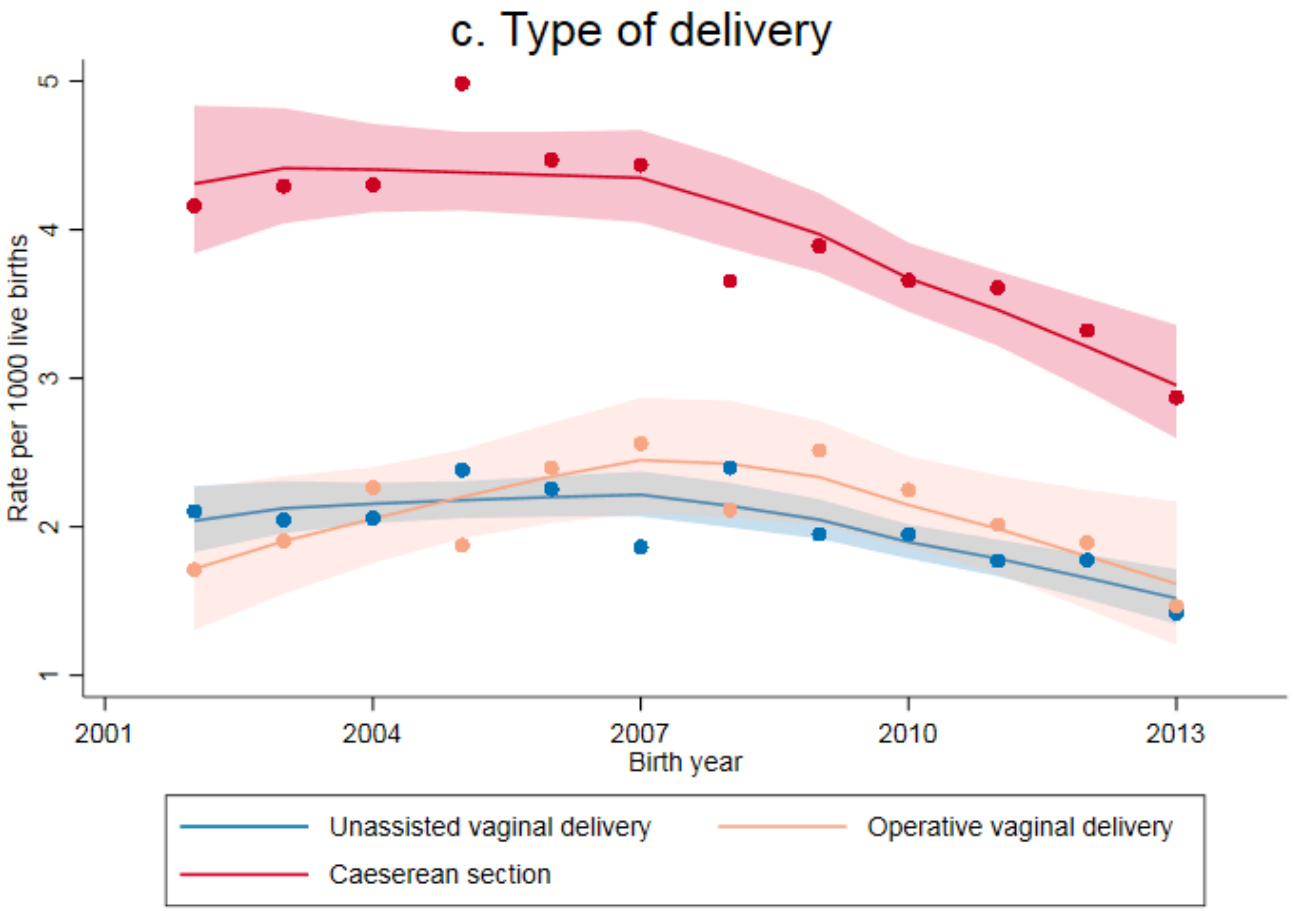


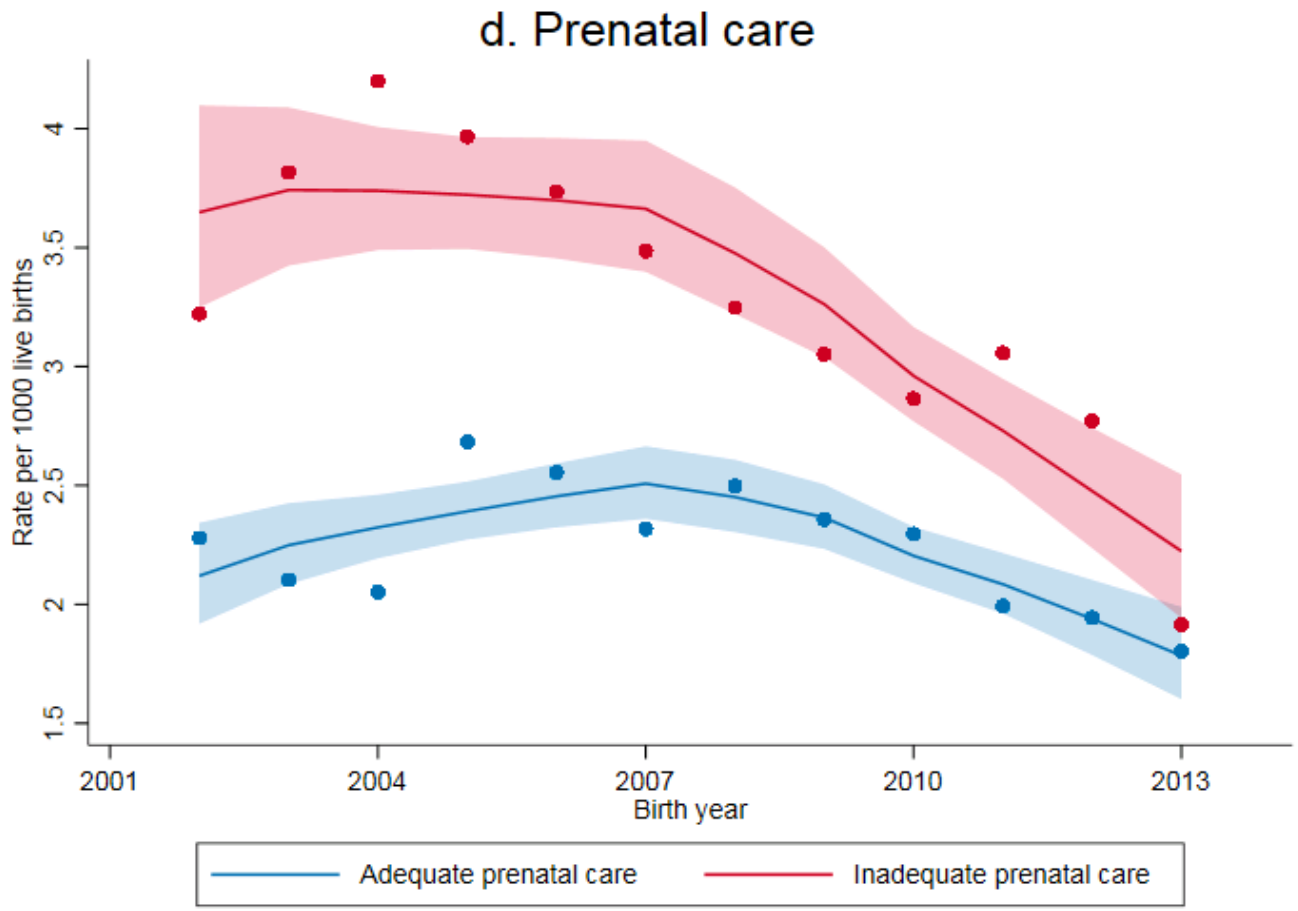
Note: The circles represent observed estimates and the lines (areas) represent predicted estimates (95% confidence intervals) based on a Poisson model with time trend modeled using restricted cubic splines with 3 knots at 2003, 2008, and 2012.

Figure 4.3. Cerebral palsy rates (95% CI) per 1000 live births by year of birth among children aged 0–4 years (N=1,587,087) in Ontario, Canada according to maternal characteristics over time ((a) maternal age (b) parity, (c) type of delivery, and (d) prenatal care)




b. Parity
Rate per 1000 live births
1
2
3
4
5
6
2001
2004
2007
2010
2013
Birth year
Primiparous
1-3 previous live births
4+ previous live births


c. Type of delivery
Rate per 1000 live births
1
2
3
4
5
2001
2004
2007
2010
2013
Birth year
Unassisted vaginal delivery
Operative vaginal delivery
Caeserean section



Note: The circles represent observed estimates and the lines (areas) represent predicted estimates (95% confidence intervals) based on a Poisson model with time trend modeled using restricted cubic splines with 3 knots at 2003, 2008, and 2012.

4.3. Supplementary Material-Manuscript 1

eMethods

Measures

Child characteristics

Gestational age at birth was categorized as a binary preterm birth variable (GA < 37 weeks) and also as a multi-category variable defined as extremely preterm (<28 weeks), very preterm (28–31 weeks), moderate or late preterm (32–36 weeks), term (37–41 weeks), and post-term (42 weeks or later). We categorized raw birth weight into extremely low birth weight (<1000g), very low birth weight (1000 to 1499g), moderate low birth weight (1500 to 2499g), normal birth weight (2500 to 3999g), and macrosomia (>4000 g).

Socioeconomic Characteristics

We used area-based socioeconomic indicators that linked census data by maternal residential postal code at delivery and aggregated at the dissemination area level (the smallest geographic unit for Canadian census, corresponding to a population of 400-700 persons). Data from the census year closest to birth year were used (2001 census for 2002-2003 births and 2006 census for 2004-2017 births). [1] Rural residence was defined according to the Rurality Index of Ontario (RIO)—a score that incorporates measures of population density and travel times to nearest basic and advanced referral center (rural if RIO>45). RIO was calculated at the Census Subdivision (CSD) level (municipalities) using the version of RIO closest to the year of birth (RIO-2004 for 2002-2006 births and RIO-2008 for 2007-2017 births). [2] We used neighborhood income (in quintiles) and the four Ontario Marginalization (ON-Marg) indices—residential instability, material deprivation, economic dependency, and ethnic concentration—that were derived from 42 census questions using principal components analysis. [1] The residential instability domain measures the area-level concentration of individuals at risk of family and housing instability (e.g., % people living alone, % dwellings that are apartment building or no owned). [1] Material deprivation includes factors closely linked to poverty, such as of low income, low education, and unemployment.[1] Economic dependency and ethnic concentration refer to area-level measures of the proportion of people with no income from employment (e.g., children, seniors) and the

proportion of recent immigrant and people from visible minorities, respectively [1] (details in Table S3). Each dimension was summarized as 5 quintiles, which represent the least (Q1) to the most (Q5) marginalized neighborhood. [1] We analyzed these four indices separately as each taps distinctive aspects of marginalization. [1] Eligibility to receive the provincial drug coverage was used as a proxy for individual-level socioeconomic status. People with financial needs due to unemployment or disability are eligible to receive the drug coverage. [3]

Statistical analysis

Poisson regression assumptions

The Poisson regression was deemed appropriate to model the rates as there was no evidence of over-dispersion in the data (both the mean and variance of the outcome = 0.002; the over-dispersion parameter=0 with *p*-value=1.00; the Poisson goodness-of-fit chi-square test being statistically insignificant with *p*-value=1.00). We compared the fit of a linear model and a non-linear model based on restricted cubic splines using the Likelihood-ratio X^2 test and the Akaike information criterion. [4,5] A non-linear Poisson model with three knots (year 2003, 2008, and 2012) had the best fit for the data.

Relative Index of Inequality (RII) and the Slope Index of Inequality (SII)

Socioeconomic inequalities in CP rates were assessed using the Relative Index of Inequality (RII) and the Slope Index of Inequality (SII), [6,7] calculated based on the four ON-Marg indices and the neighborhood income. These variables were converted into cumulative rank scores (range from 0 to 1) that account for the distribution of births across quintiles.[8] These rank scores were then used as the independent variable in a Poisson regression model with CP as the outcome [8] (glm Stata command with Poisson distribution and log link). The rate ratios calculated from these models are equivalent to the RII, which compare CP rates in the most deprived small area relative to the most affluent small area. The SII that represents the absolute difference in CP risk between the most deprived and the most affluent small areas was calculated using the glm Stata command with binary distributions and identity link. [8] We also estimated and plotted these indices over time and statistically tested for interaction between these indices and birth year to examine whether and how socioeconomic inequalities in CP rates have changed over time.

eReferences

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eTable 1. Description of different datasets at ICES and the relevant study variables

DATASET	Description	Relevant study variables
MOMBABY	Records of delivering mothers and newborns in all hospital births in Ontario (ON) since 2002	• Birth characteristics (birth weight, gestational age at birth) • Child characteristics (birth plurality, infant's sex) • Maternal characteristics (age and parity)
CIHI-DAD (The Canadian Institute for Health Information Discharge Abstract Database)	Administrative, clinical (diagnoses and procedures), and demographic information of all hospital admissions	• Inpatient diagnosis of cerebral palsy • Inpatient diagnosis of congenital malformation • Type of delivery
OHIP (The Ontario Health Insurance Plan)	Outpatient physician service information	• Outpatient diagnoses of cerebral palsy • Outpatient diagnosis of congenital malformation • Maternal use of prenatal care services
RPDB (Registered Persons Database)	Vital statistics	• Child's mortality and age at death
Census	ON data from Canadian census	• Home location (urban, rural) • Neighborhood income quintiles
ON-Marg (Ontario Marginalization Index)	Marginalization index for geographic locations in ON	• The four ON-Marg indices: material deprivation, dependency, ethnic diversity, and residential instability
ODB (Ontario Drug Benefit Claims)	Prescription medication claims for those covered under the provincial drug program	• Eligibility to receive ODB benefits as a proxy for receiving social assistance

eTable 2. Diagnostic codes used to define study variables

Variable	**ICD-10-CA (CIHI-DAD)**	**Canadian Classification of Health Interventions (CCI) codes (CIHI-DAD)**	**OHIP code**
Cerebral palsy	G80	-	343
Congenital malformations [a]			
Congenital malformations of the nervous system	Q00, Q01, Q02, Q03, Q04, Q05, Q06, Q07	-	740, 741, 742
Congenital malformations of eye, ear, face and neck	Q10, Q11, Q12, Q13, Q14, Q15, Q16, Q17, Q18	-	743-744
Congenital malformations of the circulatory system	Q20, Q21, Q22, Q23, Q24, Q25, Q26, Q27, Q28	-	745, 746, 747
Congenital malformations of the respiratory system	Q30, Q31, Q32, Q33, Q34	-	748
Cleft lip and cleft palate	Q35, Q36, Q37	-	749
Other congenital malformations of the digestive system	Q38, Q39, Q40, Q41, Q42, Q43, Q44, Q45	-	750-751
Congenital malformations of genital organs	Q50, Q51, Q52, Q53, Q54, Q55, Q56	-	752
Congenital malformations of the urinary system	Q60, Q61, Q62, Q63, Q64	-	753
Congenital malformations and deformations of the musculoskeletal system	Q65, Q66, Q67, Q68, Q69, Q70, Q71, Q72, Q73, Q74, Q75, Q76, Q77, Q78, Q79	-	754, 755, 756

Other congenital malformations	Q80, Q81, Q82, Q83, Q84, Q85, Q86, Q87, Q89	-	757, 759
Chromosomal abnormalities, not elsewhere classified	Q90, Q91, Q92, Q93, Q95, Q96, Q97, Q98, Q99	-	758
Type of delivery			
Unassisted vaginal delivery	-	5MD51, 5MD52, 5MD56	-
Operative vaginal delivery	-	5MD53, 5MD54, 5MD55	-
Caesarean section delivery	-	5MD60	-

Note

[a] Congenital malformations were ascertained based on either inpatient or outpatient diagnosis in the child between birth and the age of six years on the physician billings claims (codes 740–758) or hospitalization discharge records (ICD-10-CA: Q00–Q99).

eTable 3. The indicators that are included in each dimension of the Ontario Marginalization Index

Residential instability indicators
Proportion of the population living alone
Proportion of the population who are not youth (age 5-15)
Average number of persons per dwelling
Proportion of dwellings that are apartment buildings
Proportion of the population who are single/ divorced/widowed
Proportion of dwellings that are not owned
Proportion of the population who moved during the past 5 years
Material deprivation indicators
Proportion of the population aged 20+ without a high-school diploma
Proportion of families who are lone parent families
Proportion of the income from government transfer payments
Proportion of the population aged 15+ who are unemployed
Proportion of the population considered low- income
Proportion of households living in dwellings that are in need of major repair
Dependency indicators
Proportion of the population who are aged 65 and older
Dependency ratio (total population 0-14 and 65+ /total population 15 to 64)
Proportion of the population not participating in labour force (aged 15+)
Ethnic concentration indicators
Proportion of the population who are recent immigrants (arrived in the past 5 years)
Proportion of the population who self-identify as a visible minority

eTable 4. Age at first cerebral palsy diagnosis, n=5,317

Age at diagnosis	Number	Percentage
<1 year	1,445	27.2%
1-<2 yrs	1,667	31.4%
2-<3 yrs	849	16.0%
3-<4 yrs	428	8.1%
4-<5 yrs	283	5.3%
5-<6 yrs	187	3.5%
6-<7 yrs	121	2.3%
7-<8 yrs	79	1.5%
8-<9 yrs	72	1.4%
9+	186	3.5%

eTable 5. Cerebral palsy rates (95% CI) per 1000 live births among children aged 0-16 born between 2002-2017 in Ontario, Canada according to gestational age and birth weight categories (n=2,110,177)

Characteristics	Number of CP cases	Number of live births	CP rate per 1000 live birth (95% CI)
Gestational age			
Extremely preterm (<28 weeks)	513	7,665	66.93 (61.55, 72.74)
Very preterm (28-31 weeks)	570	14,380	39.64 (36.57, 42.95)
Moderate preterm (32-36 weeks)	882	143,200	6.16 (5.77, 6.58)
Term (37-41)	3,336	1,938,350	1.72 (1.66, 1.78)
Post-term (≥42 weeks)	16	6,582	2.43 (1.49, 3.96)
Birth weight			
Extremely low birth weight (<1000 g)	454	7,627	59.53 (54.43, 65.06)
Very low birth weight (1000-1499 g)	462	11,881	38.89 (35.55, 42.51)
Moderate low birth weight (1500-2499 g)	987	113,445	8.70 (8.18, 9.26)
Normal birth weight (2500-3999 g)	3,040	1,743,150	1.74 (1.68, 1.81)
Macrosomia (≥4000 g)	374	234,074	1.60 (1.44, 1.77)

eTable 6. Cerebral palsy rates (95% CI) per 1000 live births among children aged 0-16 born between 2002-2017 in Ontario, Canada according to the type of congenital malformations (n=2,110,177)

Characteristic	Rate per1000 live births (95% CI)
Congenital malformations of the nervous system	
No	2.05 (1.99, 2.11)
Yes	87.18 (82.20, 92.42)
Congenital malformations of eye, ear, face and neck	
No	2.35 (2.29, 2.42)
Yes	18.24 (16.56, 20.08)
Congenital malformations of the circulatory system	
No	1.93 (1.87, 1.99)
Yes	19.42 (18.43, 20.46)
Congenital malformations of the respiratory system	
No	2.41 (2.35, 2.48)
Yes	35.91 (31.75, 40.58)
Cleft lip and cleft palate	
No	2.49 (2.42, 2.55)
Yes	18.89 (15.24, 23.4)
Other congenital malformations of the digestive system	
No	2.43 (2.36, 2.50)
Yes	8.40 (7.47, 9.45)
Congenital malformations of genital organs	
No	2.43 (2.36, 2.49)
Yes	12.79 (11.29, 14.5)
Congenital malformations of the urinary system	
No	2.41 (2.35, 2.48)
Yes	14.38 (12.77, 16.19)
Congenital malformations and deformations of the musculoskeletal system	
No	2.08 (2.02, 2.15)
Yes	16.75 (15.77, 17.78)
Other congenital malformations	

No	2.06 (1.99, 2.12)
Yes	35.51 (33.45, 37.69)
Chromosomal abnormalities, not elsewhere classified	
No	2.02 (1.96, 2.08)
Yes	53.17 (50.19, 56.32)

eTable 7. Relative Index of Inequality (RII) and Slope Index of Inequality (SII)[a] according to neighborhood income and Ontario marginalization index 4 domains

	RII
Neighborhood income	1.26 (1.15, 1.40)
ON-Marg residential instability	1.22 (1.11, 1.34)
ON-Marg material deprivation	1.40 (1.27, 1.54)
ON-Marg dependence	1.15 (1.04, 1.27)
ON-Marg ethnic concentration	0.81 (0.74, 0.90)
	SII
Neighborhood income	0.06 (0.04, 0.09)
ON-Marg residential instability	0.05 (0.03, 0.08)
ON-Marg material deprivation	0.09 (0.06, 0.11)
ON-Marg dependence	0.04 (0.01, 0.06)
ON-Marg ethnic concentration	-0.05 (-0.08, -0.03)

Note

[a] The SII is expressed as a percentage, and refers to the absolute difference in the percentage CP between the most and least marginalized mothers.

eTable 8. Cerebral palsy rates (95% CI) per 1000 live births overall and by birth, maternal and sociodemographic characteristics among children aged 0-16 born between 2002-2017 in Ontario, Canada (n=2,110,177). Cerebral palsy cases included diagnoses made either in hospitals or at one or more outpatient occasions

Characteristic	Number of CP cases	Number of live births	CP rate per 1000 live births
Overall	8,813	2,110,177	4.18 (4.09, 4.26)
Birth weight			
<1000g, ELBW	605	7627	79.32 (73.47, 85.6)
1000 to 1499g, VLBW	612	11,881	51.51 (47.68, 55.63)
1500 to 2499g, MLBW	1,444	113,445	12.73 (12.09, 13.40)
2500 to 3999g, NBW	5,448	1,743,150	3.13 (3.04, 3.21)
>4000g, Macrosomia	704	234,074	3.01 (2.79, 3.24)
Birth weight for gestational age			
Appropriate for gestational age	6,527	1,691,472	3.86 (3.77, 3.95)
Small for gestational age	1,424	201,164	7.08 (6.72, 7.45)
Large for gestational age	862	217,541	3.96 (3.71, 4.24)
Gestational age categories			
extremely preterm (<28 completed	660	7,665	86.11 (80.03, 92.6)
weeks)	741	14,380	51.53 (48.03, 55.27)
very preterm (28–31 weeks)	1,364	143,200	9.53 (9.04, 10.04)
moderate or late preterm (32–36 weeks)	6,021	1,938,350	3.11 (3.03, 3.19)
term (37–41 weeks)	27	6,582	4.10 (2.81, 5.98)
post-term (42 weeks or more)			
Preterm birth			
No	6,048	1,944,932	3.11 (3.03, 3.19)
Yes	2,765	165,245	16.73 (16.13, 17.36)
Pregnancy plurality			
Single	8,033	2,038,089	3.94 (3.86, 4.03)
Multiple	780	72,088	10.82 (10.09, 11.60)
Child's sex			
Female	3,730	1,028,540	3.63 (3.51, 3.74)
Male	5,083	1,081,637	4.70 (4.57, 4.83)

Any congenital malformation			
No	3,800	1,872,311	2.03 (1.97, 2.10)
Yes	5,013	237,866	21.07 (20.51, 21.66)
Parity			
0	4,309	944,887	4.56 (4.43, 4.70)
1	2,789	748,127	3.73 (3.59, 3.87)
2	1,089	275,799	3.95 (3.72, 4.19)
3	327	84,056	3.89 (3.49, 4.33)
4+	299	57,308	5.22 (4.66, 5.84)
Maternal age			
<20 yrs	380	66,364	5.73 (5.18, 6.33)
20-24 yrs	1222	262,940	4.65 (4.39, 4.91)
25-29 yrs	2299	585,570	3.93 (3.77, 4.09)
30-34 yrs	2913	736,102	3.96 (3.82, 4.10)
35-39 yrs	1578	378,474	4.17 (3.97, 4.38)
40+ yrs	421	80,727	5.22 (4.74, 5.74)
Type of birth			
Unassisted vaginal delivery	4,452	1,299,054	3.43 (3.33, 3.53)
Operative vaginal delivery	772	211,025	3.66 (3.41, 3.93)
Caesarean section	3,589	600,098	5.98 (5.79, 6.18)
Prenatal care			
Adequate	5,648	1,444,385	3.91 (3.81, 4.01)
Inadequate	3,165	665,792	4.75 (4.59, 4.92)
Residence of rural area			
No	7,917	1,897,003	4.17 (4.08, 4.27)
Yes	894	212,379	4.21 (3.94, 4.49)
Recipient of Ontario Drug Benefit (ODB)			
No	7,667	1,932,615	3.97 (3.88, 4.06)
Yes	1,146	177,562	6.45 (6.09, 6.84)
Neighborhood income quantiles			
Q1 (highest)	1,285	347,321	3.70 (3.50, 3.91)
Q2	1,715	435,226	3.94 (3.76, 4.13)
Q3	1,796	429,620	4.18 (3.99, 4.38)

Q4	1,765	420,658	4.20 (4.00, 4.40)
Q5 (lowest)	2,223	469,691	4.73 (4.54, 4.93)
ON-Marg residential instability			
Q1 (least marginalized)	1,478	415,409	3.56 (3.38, 3.74)
Q2	1,650	417,061	3.96 (3.77, 4.15)
Q3	1,615	374,155	4.32 (4.11, 4.53)
Q4	1,788	398,022	4.49 (4.29, 4.70)
Q5 (most marginalized)	2,144	469,399	4.57 (4.38, 4.76)
ON-Marg material deprivation			
Q1 (least marginalized)	1,790	502,692	3.56 (3.40, 3.73)
Q2	1,496	382,315	3.91 (3.72, 4.12)
Q3	1,609	375,275	4.29 (4.08, 4.50)
Q4	1,631	367,034	4.44 (4.23, 4.66)
Q5 (most marginalized)	2,149	446,730	4.81 (4.61, 5.02)
ON-Marg dependence			
Q1 (least marginalized)	2,562	637,090	4.02 (3.87, 4.18)
Q2	2,019	474,534	4.25 (4.07, 4.44)
Q3	1,532	373,369	4.10 (3.90, 4.31)
Q4	1,360	316,221	4.30 (4.08, 4.54)
Q5 (most marginalized)	1,202	272,832	4.41 (4.16, 4.66)
ON-Marg ethnic concentration			
Q1 (least marginalized)	1,125	262,584	4.28 (4.04, 4.54)
Q2	1,282	302,901	4.23 (4.01, 4.47)
Q3	1,476	348,636	4.23 (4.02, 4.45)
Q4	1,895	456,665	4.15 (3.97, 4.34)
Q5 (most marginalized)	2,897	703,260	4.12 (3.97, 4.27)

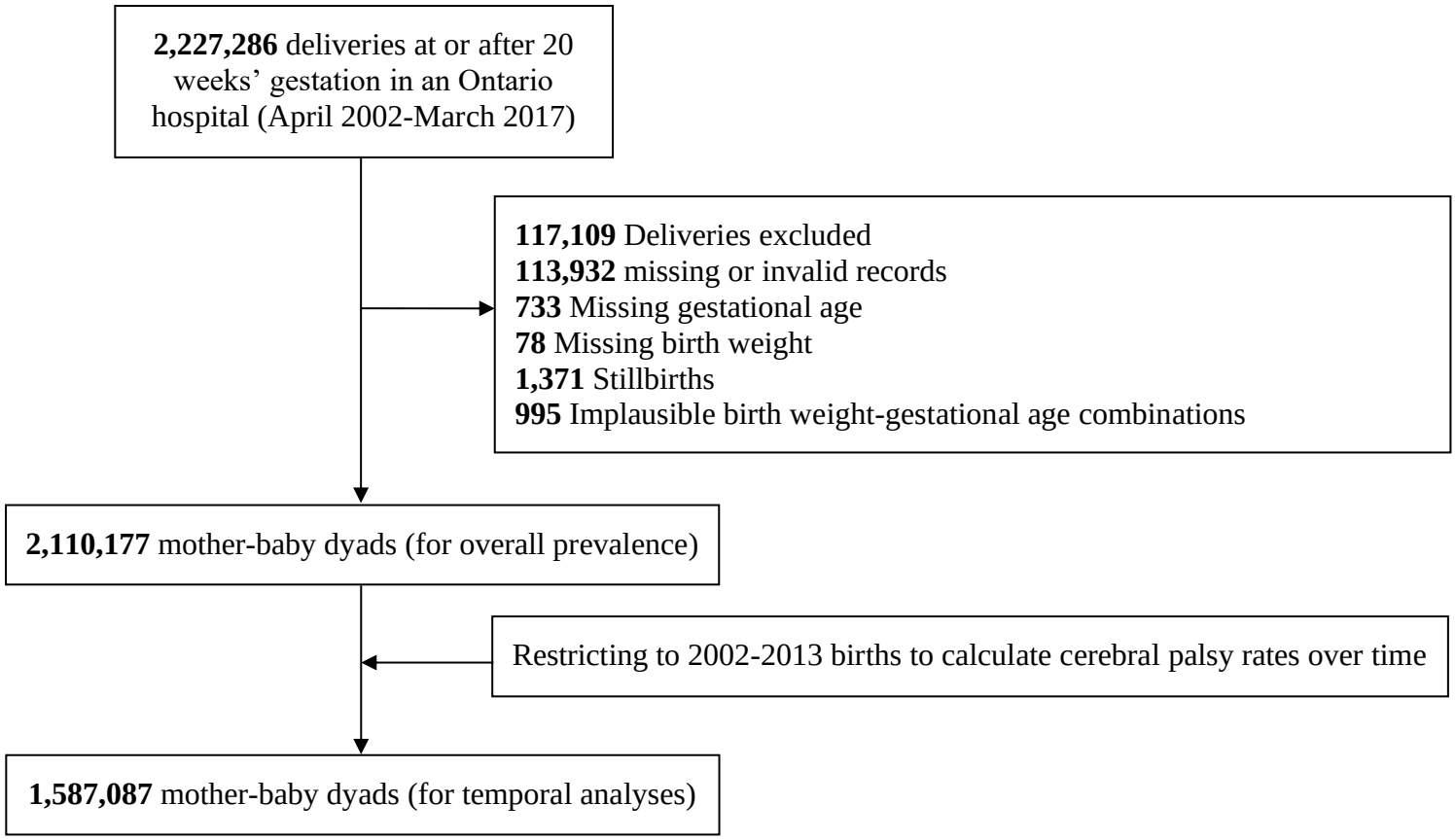
eTable 9. Cerebral palsy rates (95% CI) per 1000 neonatal survivors overall and by birth characteristics among children aged 0-16 born between 2002-2017 in Ontario, Canada (n=2,107,667)

Characteristics	N CP cases	N neonatal survivors	CP rate per 1000 neonatal survivors (95% CI)
Overall	5,314	2,107,667	2.52 (2.45, 2.59)
Birth weight for gestational age			
Appropriate for gestational age	3,933	1,689,692	2.33 (2.26, 2.40)
Small for gestational age	865	200,657	4.31 (4.03, 4.61)
Large for gestational age	516	217,318	2.37 (2.18, 2.59)
Birth weight			
<1000g, ELBW	453	6,611	68.52 (62.68, 74.87)
1000 to 1499g, VLBW	462	11,649	39.66 (36.26, 43.36)
1500 to 2499g, MLBW	986	113,037	8.72 (8.20, 9.28)
2500 to 3999g, NBW	3,039	1,742,376	1.74 (1.68, 1.81)
>4000g, Macrosomia	374	233,994	1.60 (1.44, 1.77)
Gestational age			
extremely preterm (<28 completed	512	6,629	77.24 (71.05, 83.91)
weeks)	569	14,139	40.24 (37.13, 43.61)
very preterm (28–31 weeks)	882	142,824	6.18 (5.78, 6.60)
moderate preterm (32–36 weeks)	3,335	1,937,497	1.72 (1.66, 1.78)
term (37–41 weeks)	16	6,578	2.43 (1.49, 3.97)
post-term (42 weeks or more)			
Preterm birth			
No	3,351	1,944,075	1.72 (1.67, 1.78)
Yes	1,963	163,592	12.00 (11.48, 12.54)
Pregnancy plurality			
Single	4,791	2,036,025	32.35 (2.29, 2.42)
Multiple	523	71,642	7.30 (6.70, 7.95)
Child's sex			
Female	2,218	1,027,408	2.16 (2.07, 2.25)
Male	3,096	1,080,259	2.87 (2.77, 2.97)

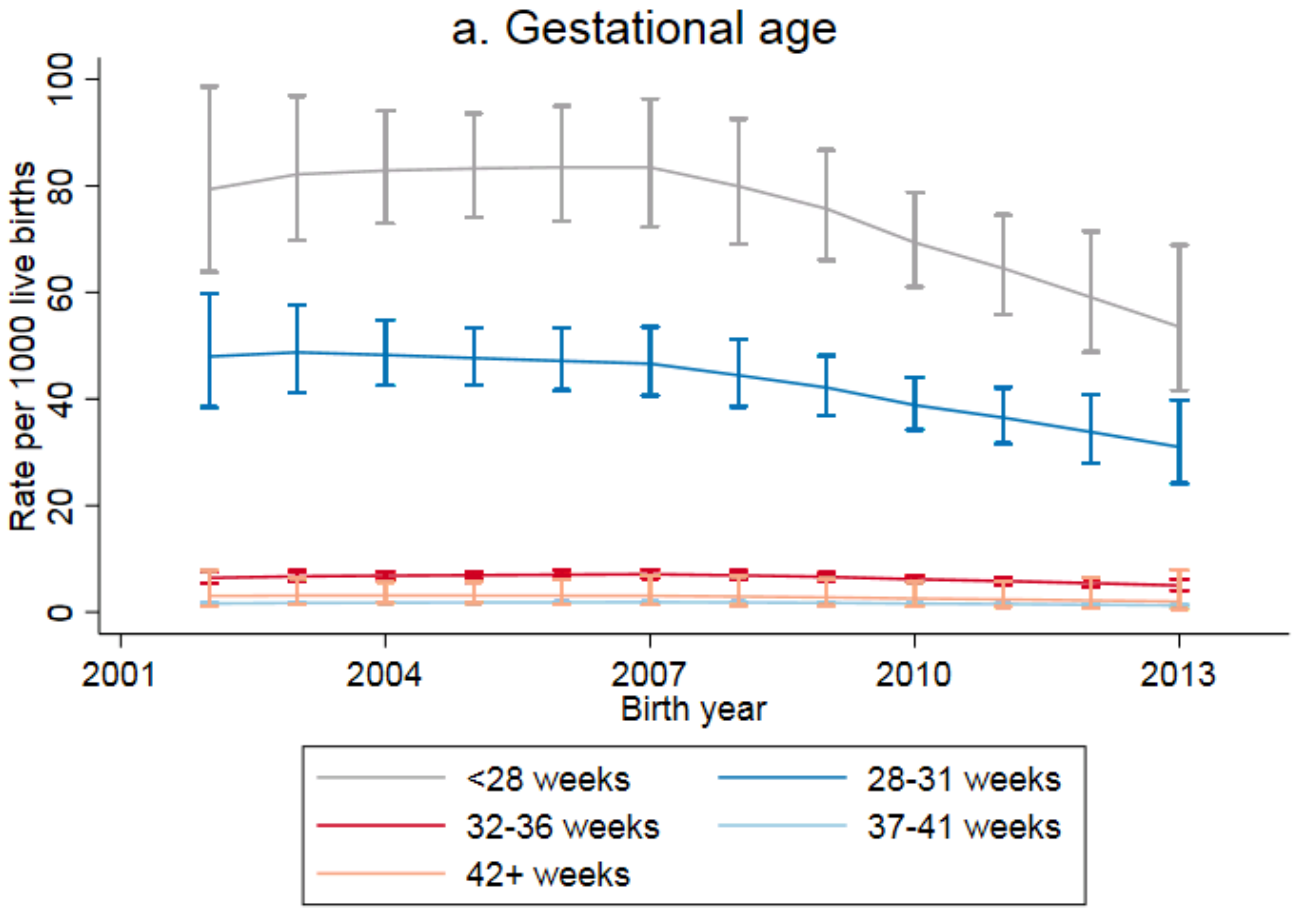
Any congenital malformation			
No	2,018	1,871,016	1.08 (1.03, 1.13)
Yes	3,296	236,651	13.93 (13.46, 14.41)
Maternal age			
<20 yrs	265	66,263	4.00 (3.55, 4.51)
20-24 yrs	755	262,570	2.88 (2.68, 3.09)
25-29 yrs	1,399	584,912	2.39 (2.27, 2.52)
30-34 yrs	1,732	735,308	2.36 (2.25, 2.47)
35-39 yrs	926	378,020	2.45 (2.30, 2.61)
40+ yrs	237	80,594	2.94 (2.59, 3.34)
Parity			
0	2,646	943,613	2.80 (2.70, 2.91)
1	1,654	747,429	2.21 (2.11, 2.32)
2	648	275,518	2.35 (2.18, 2.54)
3	187	83,954	2.23 (1.93, 2.57)
4+	179	57,153	3.13 (2.71, 3.63)
Type of birth			
Unassisted vaginal delivery	2,603	1,297,766	2.01 (1.93, 2.08)
Operative vaginal delivery	444	210,910	2.11 (1.92, 2.31)
Caesarean section	2,267	598,991	3.78 (3.63, 3.94)
Prenatal care			
Adequate	3,288	1,443,154	2.28 (2.20, 2.36)
Inadequate	2,026	664,513	3.05 (2.92, 3.18)
Residence of rural area			
No	4,752	1,894,758	2.51 (2.44, 2.58)
Yes	560	212,114	2.64 (2.43, 2.87)
Recipient of Ontario Drug Benefit (ODB)			
No	4,667	1,930,402	2.42 (2.35, 2.49)
Yes	647	177,265	3.65 (3.38, 3.94)
Neighborhood income quantiles			
Q1 (highest)	754	346,203	2.17 (2.02, 2.33)
Q2	1,069	433,738	2.46 (2.32, 2.61)
Q3	1,111	427,952	2.59 (2.44, 2.75)

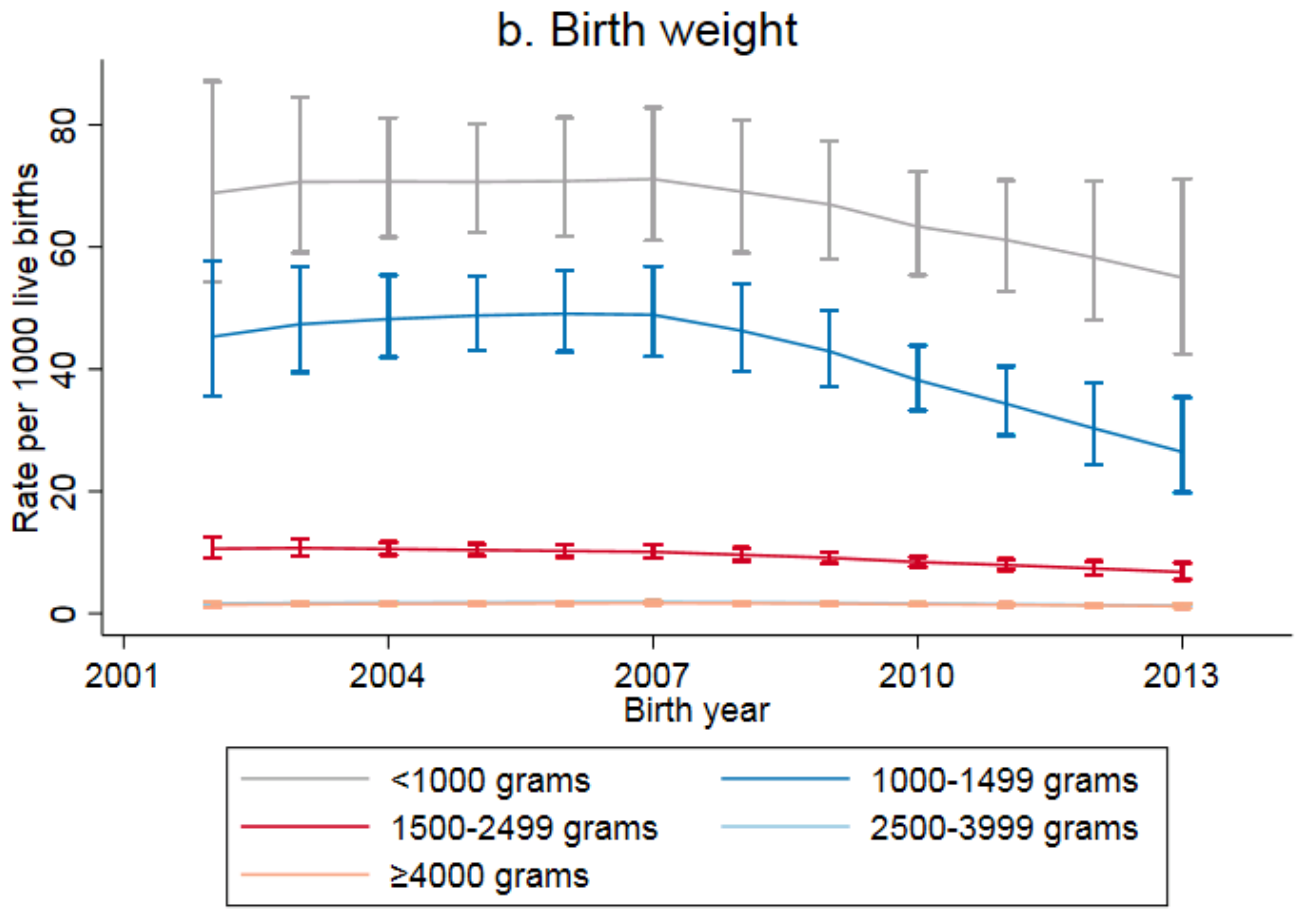
Q4	1,049	419,086	2.50 (2.35, 2.65)
Q5 (lowest)	1,308	467,741	2.79 (2.64, 2.94)
ON-Marg residential instability			
Q1 (least marginalized)	908	414,942	2.19 (2.05, 2.34)
Q2	1,040	416,621	2.50 (2.35, 2.65)
Q3	997	373,709	2.67 (2.51, 2.84)
Q4	1,038	397,534	2.61 (2.46, 2.77)
Q5 (most marginalized)	1,243	468,766	2.65 (2.51, 2.80)
ON-Marg material deprivation			
Q1 (least marginalized)	1,086	502,214	2.16 (2.04, 2.29)
Q2	887	381,845	2.32 (2.18, 2.48)
Q3	981	374,856	2.62 (2.46, 2.79)
Q4	993	366,574	2.71 (2.55, 2.88)
Q5 (most marginalized)	1,279	446,083	2.87 (2.71, 3.03)
ON-Marg dependence			
Q1 (least marginalized)	1,530	636,343	2.40 (2.29, 2.53)
Q2	1,189	473,960	2.51 (2.37, 2.66)
Q3	937	372,943	2.51 (2.36, 2.68)
Q4	841	315,829	2.66 (2.49, 2.85)
Q5 (most marginalized)	729	272,497	2.68 (2.49, 2.88)
ON-Marg ethnic concentration			
Q1 (least marginalized)	711	262,244	2.71 (2.52, 2.92)
Q2	831	302,501	2.75 (2.57, 2.94)
Q3	896	348,251	2.57 (2.41, 2.75)
Q4	1,126	456,188	2.47 (2.33, 2.62)
Q5 (most marginalized)	1,662	702,388	2.37 (2.26, 2.48)

eFigure 1. Flowchart illustrating the formation of the study cohorts



eFigure 2. Cerebral palsy rates (95% CI) per 1000 live births by year of birth among children aged 0-4 years (N=1,587,087) in Ontario, Canada according to (a) gestational age categories, and (b) birth weight categories





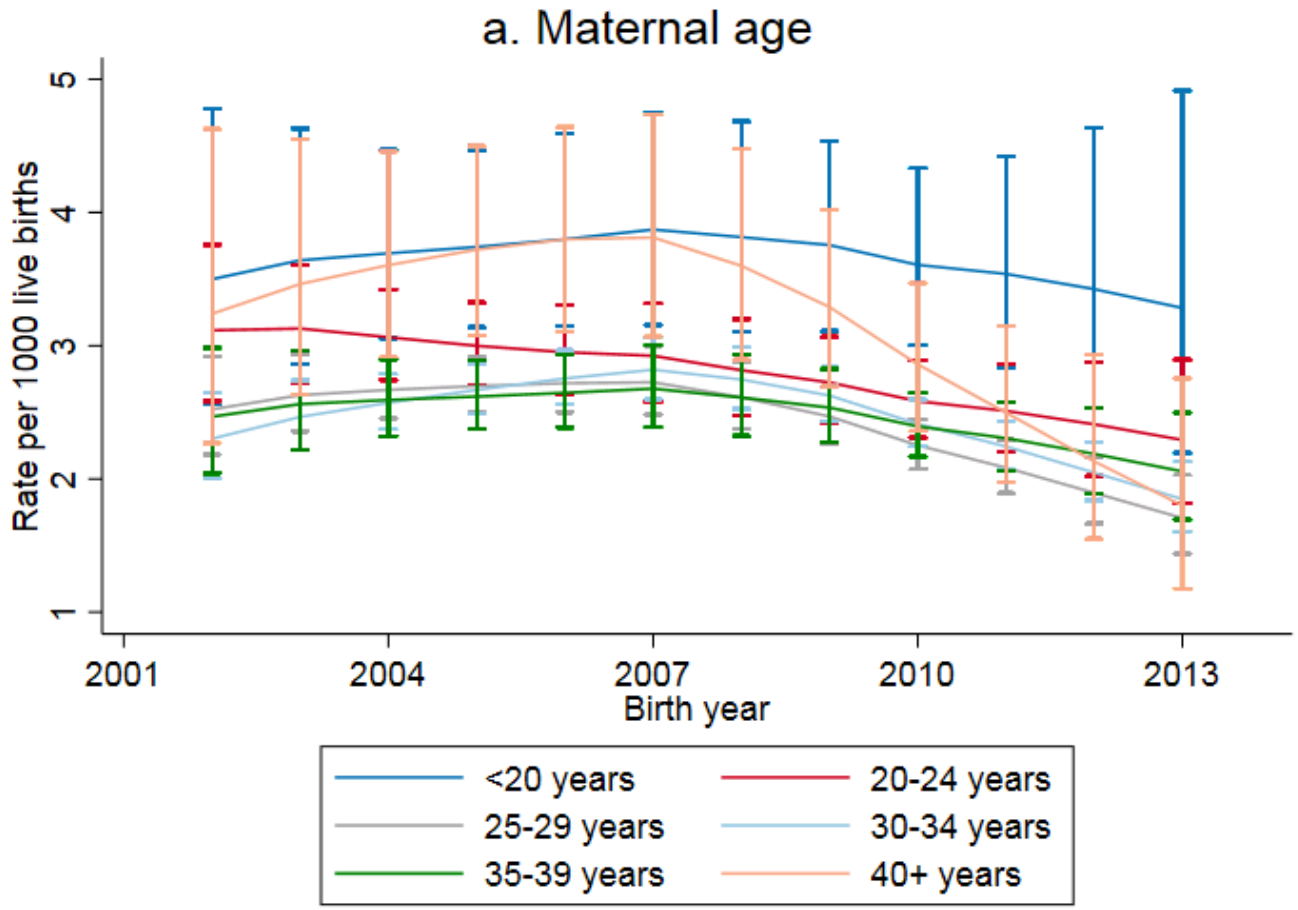
Notes:

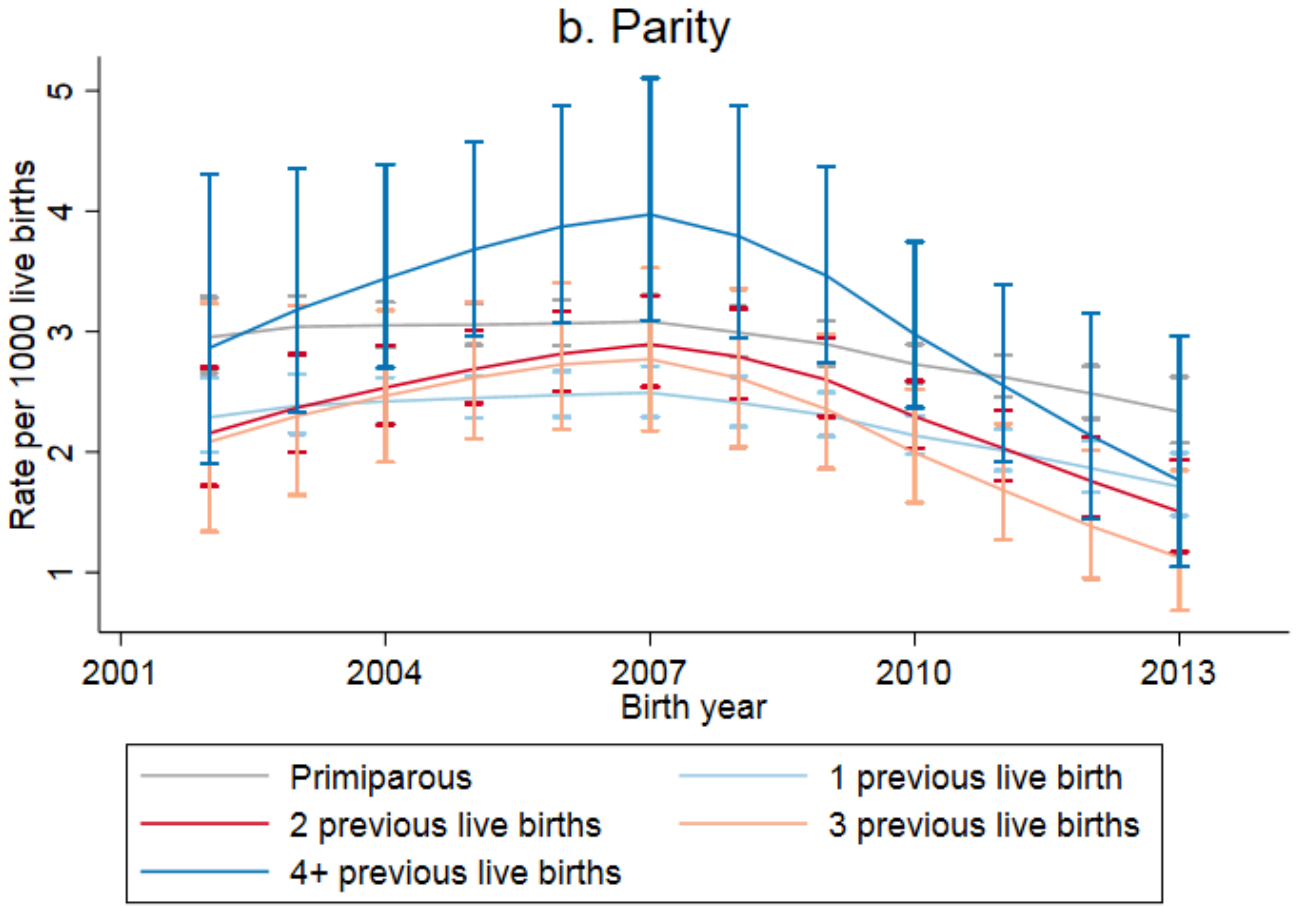
[a] Graphs represent predicted estimates (95% confidence intervals) based on a Poisson model with time trend modeled using restricted cubic splines with 3 knots at 2003, 2008, and 2012

[b] Birth weight categories: ELBW: Extremely low birth weight (<1000g); VLBW: very low birth weight (1000 to 1499g), MLBW: moderate low birth weight (1500 to 2499g); NBW: Normal birth weight (2500 to 3999g); Macrosomia (≥4000 g)

[c] Gestational age categories: EPTB: Extremely preterm birth ((<28 completed weeks); VPTB: Very preterm birth ((28–31 weeks); MPTB: Moderate preterm birth ((32–36 weeks); Term (37-41 weeks); Post-term (42 weeks or more)

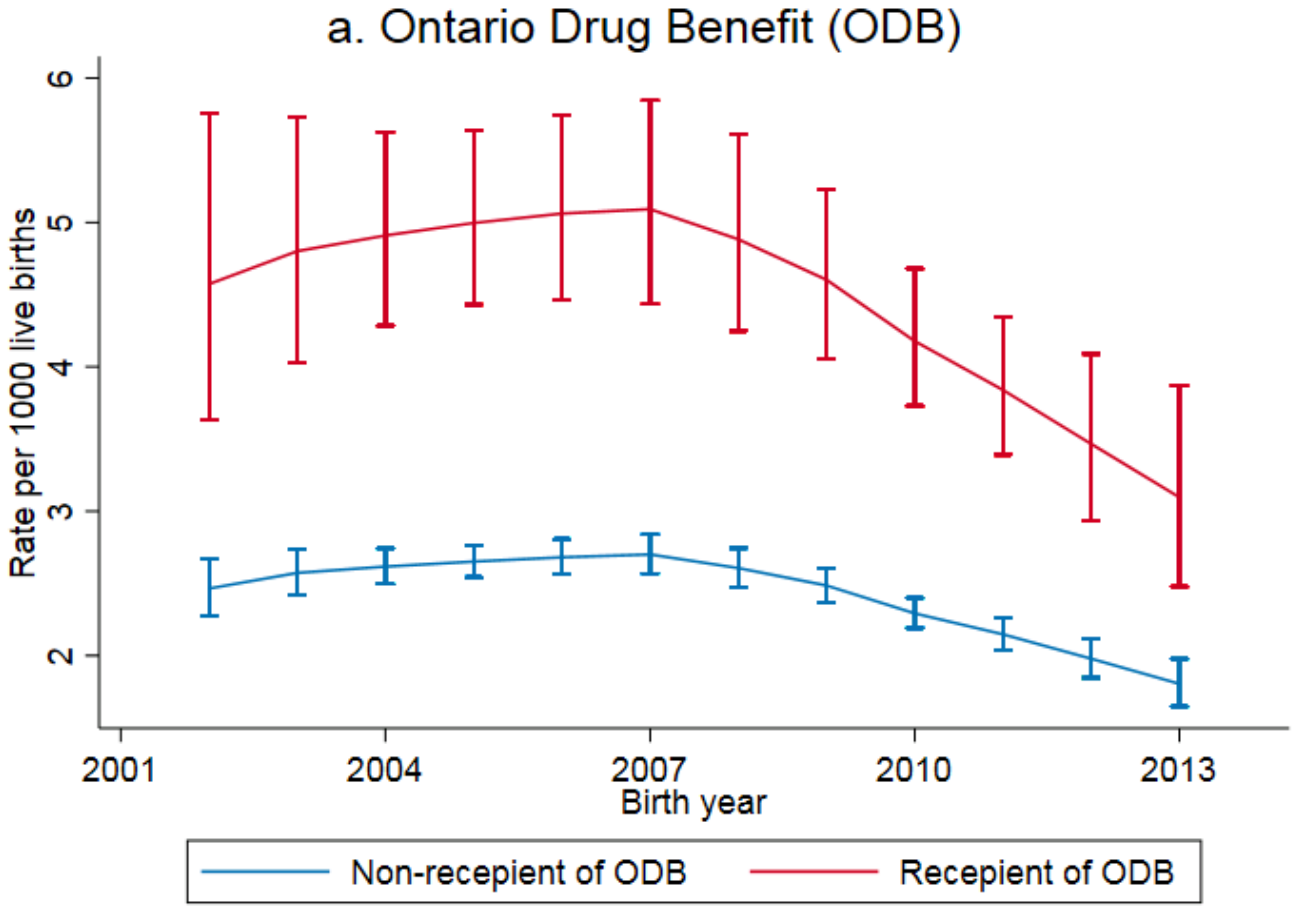
eFigure 3. Cerebral palsy rates (95% CI) per 1000 live births by year of birth among children aged 0-4 years (N=1,587,087) in Ontario, Canada according to maternal characteristics ((a) maternal age, and (b) parity)

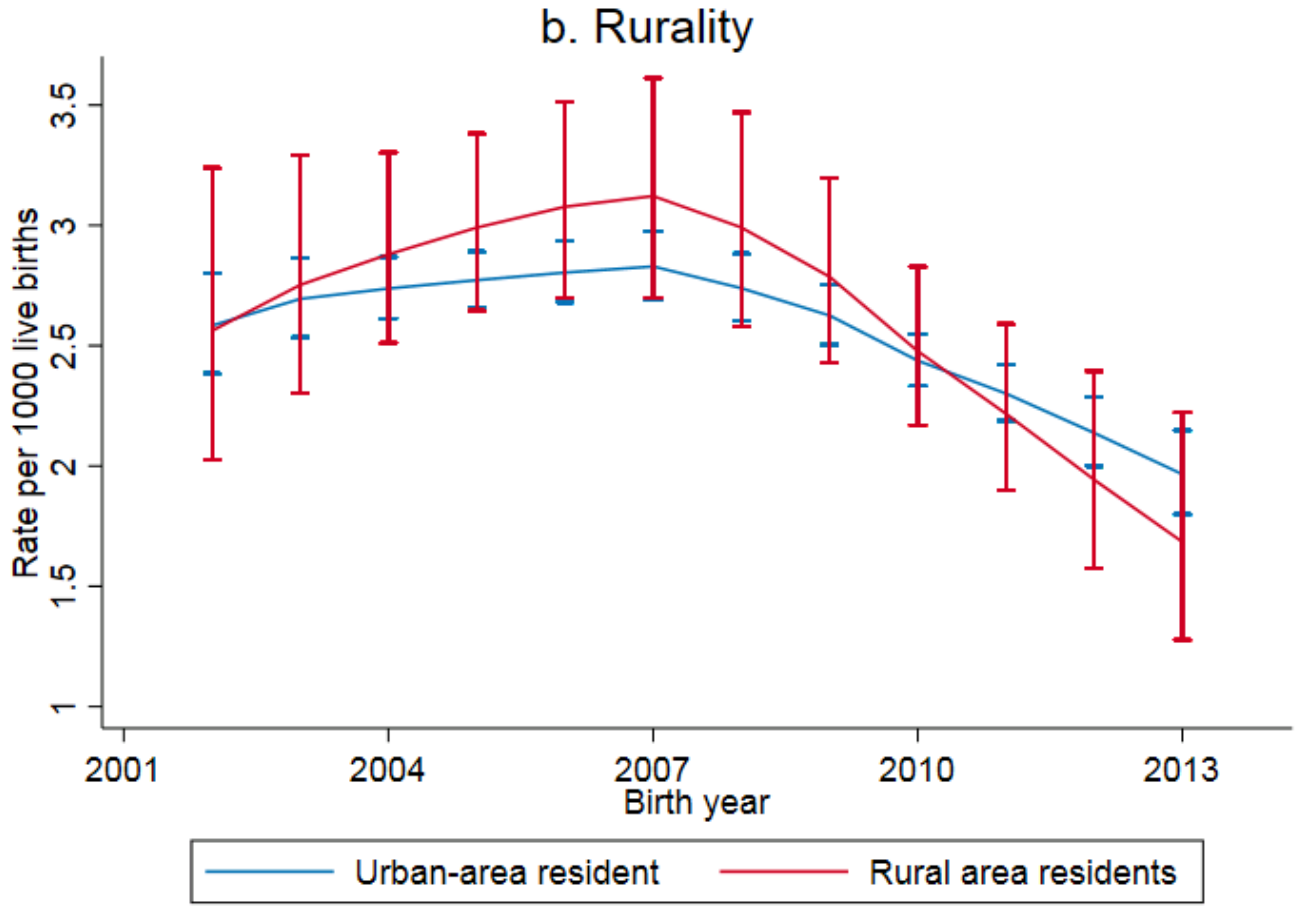


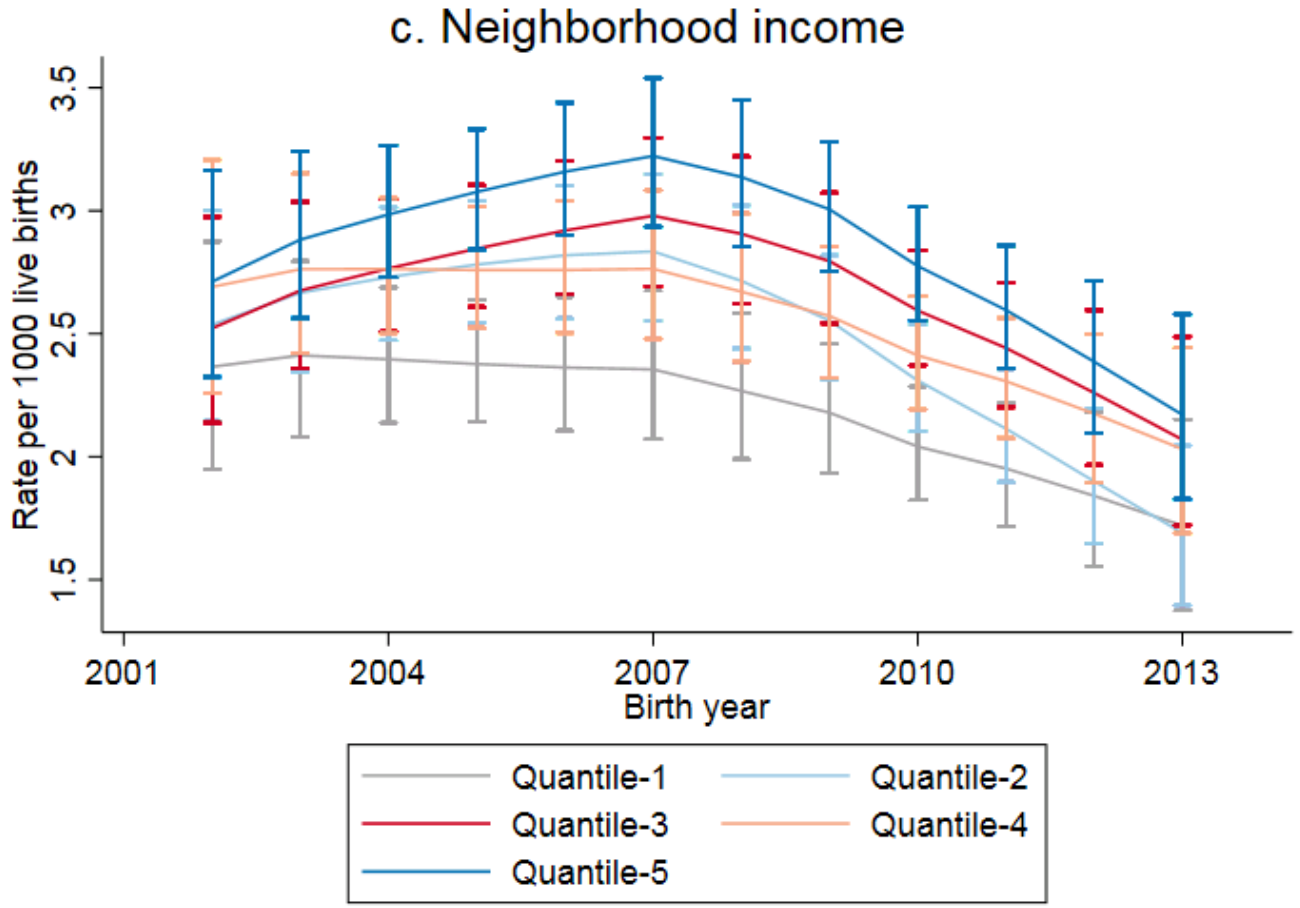


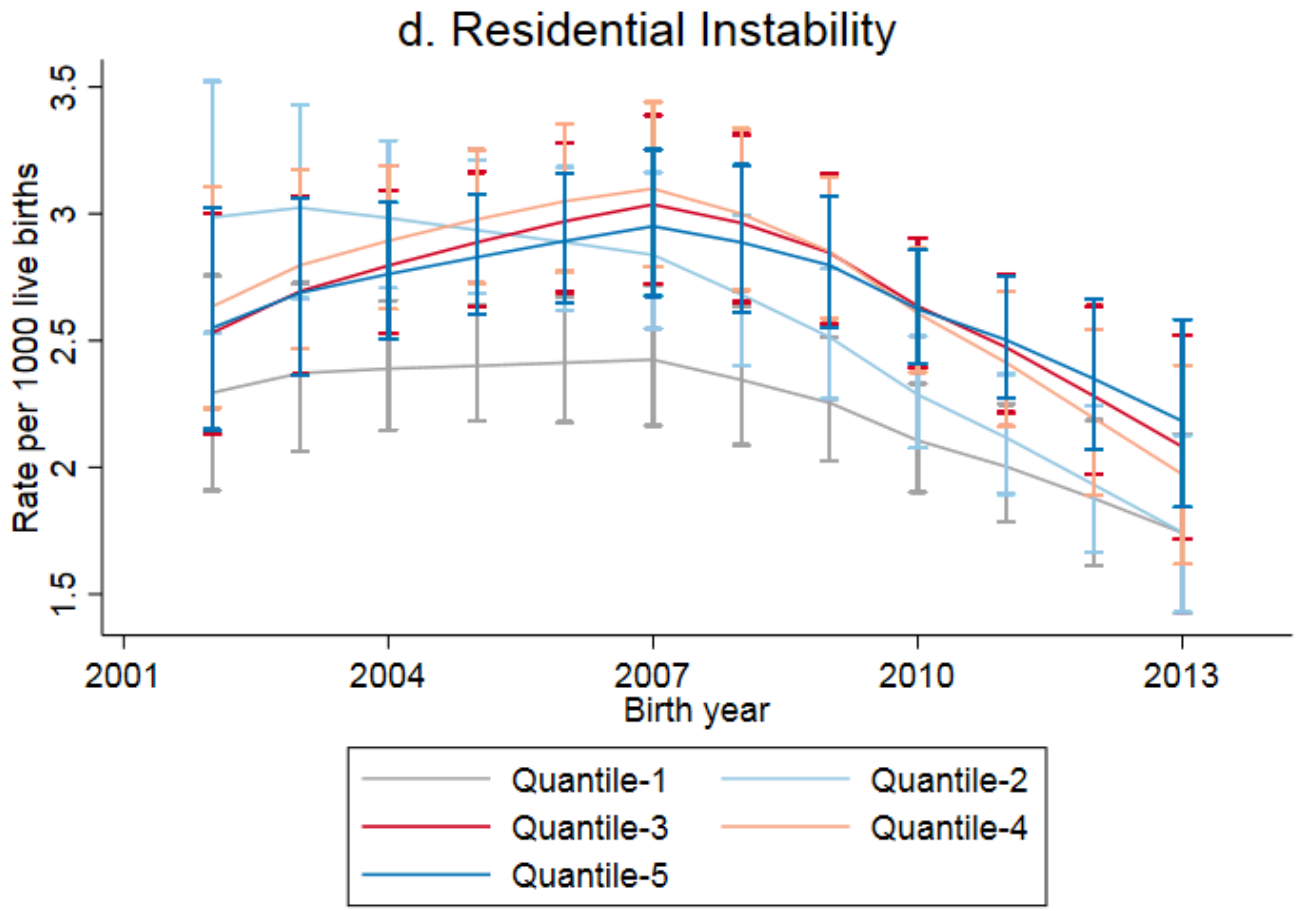
Note: Graphs represent predicted estimates (95% confidence intervals) based on a Poisson model with time trend modeled using restricted cubic splines with 3 knots at 2003, 2008, and 2012

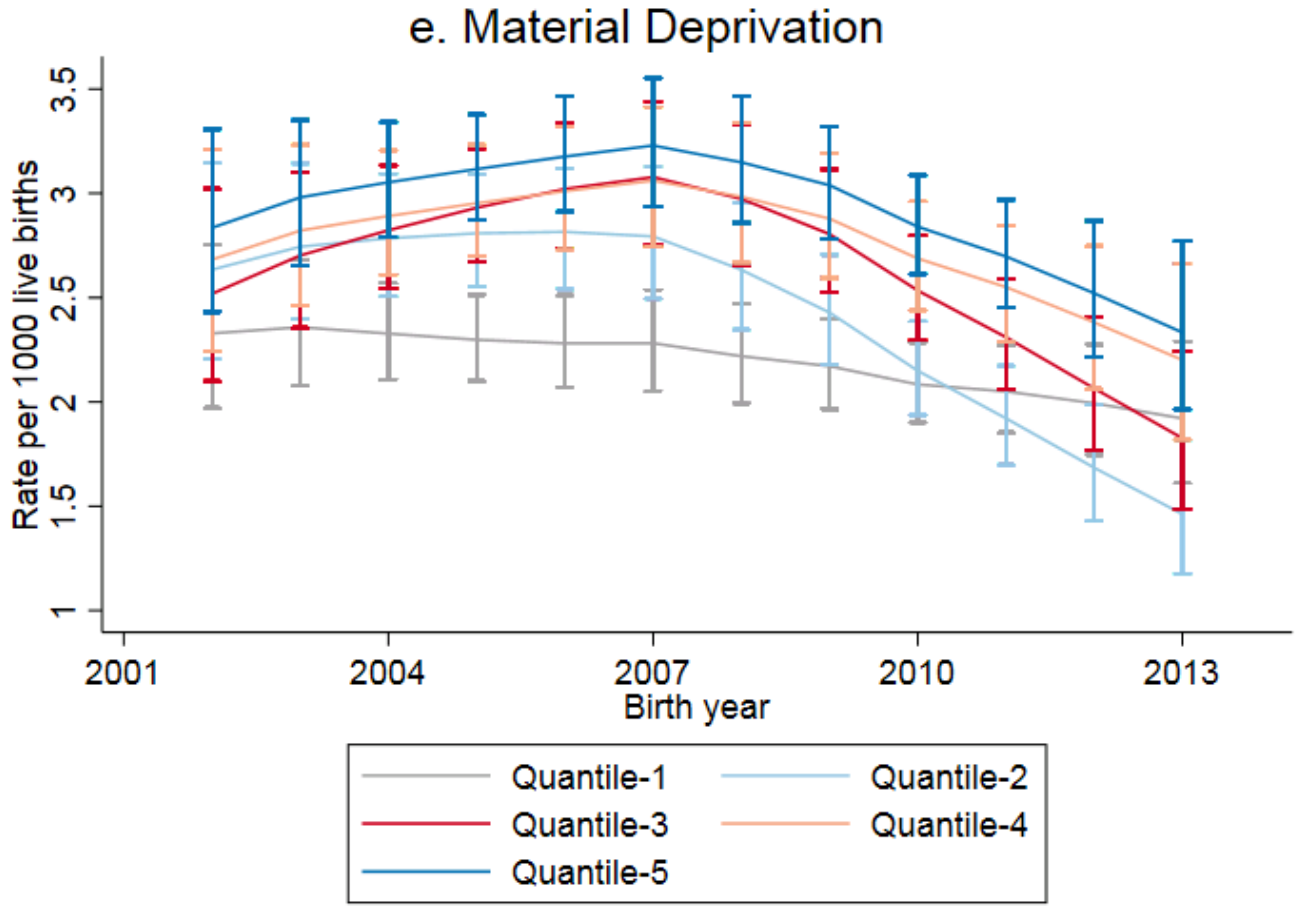
eFigure 4. Cerebral palsy rates (95% CI) per 1000 live births by year of birth among children aged 0-4 years (N=1,587,087) in Ontario, Canada according to regional and socioeconomic characteristics ((a) receiving Ontario Drug Benefits, ((b) rurality, (c) neighborhood income quintiles, (d) ON-Marg residential instability quintiles, (e) ON-Marg material deprivation quintiles, (f) ON-Marg economic dependency quintiles, and (g) ON-Marg ethnic concentration quintiles)

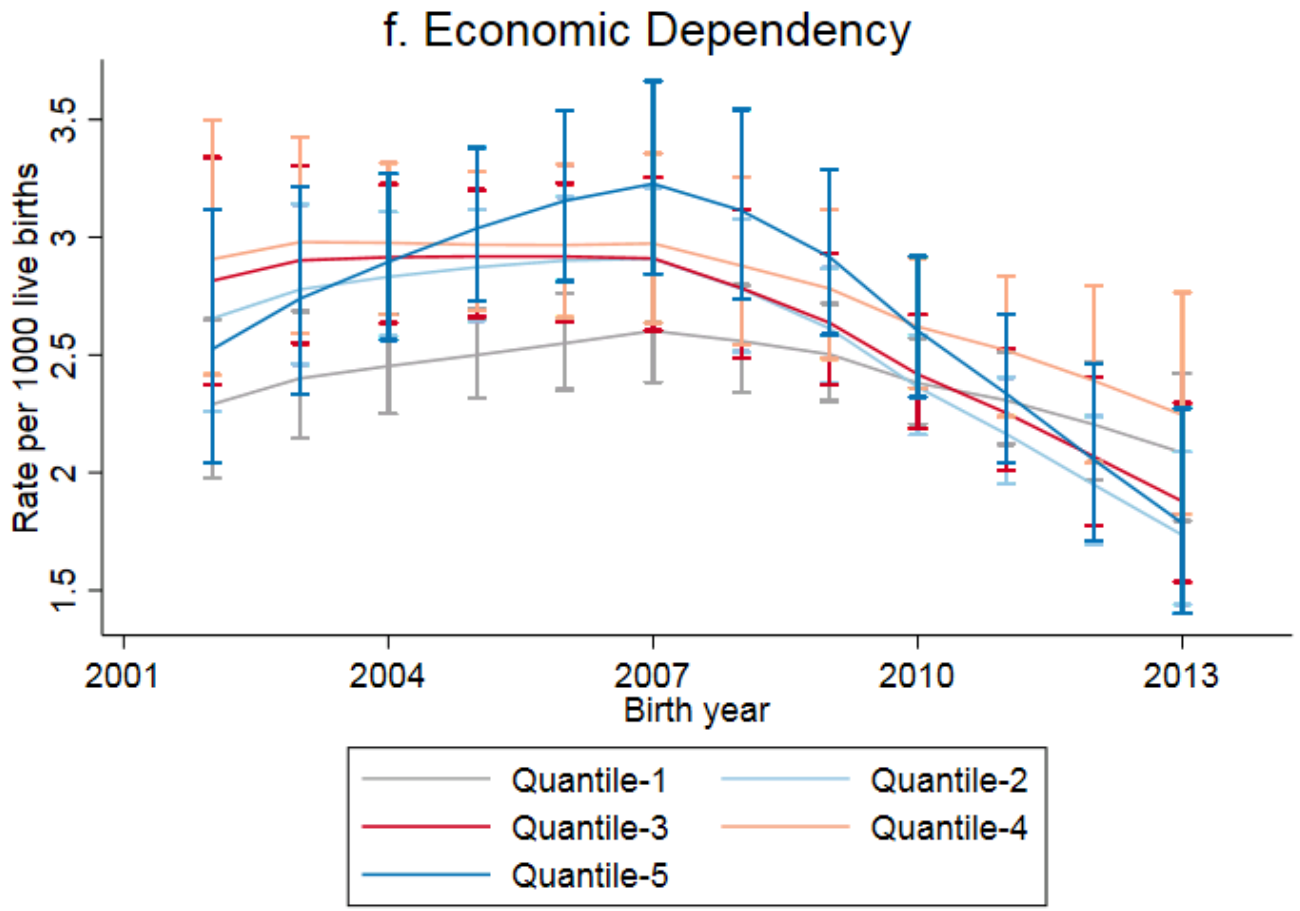


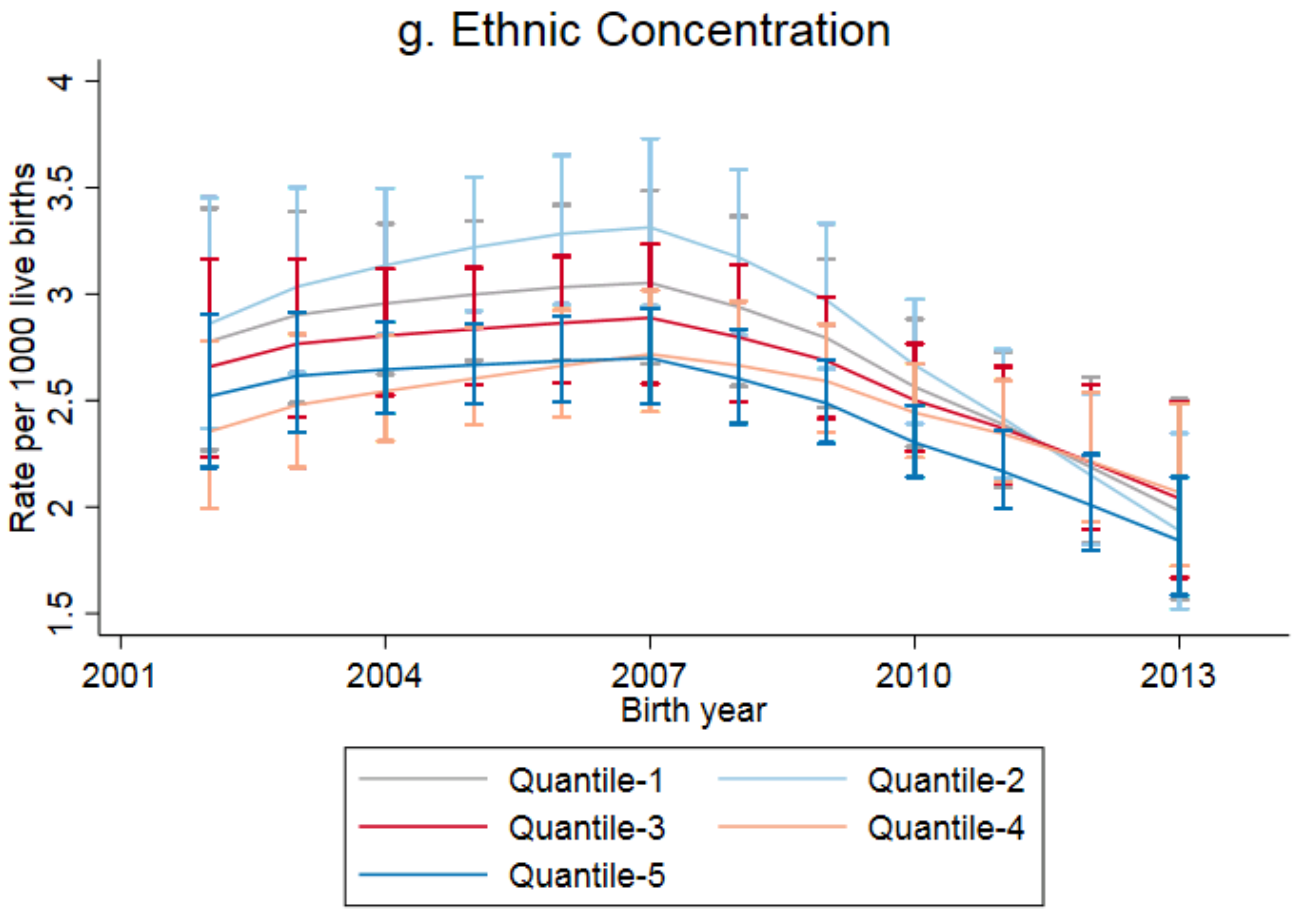

b. Rurality
Rate per 1000 live births
1
1.5
2
2.5
3
3.5
2001
2004
2007
2010
2013
Birth year
Urban-area resident
Rural area residents


c. Neighborhood income
Rate per 1000 live births
1.5
2
2.5
3
3.5
2001
2004
2007
2010
2013
Birth year
Quantile-1
Quantile-2
Quantile-3
Quantile-4
Quantile-5


d. Residential Instability
Rate per 1000 live births
1.5
2
2.5
3
3.5
2001
2004
2007
2010
2013
Birth year
Quantile-1
Quantile-2
Quantile-3
Quantile-4
Quantile-5

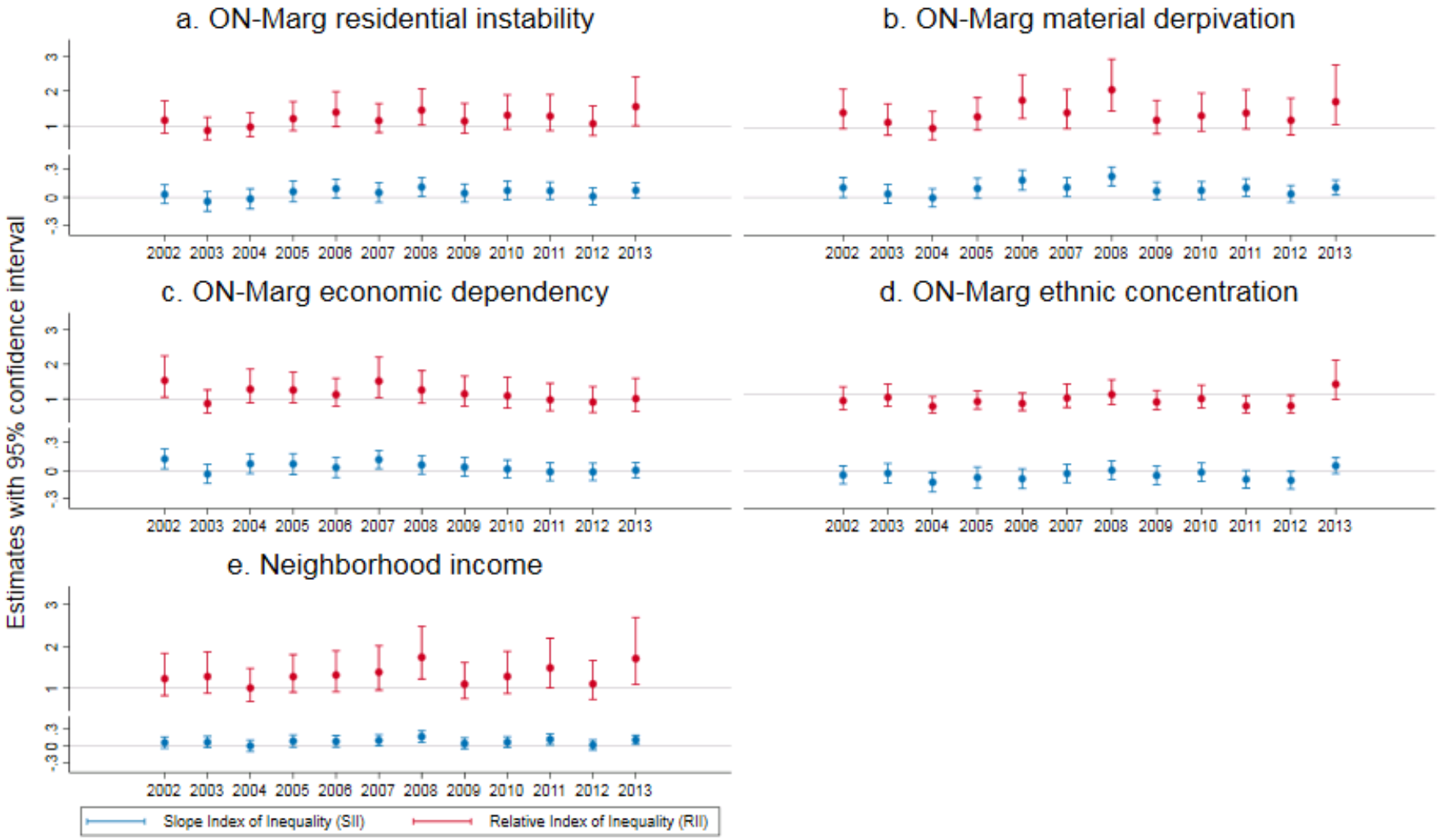

e. Material Deprivation
Rate per 1000 live births
1
1.5
2
2.5
3
3.5
2001
2004
2007
2010
2013
Birth year
Quantile-1
Quantile-2
Quantile-3
Quantile-4
Quantile-5


f. Economic Dependency
Rate per 1000 live births
1.5
2
2.5
3
3.5
2001
2004
2007
2010
2013
Birth year
Quantile-1
Quantile-2
Quantile-3
Quantile-4
Quantile-5



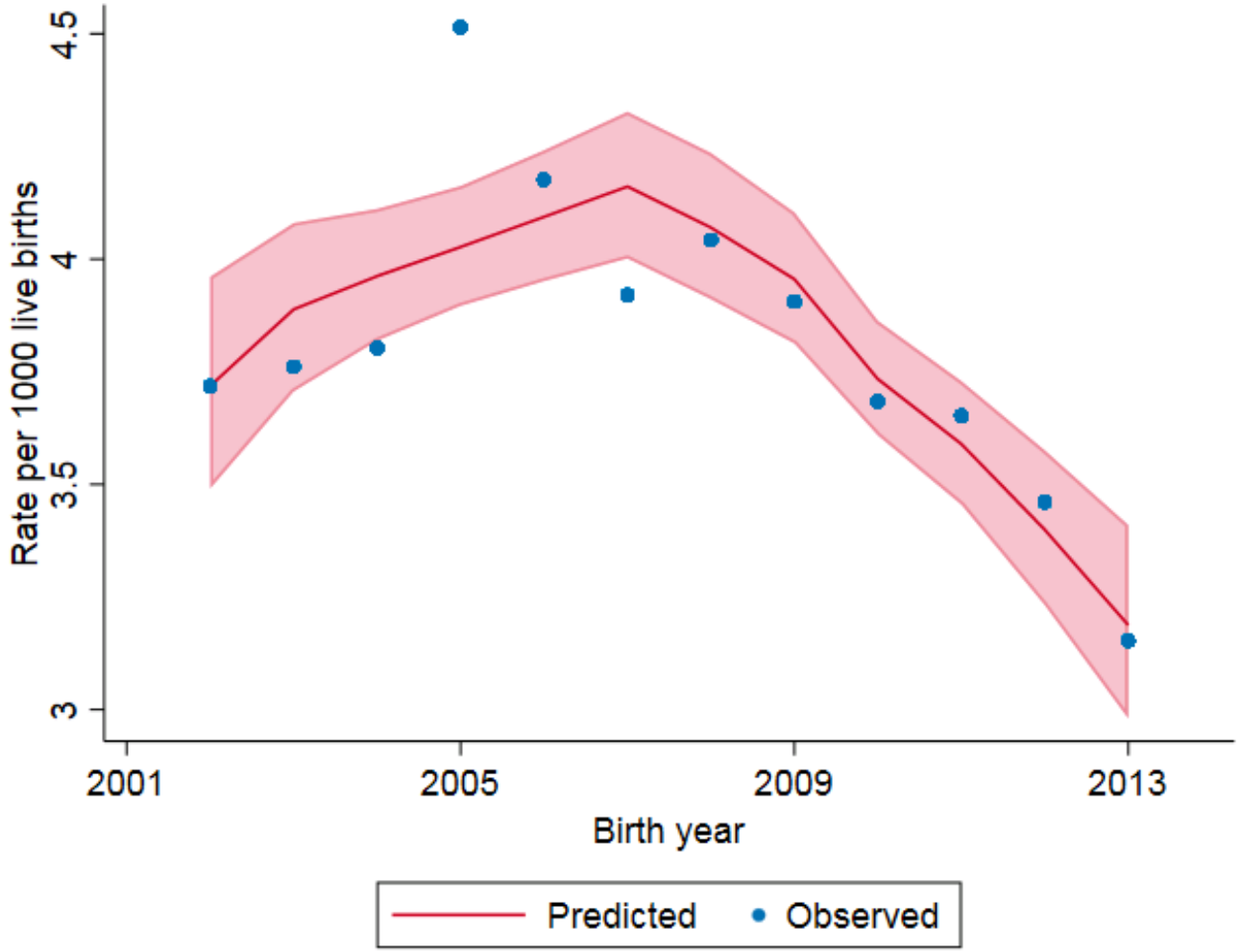
Note: Graphs represent predicted estimates (95% confidence intervals) based on a Poisson model with time trend modeled using restricted cubic splines with 3 knots at 2003, 2008, and 2012

eFigure 5. Relative Index of Inequality (RII) and Slope Index of Inequality (SII)[a] according to the Ontario marginalization index 4 domains and neighborhood income over time



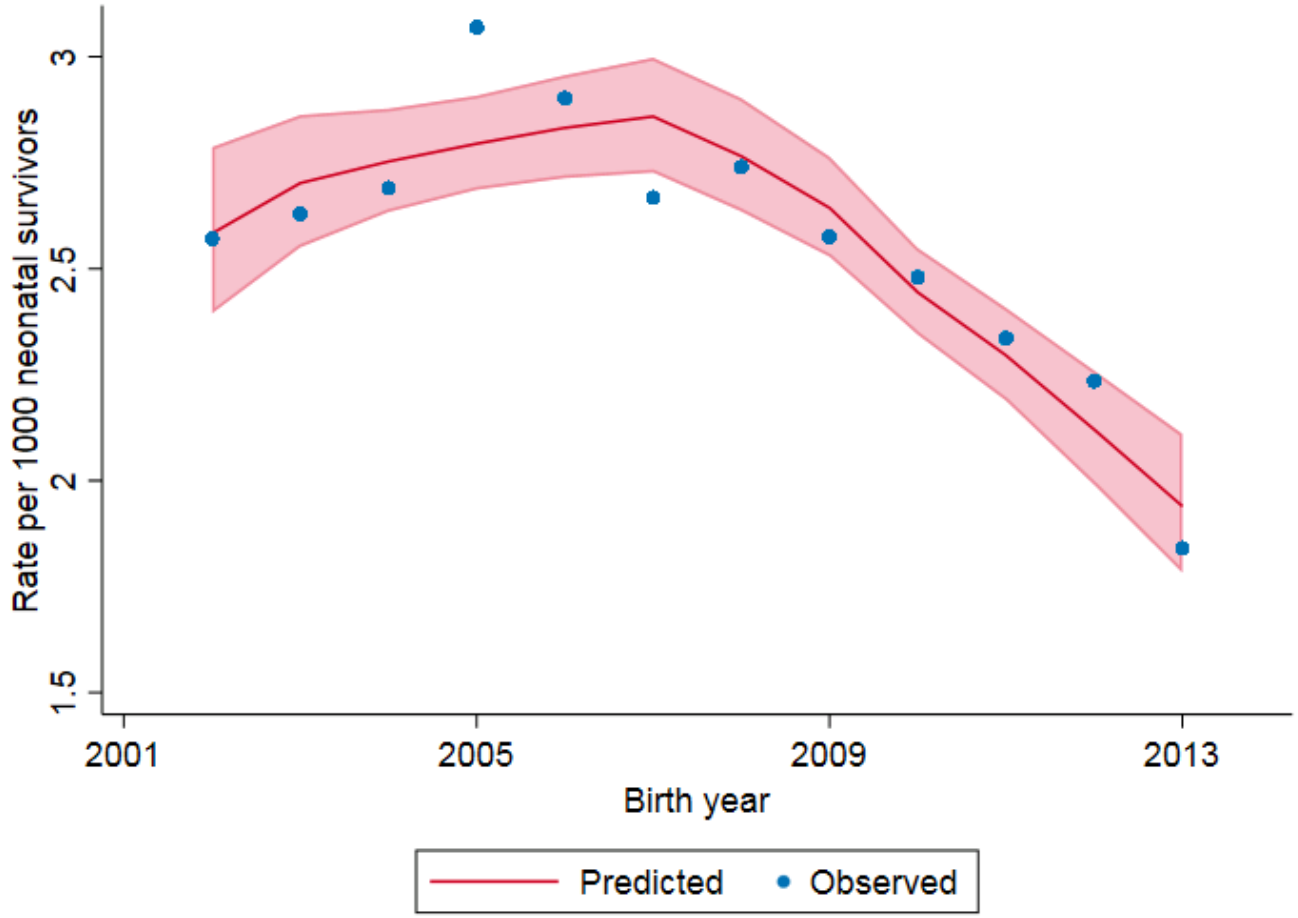
[a] The SII is expressed as a percentage, and refers to the absolute difference in the percentage CP between the most and least marginalized mothers.

eFigure 6. Cerebral palsy rates (95% CI) per 1000 live births by year of birth among children aged 0-4 years (N=1,587,087) in Ontario, Canada. Cerebral palsy cases included diagnoses made either in hospitals or at one or more outpatient occasions



Note: Predicted estimates are based on a Poisson model with time trend modeled using restricted cubic splines with 3 knots at 2003, 2008, and 2012

eFigure 7. Cerebral palsy rates (95% CI) per 1000 neonatal survivors by year of birth among children aged 0-4 years (N=1,585, 155) in Ontario, Canada



Note: Predicted estimates are based on a Poisson model with time trend modeled using restricted cubic splines with 3 knots at 2003, 2008, and 2012

Chapter 5. Manuscript 2-In-Utero Exposure to Maternal Diabetes and the Risk of Cerebral Palsy.

5.1. Preface

While the aim of manuscript 1 enclosed in Chapter 4 was purely descriptive, I shifted my focus in Chapters 5 and 6 towards etiological research to add to the existing knowledge on CP causes. In Chapter 4, I observed a high prevalence of CP in children of mothers with certain characteristics, including young, old, primiparous, and grand multiparous women, and women with low socioeconomic status. These results suggest that maternal factors might play important roles in CP etiology, despite the overall focus of the literature on the effects of preterm birth and birth asphyxia. I, therefore, focused in this chapter on two common and closely related maternal illnesses—maternal pre-gestational and gestational diabetes. The literature on the effect of maternal diabetes on CP is limited by the small number of population-based studies that examined these associations and the lack of evidence on the role of diabetes duration as well as the possible mediation by increased fetal size. My aim was to examine the effects of in-utero exposure to pre-gestational and gestational diabetes on CP. I also aimed to explore the effect of the duration of pre-gestational diabetes and estimate its controlled direct effect on CP non-mediated through large for gestational age using causal mediation techniques. This manuscript entitled “In-Utero Exposure to Maternal Diabetes and the Risk of Cerebral Palsy” is being prepared for submission to *BMJ*.

5.2. Manuscript 2

In-Utero Exposure to Maternal Diabetes and the Risk of Cerebral Palsy

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Key Points

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Question: Are maternal pre-gestational and gestational diabetes associated with increased risk of cerebral palsy (CP) in offspring?

Findings: In this population-based study of 2,110,177 births, although exposure to maternal gestational diabetes was not associated with CP, children exposed to maternal pre-gestational diabetes were at increased risk of CP. The risk of CP increased with the duration of pre-gestational diabetes and was not substantially explained by the increased size at birth.

Meaning: Maternal pre-gestational diabetes and gestational diabetes might have differential roles in CP etiology. The large fetal size as a hypothesized mechanism underlying the associations between maternal diabetes and CP appears not to contribute significantly to these associations.

ABSTRACT

Importance: Evidence on the effects of *in utero* exposure to maternal diabetes on cerebral palsy (CP) in offspring is limited.

Objective: To examine the effects of pre-gestational (PGDM) and gestational diabetes (GDM) separately on CP in offspring and the extent to which the effect is mediated through increased fetal size.

Design: Retrospective birth cohort study of all in-hospital deliveries in the province of Ontario, Canada under a single-payer health care system.

Setting: Population-based study.

Participants: All live births (n=2,110,177) born in the province between 2002–2017 followed up through 2018.

Exposures: Maternal PGDM (n = 39,704) identified from an administrative data-derived registry for diabetes in the province and GDM (n=81,325) from inpatient or outpatient diagnoses during the index pregnancy.

Outcome: CP in offspring defined as a single inpatient or $\geq$ 2 outpatient diagnoses at least two weeks apart between birth and age 16 years. We considered large for gestational age (LGA, birth weight for gestational age >90th percentile) as the mediator.

Results: During the study period, 5,317 children were diagnosed with CP (187 exposed to PGDM and 171 exposed to GDM). Children of mothers with PGDM showed an increased risk of CP (Hazard ratio (HR): 1.84 (95% confidence interval (CI): 1.59, 2.14)) after adjusting for maternal sociodemographic and clinical factors. These associations became stronger as the duration of PGDM increased (adjusted HR: 2.49 (1.76, 3.54) for PGDM>10 years**)**. No associations were found between GDM and CP in both crude and adjusted analyses (adjusted HR: 0.91 (95% CI: 0.77, 1.06)). Our mediation analysis showed that LGA explained 12% of the effect of PGDM on CP.

Conclusion and relevance: In this population-based birth cohort study, maternal pregestational but not gestational diabetes was associated with increased risk of CP, and the increased risk was not substantially mediated by the increased fetal size. These results add to the accumulating evidence on the important role of maternal pre-conception and pregnancy factors in the etiology of CP. Given the increasing prevalence of diabetes in women of reproductive age, monitoring

children exposed to maternal pre-gestational diabetes for early neurological manifestations of cerebral palsy is warranted.

BACKGROUND

Diabetes mellitus is one of the most common chronic illnesses affecting women during pregnancy [1] with increases in rates worldwide for both pre-gestational diabetes mellitus (PGDM) and gestational diabetes mellitus (GDM). [2] The diabetic in-utero environment has shown several long-term effects on offspring, including poor neurodevelopmental outcomes. [3-9] The effects of PGDM and GDM on brain development, however, may be distinct. Besides the differences in their pathophysiology, the timing of fetal exposure to hyperglycemia extends throughout the pregnancy in PGDM but is generally confined to the second half of gestation in GDM. [6,10]

Studies have reported positive associations of PGDM and GDM with autism spectrum disorders, [7,8] attention deficit hyperactivity disorder, [6] and cognitive impairment. [9,10] However, the evidence on their associations with cerebral palsy (CP) is scarce and limited. [11,12] To the best of our knowledge, only two population-based studies in Sweden and Norway have examined the link between maternal diabetes and CP; both studies have reported positive associations between PGDM and CP and no associations with GDM. [11,12] The Swedish case-control study, [11] however, was restricted to CP cases admitted to hospitals and examined crude associations only. Neither study has explored possible causal pathways for these associations nor the risk of CP according to the duration of PGDM.

Although some [12] have speculated a role of increased fetal size in explaining the increased risk of CP in infants of diabetic mothers, no study has examined this plausible causal mechanism. PGDM and GDM are important causes of both macrosomia and large-for-gestational-age (LGA). [13-16] Maternal hyperglycemia causes several metabolic changes that enhance fetal growth, [13] such as the increasing passage of nutrients to the fetus through the placenta and fetal hyperinsulinemia. [6] Studies have shown that children born LGA or with macrosomia are at higher risk of CP than those born with normal birth weight, [17,18] although the exact mechanism of increased risk of CP in large babies remains unclear. [19,20]

In a large population-based birth cohort, we examined the effects of pre-gestational and gestational diabetes separately with CP in offspring and the extent to which the effect was mediated through increased fetal size.

METHODS

Data Sources and Study Cohort

We created a birth cohort by linking individual- and area-level data across several administrative health datasets held and maintained at ICES (formerly known as Institute for Clinical Evaluative Sciences). These health datasets contain health and demographic information of all users of the universal provincial health care system in Ontario, Canada. [21,22] These datasets were linked using unique encoded identifiers and analyzed at ICES. Eligible infant-mother dyads were identified from the Mother-Baby Database (MOMBABY) that deterministically links mother and delivery records with >98% linkage rate (see eTable 1 for details of data sources). Ethics approval was received from the Institutional Review Board of the Faculty of Medicine and Health Sciences at McGill University.

Participants

We identified all births (>20 weeks' gestation) delivered in hospitals between April 1, 2002, and March 31, 2017. After excluding births with missing or invalid records and stillbirths, the final study population included 2,110,177 live births (eFigure 1).

Outcome

All children were followed from birth until death or the end of follow-up on March 31, 2018, to ascertain the study outcome. A diagnosis of CP in children was based on one or more inpatient hospitalization diagnoses using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision diagnostic codes (ICD-10-CA codes: G80) or two or more outpatient diagnoses at least two weeks apart (ICD-9 code: 343) [21,22] (eTable 2).

Exposure

PGDM was defined as any diagnosis of diabetes in the mother before the index pregnancy identified from the Ontario Diabetes Database (ODD). ODD is a validated administrative data-derived registry of Ontario residents diagnosed with non-gestational diabetes since 1991, with a sensitivity of 86% and a specificity of 97%. [23]

GDM was ascertained based on the presence of at least one inpatient diagnosis of gestational diabetes during the index pregnancy (ICD-10-CA: E10-E14, O24) or two or more outpatient diagnoses during the index pregnancy (OHIP code: 250) [24] (eTable 2).

Mediator

LGA was defined as having a birth weight >90% for gestational age [25] relative to a Canadian reference for each sex [26] (LGA vs. appropriate for gestational age (AGA, 10^{th}-90^{th} percentiles).

Potential Confounders

Potential confounders were identified *a priori* based on the literature. [22,27-31] They included maternal age (<20, 20-24, 25-29, 30-34, 35-39, or ≥40 years), parity (0, 1, 2, 3, or ≥4 previous live births), and socioeconomic characteristics including receiving the provincial drug benefit, rural residence, neighborhood income, and the four area-based indices of the Ontario Marginalization Index—material deprivation, economic dependency, instability, and ethnic concentration (details in eMethods). We also controlled for infant's sex and birth year to account for secular changes in maternal diabetes and CP rates. We adjusted for hypertension detected before a diagnosis of PGDM or GDM. For GDM as exposure, we also adjusted for the start of prenatal care (late if the first visit >13 weeks) and the presence of gestational hypertensive disorders (eTable 2). In mediation analyses, we controlled for the adequacy of prenatal care (adequate if the first visit was between 0–13 weeks' gestation and the total number of prenatal visits was >12), [32] gestational hypertensive disorders, and the presence of congenital malformations (eTable 2) (see eFigure 2 for illustration of relationships between exposure, outcome, mediators, and potential confounders).

Statistical Analysis

Effects of PGDM and GDM on CP in offspring were estimated using Cox proportional hazards models to account for the unequal follow-up time in children (from birth to CP diagnosis, death, or the end of follow-up, whichever came first). We first compared the unadjusted cumulative incidence of CP by the end of March 2018 among offspring exposed and non-exposed to PGDM (or GDM). We then fitted regression analyses that included potential confounders in the following sequence: Model 1 adjusting for birth year and infant's sex; Model 2 additionally adjusting for maternal sociodemographic characteristics (age, parity, and socioeconomic indicators) to Model 1; and Model 3 additionally adjusting for pre-gestational hypertension for PGDM or pre-gestational hypertension, gestational hypertensive disorders, and delayed onset of prenatal care for GDM to Model 2. After testing for non-linear relations between birth year and CP, [33,34] birth year was modeled using restricted cubic splines with 3 knots at 2003, 2010, 2016 years. We assessed the proportional hazards assumption both graphically and statistically by the scaled Schoenfeld residuals for nonzero slope and the Chi-squared test of proportional hazards assumption, finding no evidence that this assumption was violated for all variables except for the birth year. We, therefore, allowed the baseline hazard to vary by birth year (i.e., stratified Cox model) [35] because models with birth year as time-varying covariates did not converge. We used clustered variance estimates in all models to account for clustering by mother (n=1,021,086 siblings born to 450,929 mothers). For PGDM as exposure, we stratified the exposed group into three categories of duration of the disease (<5 years, 5–10 years, and >10 years). For all analyses with GDM as exposure, we restricted our sample to women with no PGDM.

Quantitative Bias Analysis

We assessed the robustness of our results against exposure and outcome misclassification (separately and combined) with probabilistic bias analyses on individual-level data (record-level correction) [36,37] using reported sensitivity and specificity values of administrative database-based validation studies (eTable 3).[23,38,39] Details of bias analyses are described in eMethods. In brief, we modeled bias parameters (sensitivity and specificity) using a beta distribution, and the minimum, maximum, and mode of the distribution of sensitivity values were 40%, 80%, and 60% for CP and 60%, 95%, and 86% for maternal diabetes, respectively. We assumed a near-

perfect specificity (~99%) for both CP and PGDM (or GDM) definitions, consistent with published validation studies. [23,38,39] Based on these bias parameter distributions, we re-estimated the effect of PGDM (or GDM) on CP corrected for the potential misclassifications. The entire process was repeated 1,500 times to obtain a distribution of bias-adjusted hazard ratios (HRs), which was used to calculate confidence limits adjusted for systematic and random errors.

To assess the effect of unmeasured confounding by individual-level socioeconomic characteristics, which were not available in our data, we simulated the impact of maternal education variable (dichotomized into university graduate or not) using bias parameters from existing studies. [40,41] We assigned the following range of prevalence of low education (less than university graduate) for children with CP: 0.45–0.85 (mode=0.65) in the exposed and 0.30–0.70 (mode=0.50) in the unexposed children. The corresponding figures for children without CP were 0.40–0.80 (mode=0.60) and 0.25–0.65 (mode=0.45) respectively. We then estimated HRs while adjusting for measured confounders and the simulated confounder maternal education (1,500 simulations). Additionally, we corrected for exposure and outcome misclassification and unmeasured confounding simultaneously in the final adjusted model.

Mediation Analysis

We estimated the controlled direct effect (CDE) of PGDM on the risk of CP not mediated by LGA using marginal structural models (eMethods). [42,43] This method allows for calculating the CDE in the presence of mediator-outcome confounders affected by the exposure (e.g., preeclampsia or congenital malformations). We first calculated stabilized inverse probability weights by fitting two logistic regression models—one for a binary PGDM and the other for a binary LGA. The weights were multiplied and truncated at the 99th percentile to improve precision and were then used in the outcome model that included the exposure, the mediator, and their interaction (if statistically significant). [42,43] The models used to calculate weights included covariates described above plus potential mediator-outcome confounders (eFigure 2). For mediation analysis, we excluded small for gestational age infants (n=201,164 excluded) as these infants have consistently shown a high risk of CP, and inclusion of them in the reference category would mask the true mediation effect of LGA. [17,18,44,45] In secondary analyses, we

repeated the fully-adjusted analysis for CDE after excluding one randomly selected twin (n=35,223 excluded) to examine if results would be confounded by multiple gestations. We used simple bias formulas to examine the robustness of our CDE estimate to the presence of unmeasured mediator-outcome confounders (e.g., infections or genetic factors) under multiple potential bias conditions. [46,47]

Additional Sensitivity Analyses

Given that the age of CP diagnosis would be arbitrary rather than accurately representing the onset of CP, we re-estimated associations between PGDM (or GDM) and CP using Poisson regression with the time of follow-up as the offset variable (rate ratios) and using Log-binomial regressions (risk ratios). We also further stratified the duration of PGDM into refined categories (<1, 1–2, 3–5, 6–10, and >10 years) and repeated the primary analysis. We re-examined associations between GDM and CP after excluding GDM diagnosed after 28 weeks (n=64,311 excluded) to account for the fact that children born preterm are less likely to be classified as exposed. All statistical analyses were conducted using Stata version 16.1 (StataCorp, College Station, TX, USA).

RESULTS

Of 2,110,177 live births included, 81,325 were born to women with GDM and 39,704 to women with PGDM. Women who were older, had high parity, received provincial drug benefits, or lived in neighborhoods with low income or high ethnic diversity were more likely to have PGDM or GDM. Children whose mothers had PGDM were more likely to be born LGA or have congenital malformations (Table 5.1). Children born LGA were slightly more likely to have CP (0.24%) compared to those AGA (0.23%). Crude prevalence of fetal exposure to PGDM and GDM increased between 2002 – 2017 (from 1.4% to 2.3% and 2.6% to 5.9%, respectively), while the prevalence of CP slightly increased between 2002-2006 but steadily decreased thereafter (eFigures 3 and 4).

The median follow-up duration was 8 years (interquartile range, 4–12 years) during which 5,317 children (187 PGDM exposed and 171 GDM exposed) were diagnosed with CP (Table 5.1). The incidence rate of CP was 2.99 (95% confidence interval (CI): 2.91, 3.07) per 10,000 child-year. Figure 5.1 depicts the Kaplan-Meier plot of crude cumulative incidence of CP by exposure status. Unadjusted average annual CP incidence was 6.02 and 2.90 per 10,000 child-year in those exposed and unexposed to PGDM, respectively; the corresponding figures for GDM were 2.82 and 2.94 per 10,000 child-year.

Table 5.2 shows HRs of CP by exposure to PGDM and GDM. Children of mothers with PGDM showed an increased risk of CP in crude and adjusted models (HR: 1.84 (1.59, 2.14) in the model adjusted for all measured potential confounders). The risk of CP among children exposed to PGDM increased as the duration of PGDM increased; the HRs increased from 1.70 for women with PGDM for <5 years to 2.49 for those with PGDM for > 10 years in fully adjusted models (*p*-value for a non-parametric test of trend=0.00). However, no increased risk of CP was observed in children exposed to maternal GDM.

Table 5.3 shows the distribution (median and 2.5^{th} and 97.5^{th} percentiles) of 1,500 HRs estimates corrected for misclassification and unmeasured confounding in our quantitative bias analyses. The magnitude of association between PGDM & CP became slightly larger, however, the associations for GDM remained close to the null. Accounting for possible unmeasured confounding by maternal education yielded a minimal downward change in our adjusted estimates. Effect estimates adjusted for both exposure and outcome misclassifications and unmeasured confounding, as well as for measured confounders, became slightly stronger (PGDM: 2.06 (1.73, 2.47); GDM: 0.84 (0.70, 1.02)).

Our mediation analysis showed substantial direct effects of PGDM on CP, conditional on birth weight set to be appropriate for gestational age (CDE HR=1.81 (1.51, 2.17) compared to the total effect HR=1.94 (1.62, 2.23)) in the fully adjusted model (Table 5.4). These results indicated that we would eliminate 12% of the effect of PGDM on CP if we would intervene to set all children to be appropriate for gestational age (i.e., birth weight between 10^{th}-90^{th} percentiles for

each gestational age) at birth. Mediation analysis that included one randomly selected twin did not differ from main results (HR: 1.81 (1.51, 2.17)). CDEs estimated under a range of bias conditions were robust to the presence of a moderate or strong unmeasured mediator-outcome confounder (eTable 4). It should be noted that CDE estimates would not change if the prevalence of unmeasured mediator-outcome confounder was equal in children exposed and unexposed to PGDM (e.g., genetic factors).

Rate ratios calculated from Poisson and log-binomial regression models were almost identical to HRs, particularly in adjusted estimates (eTables 5 and 6). Analyses using the different categorization of PGDM duration showed an increased risk of CP in all categories, including those with PGDM for < 1 year, with the increased risk according to the duration of diabetes (eTable 7). Results excluding GDM diagnosed >28 weeks' gestation were similar to main results (eTable 8).

DISCUSSION

In this population-based cohort study, maternal pre-gestational diabetes but not gestational diabetes was associated with an increased risk of cerebral palsy in offspring. We also found evidence that most of the effect of PGDM on CP was not mediated by having a large-for-gestational-age baby.

Our results are consistent with others that reported an increased risk of CP in children exposed to PGDM but not GDM [11,12] This supports the proposed theory that that children of mothers with PGDM may have been exposed to hyperglycemia during critical windows for brain development in early pregnancy. [12] In addition, in-utero exposure to hyperglycemia is generally more prolonged and possibly severer in PGDM than GDM. Differences in fetal metabolic sequelae, placental changes, and fetal vasculopathic changes could also explain the different associations of PGDM and GDM with CP. [48]

We also observed that the risk of CP increased with the duration of PGDM. Although we did not have information on diabetic severity or level of control of hyperglycemia, we speculate that the higher risk observed with long-term PGDM could be related to the presence of more severe hyperglycemia with longer duration of diabetes. Long-term diabetes could also be associated with higher diabetic complications. For instance, we found a higher prevalence of hypertensive disorders with a longer duration of PGDM (9.5% and 6.6% of women with PGDM for >10 years were subsequently diagnosed with pre-pregnancy hypertension and gestational hypertension respectively; corresponding figures for PGDM for <5 years were 1.6% and 3.2%). Long-term effects of PGDM on the vascular system could cause maternal hypertension and chronic kidney diseases; [49] both are linked to CP. [12] Placental changes due to the greater risk of vascular dysfunction with prolonged diabetes could also be implicated. [50] Women with long-term diabetes could more likely be on potential teratogenic medications, such as statins, and Angiotensin-converting enzyme (ACE) inhibitors that may increase thr risk of congenital malformations and subsequently CP. [51-54]

Although diagnostic criteria and screening practices for GDM have undergone some changes over time (e.g., moving from selective to universal screening), [55] most Canadian women received GDM screening between 24-28 weeks of gestation during the study period. [55] Thus, early preterm births have little opportunity to be classified as GDM-exposed if the screening occurred later in pregnancy. This may have contributed to the slightly reduced risk of CP we observed for GDM, given that preterm birth is one of the strongest risk factors of CP. [56] Nevertheless, our results excluding GDM diagnosed after 28 weeks were also close to the null.

Enhanced fetal growth is a common complication of maternal diabetes, [6] and some [17,18] but not all [57,58] studies have reported a positive association between LGA/macrosomia and CP. We found a weak association between LGA and CP but no association between macrosomia and CP. Our mediation analysis results also showed that ~12% of the risk of CP associated with PGDM would be reduced by eliminating LGA births. These findings suggest that PGDM affects brain development mostly through other pathways than large fetal size or its sequelae, such as traumatic deliveries and shoulder dystocia. [59]

Strengths and Limitations

Our results came from a large cohort of all live births in universal health care settings, potentially reducing the extent of selection bias. The large study size also allowed us to have precise estimates of the association between maternal diabetes and cerebral palsy and to examine the potential pathway through mediation analysis. In addition, our use of data prospectively collected irrespective of any specific health outcomes would have reduced the risk of biases associated with self-reported data.

Our study also has several limitations. Study variables ascertained by hospital records and physician billing claims would be subject to misclassification. [60] For example, GDM cases diagnosed in early pregnancy might represent PGDM cases undetected before pregnancy. [61] Nevertheless, only 6.7% of GDM cases were diagnosed before 23 weeks of gestation, and excluding them did not change the results. Results of our quantitative bias analyses also suggest that the misclassification might have attenuated the estimated associations and would not change our conclusion substantially. Although we adjusted for multiple covariates available in different databases, we could not rule out the possibility of residual confounding by individual-level maternal characteristics, such as maternal education, income, and immigration status, in our observed association. [22,30] Nevertheless, simulating effects of unmeasured confounding by maternal education slightly attenuated our estimates, and the association between PGDM and CP remained positive. Due to the lack of access to data, PGDM in our study combined type 1 (autoimmune) and 2 diabetes (mostly linked to obesity) that share many features but are diverse conditions [62] leading to distinct birth outcomes. [63] It is possible that children with severe brain injury may die in-utero or early in life before being diagnosed with CP. Thus, reported associations may be underestimated if in-utero or postnatal deaths of severe CP cases occur preferentially in those exposed in-utero to diabetes than the unexposed. [64]

Conclusion

In this large population-based cohort of over two million live births, maternal PGDM but not GDM was associated with increased risk of CP, and increased fetal size did not substantially explain the increased risk. Given the continuing rise in prevalence of diabetes in women of

reproductive age, close monitoring of young children exposed to maternal diabetes for early neurological manifestations of cerebral palsy is warranted because early interventions have shown improved prognosis and neurological outcomes in children with CP. [65] Future studies that consider type 1 and type 2 diabetes separately to examine potential differential effects would shed further light on the effect of PGDM on the risk of CP in children.

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Table 5.1. Maternal and child characteristics (n (%)) by exposure to maternal pre-gestational (PGDM) and gestational (GDM) diabetes mellitus in children born in Ontario, Canada in 2002–2017 (n=2,110,177)

	PGDM		GDM	
Characteristics	**No (n=2,070,473)**	**Yes (n=39,704)**	**No (n=1,989,148)**	**Yes (n=81,325)**
Maternal age				
<20 years	66,091 (3.2)	273 (0.7)	65,724 (3.3)	367 (0.5)
20–24 years	260,719 (12.6)	2,221 (5.6)	257,303 (12.9)	3,416 (4.2)
25–29 years	577,647 (27.9)	7,923 (20.0)	561,672 (28.2)	15,975 (19.6)
30–34 years	721,672 (34.9)	14,430 (36.3)	690,805 (34.7)	30,867 (38.0)
35–39 years	367,127 (17.7)	11,347 (28.6)	343,724 (17.3)	23,403 (28.8)
≥40 years	77,217 (3.7)	3,510 (8.8)	69,920 (3.5)	7,297 (9.0)
Parity				
0	931,161 (45.0)	13,726 (34.6)	896,642 (45.1)	34,519 (42.5)
1	733,262 (35.4)	14,865 (37.4)	704,407 (35.4)	28,855 (35.5)
2	268,924 (13.0)	6,875 (17.3)	257,316 (12.9)	11,608 (14.3)
3	81,629 (3.9)	2,427 (6.1)	77,816 (3.9)	3,813 (4.7)
4+	55,497 (2.7)	1,811 (4.6)	52,967 (2.7)	2,530 (3.1)
Neighborhood income quintile				
Q1 (highest)	342,071 (16.5)	5,250 (13.2)	331,762 (16.7)	10,309 (12.7)
Q2	427,409 (20.6)	7,817 (19.7)	412,048 (20.7)	15,361 (18.9)
Q3	421,411 (20.4)	8,209 (20.7)	404,667 (20.3)	16,744 (20.6)
Q4	412,862 (19.9)	7,796 (19.6)	395,419 (19.9)	17,443 (21.5)
Q5 (lowest)	459,230 (22.2)	10,461 (26.4)	437,946 (22.0)	21,284 (26.2)
Missing	7,490 (0.4)	171 (0.4)	7,306 (0.4)	184 (0.2)
ON-Marg residential instability quintile [a]				
Q1 (least marginalized)	406,744 (19.6)	8,665 (21.8)	388,173 (19.5)	18,571 (22.8)
Q2	409,426 (19.8)	7,635 (19.2)	394,567 (19.8)	14,859 (18.3)
Q3	367,711 (17.8)	6,444 (16.2)	355,663 (17.9)	12,048 (14.8)
Q4	390,880 (18.9)	7,142 (18.0)	376,485 (18.9)	14,395 (17.7)
Q5 (most marginalized)	460,396 (22.2)	9,003 (22.7)	439,953 (22.1)	20,443 (25.1)
Missing	35,316 (1.7)	815 (2.1)	34,307 (1.7)	1,009 (1.2)

ON-Marg material deprivation quintile [a]				
Q1 (least marginalized)	493,704 (23.8)	8,988 (22.6)	474,996 (23.9)	18,708 (23.0)
Q2	375,490 (18.1)	6,825 (17.2)	361,214 (18.2)	14,276 (17.5)
Q3	368,598 (17.8)	6,677 (16.8)	354,111 (17.8)	14,487 (17.8)
Q4	360,253 (17.4)	6,781 (17.1)	346,189 (17.4)	14,064 (17.3)
Q5 (most marginalized)	437,112 (21.1)	9,618 (24.2)	418,331 (21.0)	18,781 (23.1)
Missing	35,316 (1.7)	815 (2.1)	34,307 (1.7)	1,009 (1.2)
ON-Marg economic dependency quintile [a]				
Q1 (least marginalized)	623,482 (30.1)	13,608 (34.3)	594,116 (29.87)	29,366 (36.1)
Q2	465,229 (22.5)	9,305 (23.4)	445,360 (22.39)	19,869 (24.4)
Q3	366,845 (17.7)	6,524 (16.4)	353,558 (17.77)	13,287 (16.3)
Q4	311,161 (15.0)	5,060 (12.7)	301,379 (15.15)	9,782 (12.0)
Q5 (most marginalized)	268,440 (13.0)	4,392 (11.1)	260,428 (13.09)	8,012 (9.9)
Missing	35,316 (1.7)	815 (2.1)	34,307 (1.72)	1,009 (1.2)
ON-Marg ethnic concentration quintile [a]				
Q1 (least marginalized)	258,857 (12.5)	3,727 (9.4)	253,988 (12.8)	4,869 (6.0)
Q2	298,765 (14.4)	4,136 (10.4)	292,474 (14.7)	6,291 (7.7)
Q3	343,152 (16.6)	5,484 (13.8)	333,851 (16.8)	9,301 (11.4)
Q4	448,495 (21.7)	8,170 (20.6)	432,429 (21.7)	16,066 (19.8)
Q5 (most marginalized)	685,888 (33.1)	17,372 (43.8)	642,099 (32.3)	43,789 (53.8)
Missing	35,316 (1.7)	815 (2.1)	34,307 (1.7)	1,009 (1.2)
Recipient of Ontario Drug Benefit				
No	1,901,143 (91.8)	31,472 (79.3)	1,828,203 (91.9)	72,940 (89.7)
Yes	169,330 (8.2)	8,232 (20.7)	160,945 (8.1)	8,385 (10.3)
Living in rural area				
No	1,860,305 (89.9)	36,698 (92.4)	1,781,777 (89.6)	78,528 (96.6)
Yes	209,390 (10.1)	2,989 (7.5)	206,625 (10.4)	2,765 (3.4)
Missing	778 (0.0)	17 (0.0)	746 (0.0)	32 (0.0)
Pre-gestational hypertension				
No	2,021,122 (97.6)	36,702 (92.4)	1,944,070 (97.7)	77,052 (94.8)
Yes	49,351 (2.4)	3,002 (7.6)	45,078 (2.3)	4,273 (5.3)

Gestational hypertension				
No	2,0293,53 (98.0)	38,202 (96.2)	1,950,285 (98.1)	79,068 (97.2)
Yes	41,120 (2.0)	1,502 (3.8)	38,863 (2.0)	2,257 (2.8)
Start of prenatal care				
Early (≤13 weeks)	1,865,179 (90.1)	37,982 (95.7)	1,789,668 (90.0)	75,511 (92.9)
Late (>13 weeks)	205,294 (9.9)	1,722 (4.3)	199,480 (10.0)	5,814 (7.2)
Quality of prenatal care [b]				
Adequate	1,409,414 (68.1)	34,971 (88.1)	1,336,671 (67.2)	72,743 (89.5)
Inadequate	661,059 (31.9)	4,733 (11.9)	652,477 (32.8)	8,582 (10.6)
Infant's sex				
Female	1,009,287 (48.8)	19,253 (48.5)	970,162 (48.8)	39,125 (48.1)
Male	1,061,186 (51.3)	20,451 (51.5)	1,018,986 (51.2)	42,200 (51.9)
Birth plurality				
Singleton	1,999,995 (96.6)	38,094 (95.9)	1,922,238 (96.6)	77,757 (95.6)
Multiple	70,478 (3.4)	1,610 (4.1)	66,910 (3.4)	3,568 (4.4)
Any congenital malformations				
No	1,838,772 (88.8)	33,539 (84.5)	1,766,763 (88.8)	72,009 (88.5)
Yes	231,701 (11.2)	6,165 (15.5)	222,385 (11.2)	9,316 (11.5)
Birth weight for gestational age				
Appropriate for gestational age	1,664,091 (80.4)	27,381 (69.0)	1,601,080 (80.5)	63,011 (77.5)
Small for gestational age	198,060 (9.6)	3,104 (7.8)	189,886 (9.6)	8,174 (10.1)
Large for gestational age	208,322 (10.1)	9,219 (23.2)	198,182 (10.0)	10,140 (12.5)
Cerebral palsy				
No	2,065,343 (99.8)	39,517 (99.5)	1984189 (99.8)	81154 (99.8)
Yes	5,130 (0.3)	187 (0.5)	4959 (0.3)	171 (0.2)

[a] ON-Marg – Ontario Marginalization Index

[b] Adequate prenatal care if the first visit is between 0–13 weeks' gestation and the total number of prenatal visits is >12 [188]

Table 5.2. Hazard ratios (95% confidence interval) of cerebral palsy associated with exposure to maternal pre-gestational and gestational diabetes among 2,110,177 children at ages 0–16 years

	Crude	**Model 1** [a] (birth year and infant's sex)	**Model 2** [b] (birth year, infant's sex, and sociodemographic factors)	**Model 3** [c] (birth year, infant's sex, and sociodemographic and pre-existing factors)
PGDM [d]				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.96 (1.69, 2.27)	1.98 (1.70, 2.29)	1.88 (1.62, 2.19)	1.84 (1.59, 2.14)
PGDM-duration				
No PGDM	Ref.	Ref.	Ref.	Ref.
<5 years (n=23,025)	1.80 (1.47, 2.20)	1.81 (1.48, 2.22)	1.75 (1.43, 2.14)	1.70 (1.39, 2.08)
5–10 years (n=10,975)	1.97 (1.49, 2.61)	1.98 (1.50, 2.60)	1.86 (1.41, 2.45)	1.83 (1.39, 2.41)
> 10 years (n=5,704)	2.62 (1.85, 3.70)	2.69 (1.89, 3.88)	2.47 (1.74, 3.51)	2.49 (1.76, 3.54)
GDM [e]				
No	Ref.	Ref.	Ref.	Ref.
Yes	0.89 (0.76, 1.04)	0.92 (0.79, 1.07)	0.92 (0.79, 1.08)	0.91 (0.77, 1.06)

[a] Model 1 included birth year and infant's sex. Birth year was modeled using restricted cubic splines with 3 knots at 2003, 2010, 2016 years.

[b] model 2 included all covariates in model 1 plus maternal sociodemographic characteristics (age, parity, and socioeconomic indicators).

[c] Model 3 included all covariates in model 1 and 2 plus pre-gestational hypertension for PGDM or pre-gestational hypertension, gestational hypertensive disorders, and delayed onset of prenatal care for GDM.

[d] PGDM: Pre-gestational diabetes mellitus

[e] GDM: Gestational diabetes mellitus

Table 5.3. Hazard ratios (95% simulated interval) of cerebral palsy associated with maternal pre-gestational and gestational diabetes corrected for exposure and outcome misclassifications and unmeasured confounding

Crude analyses				
	Naïve crude estimate	**Corrected for outcome misclassification [a]**	**Corrected for exposure misclassification [a]**	**Corrected for outcome and exposure misclassification [a]**
PGDM [b]	1.96 (1.69, 2.27)	2.14 (1.82, 2.52)	2.29 (1.95, 2.74)	2.24 (1.90, 2.68)
GDM [c]	0.89 (0.76, 1.04)	0.93 (0.79, 1.11)	0.86 (0.72, 1.04)	0.91 (0.77, 1.09)
Adjusted analyses [d]				
	Naïve adjusted estimate	**Corrected for unmeasured confounding [a]**	**Corrected for outcome and exposure misclassification and unmeasured confounding [a]**	
PGDM [b]	1.84 (1.59, 2.14)	1.79 (1.55, 2.09)	2.07 (1.73, 2.48)	
GDM [c]	0.91 (0.77, 1.06)	0.88 (0.76, 1.04)	0.84 (0.70, 1.02)	

Notes

[a] Adjusted for both systematic and random errors

[b] PGDM: Pre-gestational diabetes mellitus

[c] GDM: Gestational diabetes mellitus

[d] Adjusted analyses included birth year, infant's sex, maternal sociodemographic characteristics (age, parity, and socioeconomic indicators), and pre-gestational hypertension for PGDM or pre-gestational hypertension, gestational hypertensive disorders, and delayed onset of prenatal care for GDM.

Table 5.4. Controlled direct effect (95% confidence interval) of maternal pre-gestational diabetes on the risk of cerebral palsy in offspring (n=1,909,013) [a]

	Crude model	**Adjusted model [b]**
Total effect	2.04 (1.75, 2.39)	1.94 (1.62, 2.23)
CDE [c,d]	2.05 (1.75, 2.40)	1.81 (1.51, 2.17)

Notes:

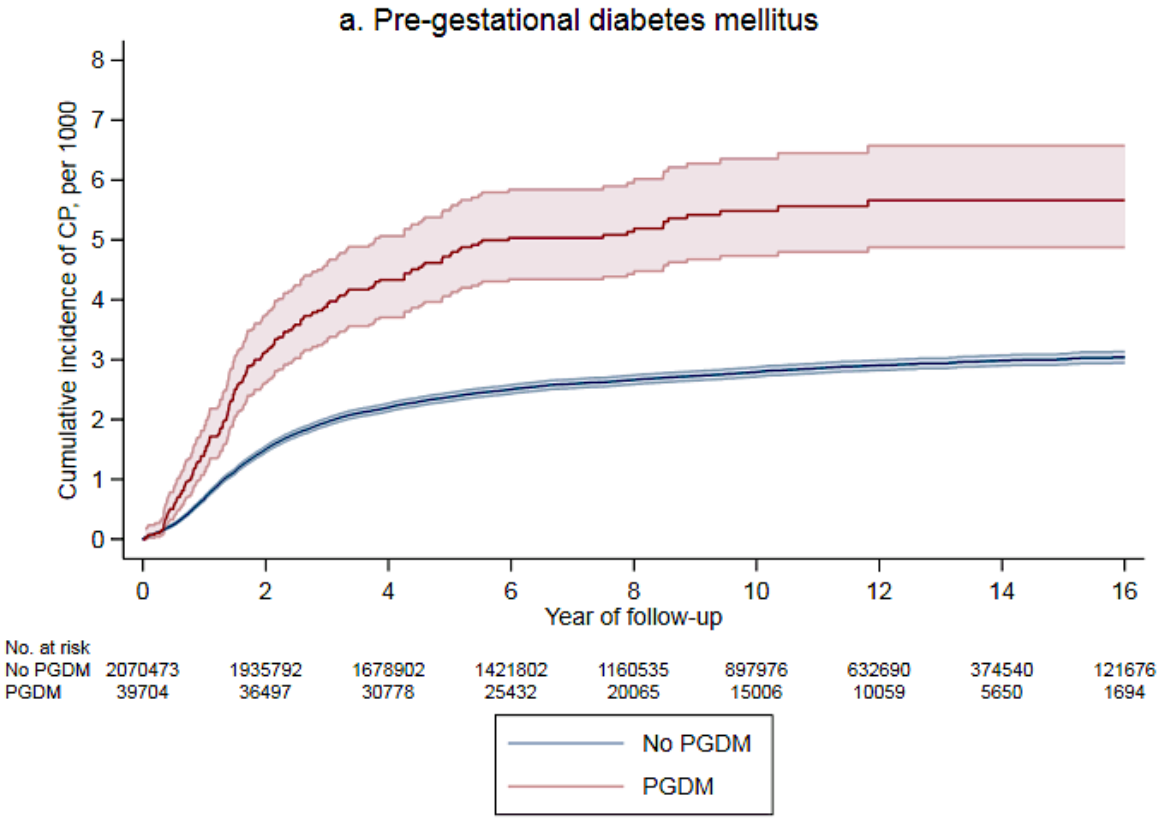
[a] Children born small for gestational age (n=201,164) were excluded.

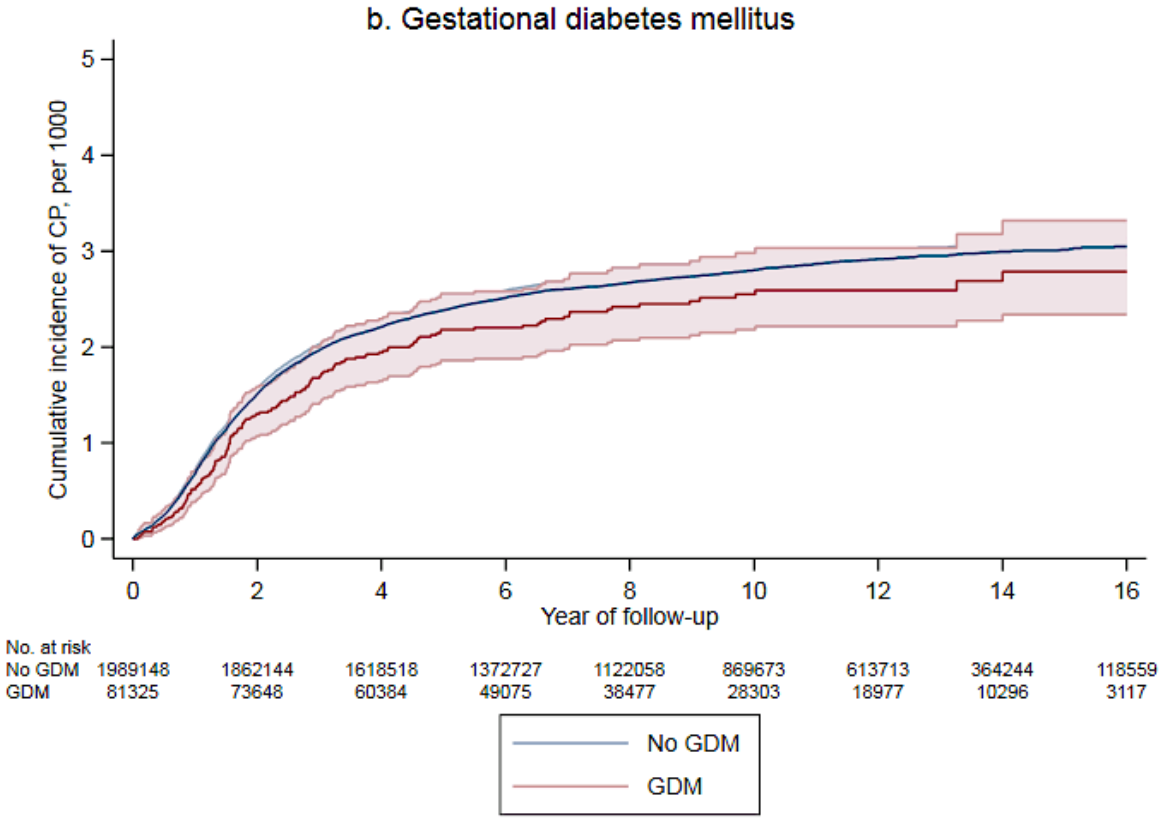
[b] Adjusted model for total effect included birth year, infant's sex, maternal sociodemographic characteristics, and pre-gestational hypertension. Adjusted model for CDE included birth year, infant's sex, maternal sociodemographic characteristics, pre-gestational hypertension, gestational hypertensive disorders, inadequate prenatal care, and the presence of congenital malformations in the child.

[c] CDE: Controlled direct effect.

[d] Controlled direct effects were calculated using marginal structural models with mediator (large for gestational age) set at 0 (i.e., appropriate for gestational age (10^{th}–90^{th} percentiles)).

Figure 5.1. Unadjusted cumulative incidence of cerebral palsy by exposure to (a) maternal pre-gestational diabetes (PGDM) and (b) maternal gestational diabetes (GDM)




b. Gestational diabetes mellitus
Cumulative incidence of CP, per 1000
0
1
2
3
4
5
0
2
4
6
8
10
12
14
16
Year of follow-up
No. at risk
No GDM 1989148 1862144 1618518 1372727 1122058 869673 613713 364244 118559
GDM 81325 73648 60384 49075 38477 28303 18977 10296 3117
No GDM
GDM

5.3. Supplementary Material-Manuscript 2

eMethods

Measures

Socioeconomic Indicators

Rural residence was categorized based on the Rurality Index of Ontario (RIO) and defined as having RIO>45. RIO is a score that incorporates measures of population density and travel times to nearest basic and advanced referral center. RIO was calculated at the Census Subdivision (CSD) level (municipalities) using the version of RIO closest to the year of birth (RIO-2004 for 2002-2006 births and RIO-2008 for 2007-2017 births).[1]

Area-based socioeconomic indicators were ascertained by linking census data with maternal residential postal code at delivery and were calculated at the dissemination area level (the smallest geographic unit for Canadian census, corresponding to a population of 400-700 persons). Data from the census year closest to birth year were used (2001 census for 2002-2003 births and 2006 census for 2004-2017 births).[2] Neighborhood income was used as quintiles from the highest (Q1) to the lowest (Q5) income.

We also used Ontario Marginalization (ON-Marg) indices—residential instability, material deprivation, economic dependency, and ethnic concentration—that were derived from 42 census questions using principal components analysis.[2] Residential instability measures the area-level concentration of individuals at risk of family and housing instability and includes the following: proportion of the population living alone; proportion of the population who are not youth (age 5-15); average number of persons per dwelling; proportion of dwellings that are apartment buildings; proportion of the population who are single/ divorced/widowed; proportion of dwellings that are not owned,; and proportion of the population who moved during the past 5 years).[2] Material deprivation includes the proportion of the population aged 20+ without a high-school diploma, the proportion of families who are lone parent families, the proportion of the income from government transfer payments, the proportion of the population aged 15+ who are unemployed, the proportion of the population considered low- income, and proportion of

households living in dwellings that are in need of major repair.[2] Economic dependency measures the proportion of people with no income from employment (proportion of the population who are aged 65 and older; dependency ratio (total population 0-14 and 65+ /total population 15 to 64); and proportion of the population not participating in labour force (aged 15+)).[2] Ethnic concentration measures the proportion of recent immigrant (arrived in the past 5 years) and people who self-identify as a visible minority.[2] Each ON-Marg index was summarized as 5 quintiles, which represent the least (Q1) to the most (Q5) marginalized neighborhood.[2]

We used eligibility to receive the provincial drug coverage as a proxy for individual-level socioeconomic status. These benefits are available for individuals with financial needs due to unemployment or disability. [3]

Quantitative Bias Analysis

Misclassification Bias

We used bias estimates from the literature [4-6] to conduct a probabilistic bias analysis with Monte Carlo sampling techniques to adjust for non-differential exposure and outcome misclassification [7,8]. We started by modeling bias parameters (sensitivity and specificity) using a beta distribution. The shape of the distribution is determined by two parameters: α and β. We calculated α and β according to plausible minimum and maximum values and adjusted the values as needed so the mean of the beta distribution accurately reflected the sensitivity and specificity values obtained from published validation studies [4-6]. The minimum, maximum, and mode of the distribution of bias parameters were 40%, 80%, and 60% for sensitivity of CP definition; 99.9%, 99.999%, and 99.99% for specificity of CP definition; 60%, 95%, and 86% for sensitivity of maternal diabetes definition; and 99.0%, 99.9%, and 99.5% for specificity of maternal diabetes definition respectively.

We then used these bias parameters to calculate the positive and negative predicted values based on observed data and exposure and outcome status. These predicted values were then applied to each record in the dataset to check whether the exposure or outcome status for each individual was correctly classified using a Bernoulli trial with a probability equal to the relevant predicted probability. The result of this trial was used as the bias-adjusted exposure or outcome variable.

Using the bias-adjusted dataset, we then used a Cox proportional hazards model to estimate the association between the exposure (PGDM or GDM) and CP, adjusted for misclassification. The entire process was repeated 1,500 times to generate a distribution of bias-adjusted estimates. The bias-adjusted effect estimate is the 50th percentile of the distribution and the 2.5th and 97.5th percentiles of the distribution provide a 95% simulation interval that only accounts for systematic error. We then estimated total error (systematic plus random error) by subtracted the conventional standard error (i.e. those calculated from main analyses) and a random normal deviate from each of the bias-adjusted estimates.

Unmeasured Confounding

To assess the effect of unmeasured confounding by maternal education, we created a dichotomous variable (U) that represent maternal education (some secondary or lower vs. university degree or higher) and we guessed its value for each child, based on their exposure and outcome status [9,10]. We modeled the prevalence of the unmeasured confounding according to a beta distribution for each exposure-outcome combination. We assumed the prevalence of U to range between 0.45-0.85 (mode=0.65) in children of mother with maternal diabetes who have CP, 0.30-0.70 (mode=0.50) in children of mothers with no maternal diabetes who have CP, 0.40-0.80 (mode=0.60) in children of mothers with maternal diabetes who do not have CP, and 0.25-0.65 (mode=0.45) in children of mothers with no maternal diabetes who do not have CP.

We then conducted a Bernoulli trial to determine if each subject has the dichotomous confounder, based on the assigned probability according to their exposure and outcome status. We then estimated the effect of PGDM on CP, adjusted for measured confounders and the new confounder using the Cox proportional hazards models. The entire process was then repeated 1,500 to create a distribution of bias-adjusted estimates and effect estimates with 95% limits corrected for systematic and random errors were calculated as mentioned above. [7]

Mediation Analysis

Controlled direct effects (CDE) were estimated using marginal structural models, which handle potential confounding by weighting rather than adjustment in the outcome regression models,

allowing for estimating CDE in the presence of mediator-outcome confounders that are potentially affected by the exposure. [11-13]

Potential exposure-outcome (C_1 in eFigure2) and mediator-outcome (C_2) confounders were accounted for using stabilized inverse-probability weights of the form $W=w_i^A*w_i^M$, where

$w_i^A=(P(A=a_i))/(P(A=a_i|C_1=c_{1i}))$

$w_i^M=(P(M=m_i|A=a_i))/(P(M=m_i|A=a_i,C_1=c_{1i},C_2=c_{2i}))$

The weight w_i^A accounts for measured confounding of the relation between PGDM and CP (C_1), and the weight w_i^M accounts for measured confounding of the relation between the mediator and the outcomes (C_2). [11,12]

The denominator of w_i^A is the probability of the PGDM status observed in each individual, conditional on the set of confounders C_1. The denominator of w_i^M is the probability of having the value of the mediator (LGA) the individual in fact had, conditional on PGDM, and confounders C_1 & C_2. Both w_i^A and w_i^M weights were calculated based on probabilities estimated from logistic regression models. We stabilized the weights by including probabilities in the numerator to produce more efficient estimation. Predicted probabilities for the numerators and denominators were assigned based on the actual level PGDM or mediator each individual had and were divided to obtain stabilized weights. [11,12] The distribution of W, w_i^A & w_i^M. is presented in eTable 8.

We then fitted a weighted cox proportional regression model in the form of:

$$ln[h(t)/ h_0(t)] = \beta_1 * A_i + \beta_2 * M_i + \beta_3*A_i*M_i$$

, where $h(t)$ is the expected hazard at time t, $h_0(t)$ is the baseline hazard (the hazard when all of the independent variables are equal to zero), A_i is the exposure (PGDM), M_i is the mediator (LGA), and A_i*M_i is a cross-product term between the exposure and mediator. The cross-

product term was statistically non-significant (*P*-value=0.38) and hence was omitted from the model. The coefficient β_1 in the weighted model gives the controlled direct effect of PGDM not through LGA provided that (i) the measured confounders C_1 suffice to control for confounding between PGDM and CP, (ii) the measured confounders C_1 & C_2 suffice to control for confounding between LGA and CP, and (iii) the probability in the denominator of the weights is nonzero (probability of exposure is neither zero nor 1 for each combination of confounders; the positivity assumption). [11,12] It should be noted that because the outcome is rare (prevalence of 0.2%), these hazard ratios approximate the risk ratios.

Bias Analyses for Controlled Direct Effect

To test the robustness of our CDE estimate to the presence of unmeasured mediator-outcome confounders (e.g., infections or genetic factors), we used simple bias formulas under a range of potential bias conditions. [14-16] We used the simple bias formulas for CDE on the ratio scale:

$$\text{Bias } (CDE^{RR}_{a,a*|c}\ (m)) = \frac{1+(\gamma-1)P(U==1|a,m,c)}{1+(\gamma-1)P(U==1|a*,m,c)}$$

where *a* is the binary exposure (PGDM) with 2 levels (a and a*), *m* is a binary mediator (LGA), *Y* is a binary outcome (CP), *c* is a set of measured covariates, and *U* is a binary unmeasured confounder in the mediator-outcome association. γ represent the effect estimate of the association between U and Y and equals to $\gamma = \frac{P(Y|a,m,c,U=1)}{P(Y|a,m,c,U=0)}$, and was assumed to be constant across strata of *a*. [14]

We used this formula to test the robustness of our CDE of PGDM that assumes a hypothetical intervention that would set all children to be born appropriate for gestational age (AGA (LGA fixed at 0)). Because of limited information on the prevalence of these mediator-outcome confounders by exposure status and their effect on CP in the literature, we performed the sensitivity analyses for CDE under multiple potential bias conditions. We allowed the prevalence of a binary unmeasured confounder to vary between 1%-5% in those exposed to PGDM and between 0.5%-3% in those unexposed and the risk ratio of CP associated with the unmeasured

mediator-outcome confounder to vary between 1.5-6. [17-20] We then calculated the bias-adjusted CDE of PGDM under different combinations of these bias parameters.

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eTable 1. Description of different datasets at ICES and the relevant study variables

DATASET	Description	Relevant study variables
MOMBABY	Records of delivering mothers and newborns in all hospital births in Ontario (ON) since 2002	• Birth characteristics (birth weight, gestational age at birth) • Child characteristics (birth plurality, infant's sex) • Maternal characteristics (age and parity)
CIHI-DAD (The Canadian Institute for Health Information Discharge Abstract Database)	Administrative, clinical (diagnoses and procedures), and demographic information of all hospital admissions	• Inpatient diagnosis of cerebral palsy • Inpatient diagnosis of congenital malformation • Inpatient diagnosis of traumatic brain injury • Inpatient diagnosis of maternal gestational diabetes • Inpatient diagnosis of maternal gestational hypertensive disorders
OHIP (The Ontario Health Insurance Plan)	Outpatient physician service information	• Outpatient diagnoses of cerebral palsy • Outpatient diagnosis of congenital malformation • Maternal use of prenatal care services • Outpatient diagnosis of maternal gestational diabetes • Outpatient diagnosis of maternal gestational hypertensive disorders
ODD (Ontario Diabetes Database)	An administrative registry of Ontario residents diagnosed with non-gestational diabetes since 1991.	• Maternal pre-gestational diabetes
HYPER (Ontario Hypertension database)	An annually-updated cohort of all patients in Ontario with hypertension.	• Pre-pregnancy hypertension
ON-Marg (Ontario Marginalization Index)	Marginalization index for geographic locations in ON	• The four ON-Marg indices: material deprivation, dependency, ethnic diversity, and residential instability
Census-data	Links postal code of the mothers to a range of socioeconomic indicators by geographic region.	• Home location (urban, rural) • Neighborhood income

ODB (Ontario Drug Benefit Claims)	Prescription medication claims for those covered under the provincial drug program	• Eligibility to receive ODB benefits as a proxy for receiving social assistance

eTable 2. Diagnostic codes used to define study variables

Variable	ICD-10-CA (CIHI-DAD)	OHIP code	Period of assessment
Cerebral palsy	G80	343	From birth to death or end of follow-up
Congenital malformations			
Congenital malformations of the nervous system	Q00, Q01, Q02, Q03, Q04, Q05, Q06, Q07	740, 741, 742	From birth to age 6 years
Congenital malformations of eye, ear, face and neck	Q10, Q11, Q12, Q13, Q14, Q15, Q16, Q17, Q18	743-744	From birth to age 6 years
Congenital malformations of the circulatory system	Q20, Q21, Q22, Q23, Q24, Q25, Q26, Q27, Q28	745, 746, 747	From birth to age 6 years
Congenital malformations of the respiratory system	Q30, Q31, Q32, Q33, Q34	748	From birth to age 6 years
Cleft lip and cleft palate	Q35, Q36, Q37	749	From birth to age 6 years
Other congenital malformations of the digestive system	Q38, Q39, Q40, Q41, Q42, Q43, Q44, Q45	750-751	From birth to age 6 years
Congenital malformations of genital organs	Q50, Q51, Q52, Q53, Q54, Q55, Q56	752	From birth to age 6 years
Congenital malformations of the urinary system	Q60, Q61, Q62, Q63, Q64	753	From birth to age 6 years
Congenital malformations and deformations of the musculoskeletal system	Q65, Q66, Q67, Q68, Q69, Q70, Q71, Q72, Q73, Q74, Q75, Q76, Q77, Q78, Q79	754, 755, 756	From birth to age 6 years

Other congenital malformations	Q80, Q81, Q82, Q83, Q84, Q85, Q86, Q87, Q89	757, 759	From birth to age 6 years
Chromosomal abnormalities, not elsewhere classified	Q90, Q91, Q92, Q93, Q95, Q96, Q97, Q98, Q99	758	From birth to age 6 years
Gestational diabetes [a]	E10, E11, E12, E13, E14, O24	250	294 days before the index delivery date
Gestational hypertensive disorders [b]	O10, O11, O13, O14, O15, O16	642	294 days before the index delivery date

Notes

[a] Gestational diabetes was defined based on the following criteria: a) the mother is not in the Ontario Diabetes Databases before the index pregnancy, and b) either a single inpatient diagnosis (ICD-10-CA: E10-E14, O24) or 2 or more outpatient diagnosis (codes 250, not recorded on the same day) during the 294 days before the index delivery date.

[b] Gestational hypertensive disorder was defined based on the following criteria: a) the mother is not in the Ontario Hypertension Databases before the index pregnancy, and b) either inpatient diagnosis or outpatient diagnosis during the 294 days before the index delivery date.

eTable 3. Bias parameters used in the quantitative bias analysis

Variable	Algorithm	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)
Maternal diabetes [a,b]	One inpatient diagnosis or two outpatient diagnoses within a 2-year period [c,d]	86.1 (82.3, 89.4)	97.1 (96.4, 97.7)
	One inpatient diagnosis or two outpatient diagnoses within a 1-year period [e]	88.4 (87.9, 88.8)	97.8 (97.7, 97.9)
	One inpatient diagnosis or two outpatient diagnoses within a 2-year period [e]	89.3 (88.9, 89.8)	97.6 (97.5, 97.7)
Cerebral palsy [f]	One inpatient diagnosis or one outpatient diagnosis between 2–15 years of age [g]	65.5 (59.8, 70.8)	99.9 (99.9, 99.9)

[a] Minimum specificity compatible with the observed data was 98.1 for PGDM and 96.8 for GDM

[b] ICD-10 codes: E10, E11, E12, E13, E14; ICD-9 codes: 250

[c] The Ontario Diabetes Database (ODD) is using this algorithm for pre-gestational diabetes

[d] Source: Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes care.* 2002;25(3):512-516.

[e] Source: Lipscombe LL, Hwee J, Webster L, Shah BR, Booth GL, Tu K. Identifying diabetes cases from administrative data: a population-based validation study. *BMC health services research.* 2018;18(1):1-8.

[f] ICD-10 codes: G80; ICD-9 codes: 343

[g] Source: Oskoui M, Ng P, Dorais M, et al. Accuracy of administrative claims data for cerebral palsy diagnosis: a retrospective cohort study. *CMAJ open.* 2017;5(3):E570.

eTable 4. Controlled direct effect (CDE) of pre-gestational diabetes (PGDM) on the risk of cerebral palsy (CP) in offspring with large for gestational age (LGA) as the mediator (set at appropriate for gestational age (AGA, 10th-90th percentiles)) corrected for residual confounding by an unmeasured confounder U

Prevalence of binary unmeasured confounder (e.g., infection or genetic factors)		Risk ratios of the association between U and CP		
Children with AGA born to women with PGDM (%)	Children with AGA born to women with no PGDM (%)	1.5	3	6
1	0.5	1.81	1.79	1.77
1	1	1.81	1.81	1.81
1	2	1.82	1.85	1.90
1	3	1.83	1.88	1.98
3	0.5	1.79	1.72	1.61
3	1	1.79	1.74	1.65
3	2	1.80	1.78	1.73
3	3	1.81	1.81	1.81
5	0.5	1.77	1.66	1.48
5	1	1.77	1.68	1.52
5	2	1.78	1.71	1.59
5	3	1.79	1.74	1.67

Notes
The naïve adjusted estimate of the CDE of PGDM was 1.81, adjusted for birth year, infant's sex, maternal sociodemographic characteristics (age, parity, and socioeconomic indicators), pre-gestational hypertension, gestational hypertensive disorders, inadequate prenatal care, and the presence of congenital malformations in the child.

eTable 5. Poisson regression-based rate ratios for the associations between maternal pre-gestational and gestational diabetes and cerebral palsy in offspring.

	Crude	**Model 1** [a] (birth year and infant's sex)	**Model 2** [b] (birth year, infant's sex, and sociodemographic factors)	**Model 3** [c] (birth year, infant's sex, and sociodemographic and pre-existing factors)
PGDM [d]				
No	Ref.	Ref.	Ref.	Ref.
Yes	2.05 (1.77, 2.38)	1.99 (1.72, 2.31)	1.90 (1.63, 2.21)	1.86 (1.60, 2.16)
GDM [e]				
No	Ref.	Ref.	Ref.	Ref.
Yes	0.96 (0.82, 1.12)	0.92 (0.79, 1.07)	0.92 (0.79, 1.08)	0.91 (0.77, 1.06)

Notes:

[a] Model 1 included birth year and infant's sex. Birth year was modeled using restricted cubic splines with 3 knots at 2003, 2010, 2016 years.

[b] model 2 included all covariates in model 1 plus maternal sociodemographic characteristics (age, parity, and socioeconomic indicators).

[c] Model 3 included all covariates in model 1 and 2 plus pre-gestational hypertension for PGDM or pre-gestational hypertension, gestational hypertension, and delayed onset of prenatal care for GDM.

[d] PGDM: Pre-gestational diabetes mellitus

[e] GDM: Gestational diabetes mellitus

eTable 6. Log-binomial regression-based risk ratios for the associations between maternal pre-gestational and gestational diabetes and cerebral palsy in offspring.

	Crude	**Model 1** [a] (birth year and infant's sex)	**Model 2** [b] (birth year, infant's sex, and sociodemographic factors)	**Model 3** [c] (birth year, infant's sex, and sociodemographic and pre-existing factors)
PGDM [d]				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.91 (1.64, 2.21)	1.99 (1.71, 2.31)	1.90 (1.63, 2.20)	1.86 (1.60, 2.16)
GDM [e]				
No	Ref.	Ref.	Ref.	Ref.
Yes	0.84 (0.72, 0.99)	0.92 (0.78, 1.07)	0.92 (0.79, 1.08)	0.91 (0.77, 1.06)

Notes:

[a] Model 1 included birth year and infant's sex. Birth year was modeled using restricted cubic splines with 3 knots at 2003, 2010, 2016 years.

[b] model 2 included all covariates in model 1 plus maternal sociodemographic characteristics (age, parity, and socioeconomic indicators).

[c] Model 3 included all covariates in model 1 and 2 plus pre-gestational hypertension for PGDM or pre-gestational hypertension, gestational hypertension, and delayed onset of prenatal care for GDM.

[d] PGDM: Pre-gestational diabetes mellitus

[e] GDM: Gestational diabetes mellitus

eTable 7. Associations between maternal pre-gestational diabetes and cerebral palsy in offspring, according to the alternative categorization of duration of diabetes.

	Crude	**Model 1** [a] (birth year and infant's sex)	**Model 2** [b] (birth year, infant's sex, and sociodemographic factors)	**Model 3** [c] (birth year, infant's sex, and sociodemographic and pre-existing factors)
PGDM-duration [d]				
No PGDM (n=2,070,473)	Ref.	Ref.	Ref.	Ref.
<1 years (n=4,911)	1.61 (1.02, 2.52)	1.63 (1.04, 2.56)	1.62 (1.03, 2.55)	1.58 (1.00, 2.48)
1-2 years (n=11,422)	1.55 (1.14, 2.09)	1.55 (1.15, 2.09)	1.48 (1.10, 2.01)	1.44 (1.06, 1.94)
3-5 years (n=9,363)	2.26 (1.72, 2.98)	2.29 (1.74, 3.00)	2.19 (1.67, 2.88)	2.13 (1.62, 2.80)
6-10 years (n=8,304)	1.97 (1.42, 2.72)	1.96 (1.43, 2.69)	1.84 (1.34, 2.52)	1.81 (1.32, 2.49)
>10 years (n=5,704)	2.62 (1.85, 3.70)	2.69 (1.89, 3.83)	2.47 (1.74, 3.51)	2.49 (1.76, 3.54)

Notes:

[a] Model 1 included birth year and infant's sex. Birth year was modeled using restricted cubic splines with 3 knots at 2003, 2010, 2016 years.

[b] model 2 included all covariates in model 1 plus maternal sociodemographic characteristics (age, parity, and socioeconomic indicators).

[c] Model 3 included all covariates in model 1 and 2 plus pre-gestational hypertension for PGDM or pre-gestational hypertension, gestational hypertension, and delayed onset of prenatal care for GDM.

[d] PGDM: Pre-gestational diabetes mellitus

eTable 8. Associations between maternal gestational diabetes diagnosed at or before 28 weeks of gestation (n=17,014) and cerebral palsy in offspring.

	Crude	**Model 1** [a] (birth year and infant's sex)	**Model 2** [b] (birth year, infant's sex, and sociodemographic factors)	**Model 3** [c] (birth year, infant's sex, and sociodemographic and pre-existing factors)
GDM [d,e]				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.10 (0.81, 1.50)	1.12 (0.82, 1.54)	1.13 (0.82, 1.54)	1.10 (0.80, 1.50)

Notes:

[a] Model 1 included birth year and infant's sex. Birth year was modeled using restricted cubic splines with 3 knots at 2003, 2010, 2016 years.

[b] model 2 included all covariates in model 1 plus maternal sociodemographic characteristics (age, parity, and socioeconomic indicators).

[c] Model 3 included all covariates in model 1 and 2 plus pre-gestational hypertension for PGDM or pre-gestational hypertension, gestational hypertension, and delayed onset of prenatal care for GDM.

[d] GDM: Gestational diabetes mellitus

[e] Women with GDM>28 weeks (n=64,311) were excluded from the analysis

eTable 9. Distribution of weights W, w_i^A & w_i^M used to calculate controlled direct effects using marginal structural models

Model 1 [a]					Model 2 [e]				
Weight	**Mean (SD)**	**Min, Max**	**1%, 99%**	**IQR (25%, 75%)**	**Weight**	**Mean (SD)**	**Min, Max**	**1%, 99%**	**IQR (25%, 75%)**
w_i^A [c]	1.00 (0.02)	0.84, 1.29	0.96, 1.00	1.00, 1.00	W [b]	1.00 (0.09)	0.09, 12.76	0.86, 1.10	0.99, 1.00
w_i^M [d]	1.00 (0.02)	0.90, 1.10	0.91, 1.08	0.99, 1.01	w_i^A [c]	1.00 (0.11)	0.31, 2.82	0.67, 1.45	0.97, 1.03
W [e]	1.00 (0.03)	0.82, 1.34	0.90, 1.09	1.00, 1.00	w_i^M [d]	1.00 (0.16)	0.05, 13.88	0.61, 1.57	0.97, 1.03
Model 3 [f]					**Model 4 [g]**				
Weight	**Mean (SD)**	**Min, Max**	**1%, 99%**	**IQR (25%, 75%)**	**Weight**	**Mean (SD)**	**Min, Max**	**1%, 99%**	**IQR (25%, 75%)**
w_i^A [c]	1.00 (0.11)	0.06, 12.50	0.87, 1.10	0.99, 1.00	W [b]	1.00 (0.11)	0.06, 12.50	0.87, 1.10	0.99, 1.00
w_i^M [d]	1.00 (0.11)	0.29, 2.84	0.67, 1.45	0.97, 1.03	w_i^A [c]	1.00 (0.11)	0.27, 2.87	0.67, 1.45	0.97, 1.03
W [e]	1.00 (0.16)	0.05, 13.68	0.60, 1.57	0.97, 1.03	w_i^M [d]	1.00 (0.16)	0.05, 13.10	0.60, 1.57	0.97, 1.03

Notes:

[a] Model 1 included birth year and infant's sex. Birth year was modeled using restricted cubic splines with 3 knots at 2003, 2010, 2016 years.

[b] model 2 included all covariates in model 1 plus maternal sociodemographic characteristics (age, parity, and socioeconomic indicators).

[c] The weight w_i^A accounts for measured confounding of the relation between maternal pre-gestational diabetes and cerebral palsy

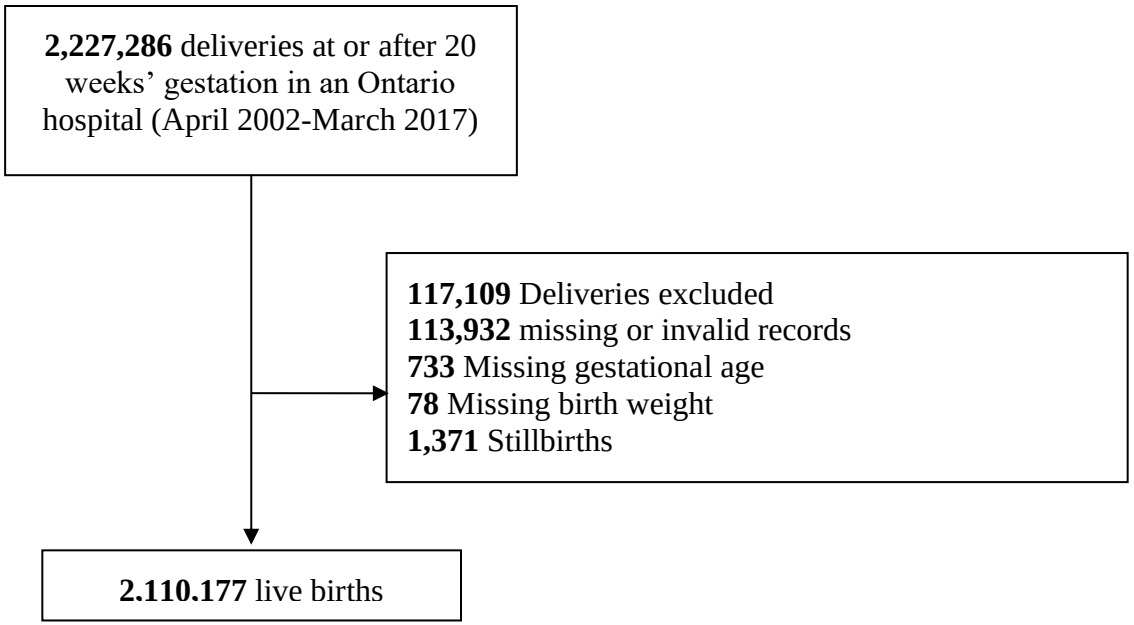
[d] The weight w_i^M accounts for measured confounding of the relation between the mediators and the outcomes

[e] The weight W was calculated as $w_i^A \times w_i^M$

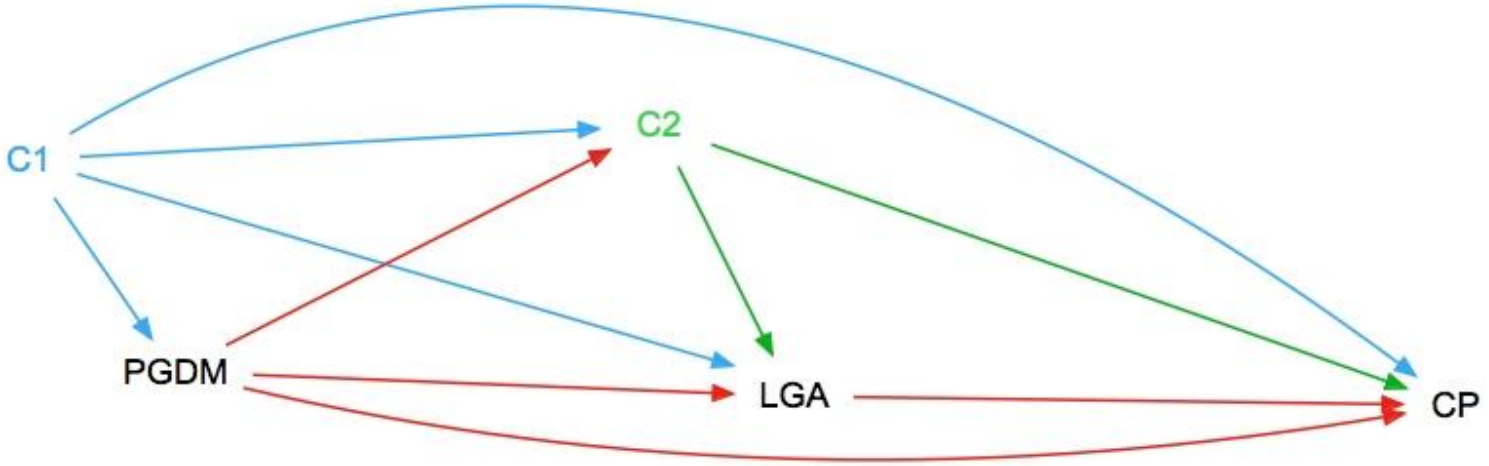
[f] Model 3 included all covariates in model 1 and 2 plus pre-gestational hypertension

[g] Model 4 Model 4 included all covariates in model 1, 2, and 3 plus gestational hypertensive disorders, inadequate prenatal care, and the presence of congenital malformations in the child.

eFigure 1. Flowchart illustrating the formation of the study cohorts



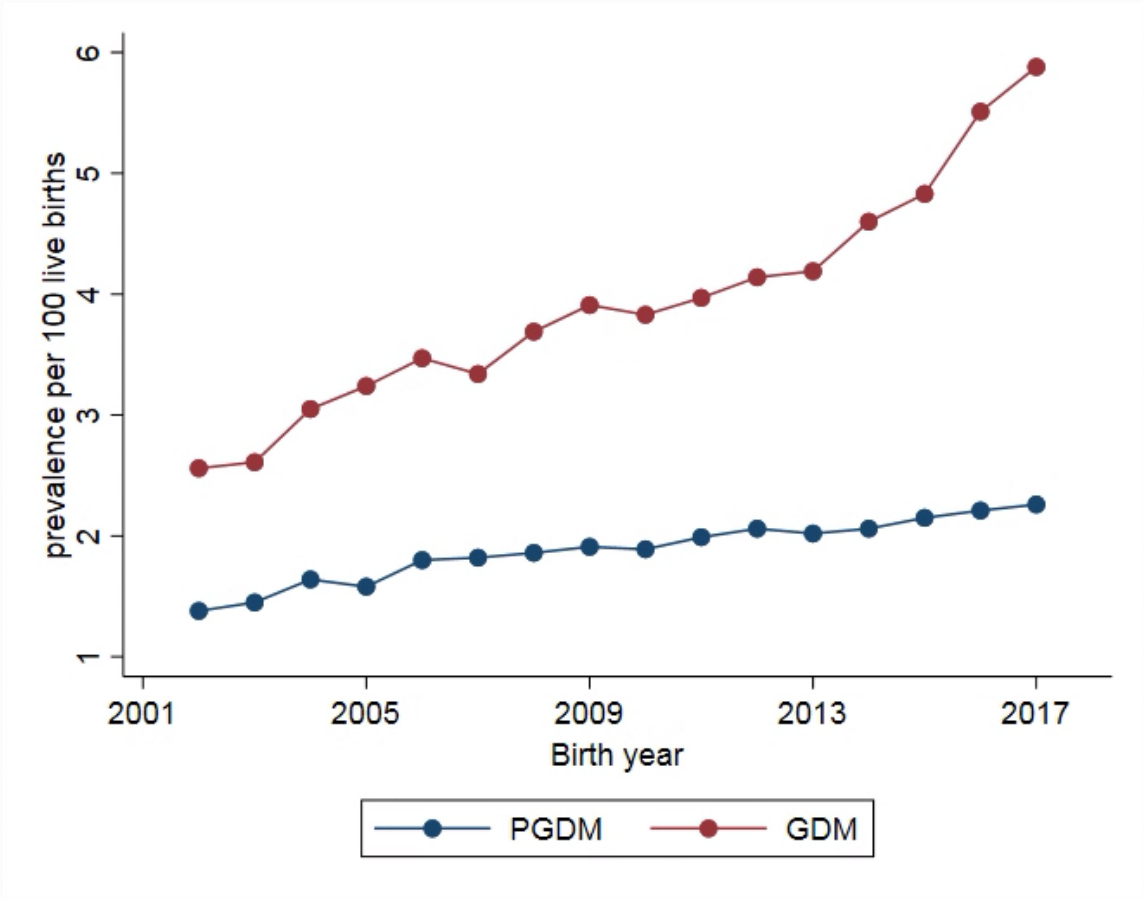
eFigure 2. Illustration of the relationship between exposure, outcome, mediators, and potential confounders.



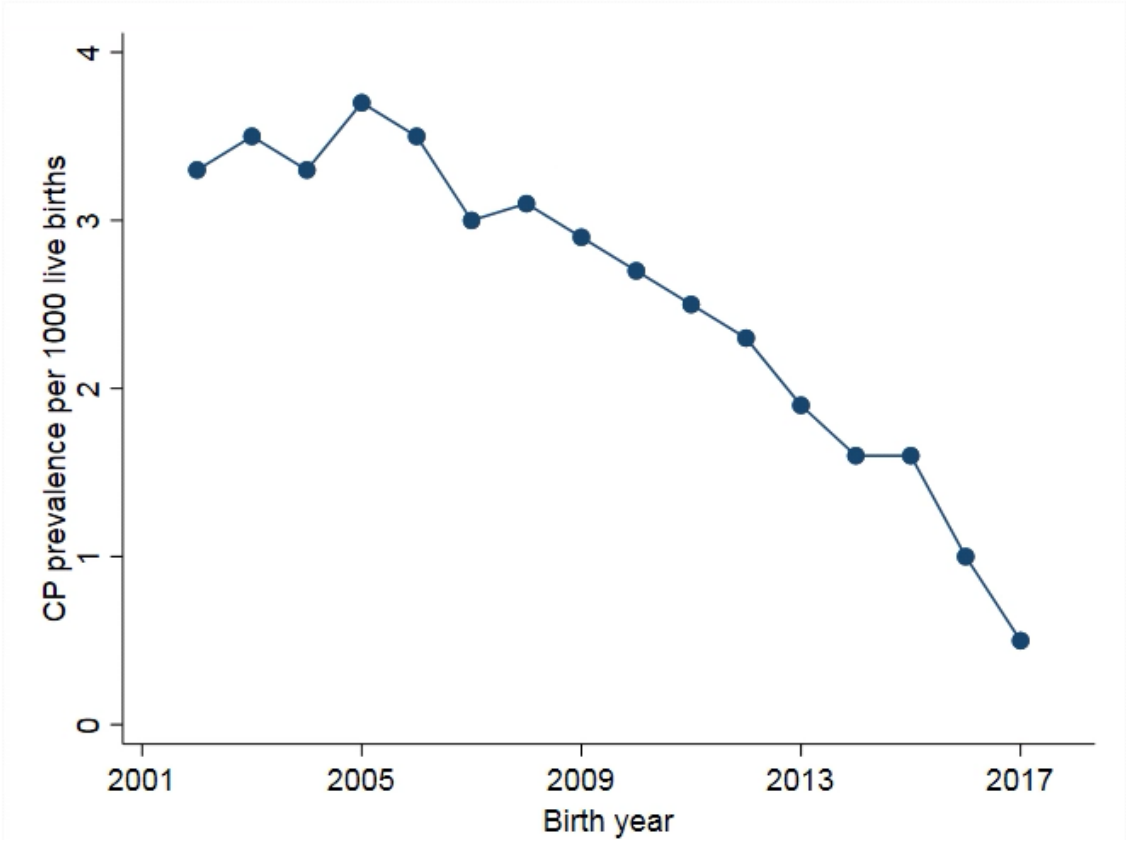
Notes

- PGDM: Pre-gestational diabetes mellitus
- LGA: Large for gestational age
- CP: Cerebral Palsy
- C1 represents measured exposure-outcome confounders and includes birth year, child's sex, maternal age, parity, socioeconomic status, and pre-pregnancy hypertension
- C2 represents measured mediator-outcome confounders and includes gestational hypertensive disorders, adequacy of prenatal care, and the presence of congenital malformations in the child
- Some variables in C2 may not be a consequence of exposure-outcome confounders (C1) (e.g., adequacy of prenatal care and child's sex)

eFigure 3. Crude prevalence of maternal pre-gestational (PGDM) and gestational diabetes (GDM) by year of birth.



eFigure 4. Crude prevalence of cerebral palsy (CP) by year of birth.



Chapter 6. Manuscript 3-In-Utero Exposure to Maternal Unintentional Injury and the Risk of Cerebral Palsy: A Population-based Retrospective Cohort Study.

6.1. Preface

In Chapter 5, I showed the importance of the intrauterine environment in the etiology of CP by documenting an increased risk of CP in children exposed to maternal PGDM. In this chapter, I focused on another maternal exposure—unintentional injury—that commonly affects pregnant women but its long-term effect on children has received little attention in the literature. While several reports have documented the harmful effects of maternal injuries on short-term child outcomes (e.g., preterm birth, early neonatal respiratory distress), there is little published research on its effects on the child's neurodevelopmental outcomes, including CP. In this manuscript, my goal was to estimate the effect of in-utero exposure to maternal unintentional injury on the risk of CP. I also assessed the effect of the severity of injury by examining the role of different characteristics of the injury, such as frequency of injury, hospitalization required for the injury, or giving birth shortly after. The resulting manuscript, entitled "In-Utero Exposure to Maternal Unintentional Injury and the Risk of Cerebral Palsy: A Population-based Retrospective Cohort Study" is being prepared for submission to *JAMA*.

6.2. Manuscript 3

In-Utero Exposure to Maternal Injury and the Risk of Cerebral Palsy: A Retrospective Longitudinal Cohort study

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What is already known on this topic

- Maternal unintentional injury during pregnancy has shown negative impacts on the mother and infants.
- The evidence on the long-term effects of maternal unintentional injury on offspring's neurodevelopment is limited.

What this study adds

- This population-based study highlights the role of maternal injury during pregnancy on fetal neurodevelopment by showing an increased risk of cerebral palsy in children exposed *in-utero* to maternal unintentional injury.
- The risk of cerebral palsy was further elevated in children exposed to maternal injuries that resulted in hospitalization and those who delivered shortly after the injury.

ABSTRACT

Objectives: To examine the effect of maternal unintentional injury on cerebral palsy (CP) in offspring.

Design: Retrospective-cohort study of all live births born between 2002–2017 in a publicly-funded health care system setting of Ontario, Canada.

Setting: Population-based study

Participants: All live births (n=2,110,177) born in Ontario hospitals between 2002–2017.

Exposures: Maternal unintentional injury (n = 82,281) ascertained based on inpatient or emergency department diagnoses during pregnancy.

Outcome: All children were followed for a CP diagnosis between birth and the end of follow-up in 2018. CP definition was based on a single inpatient or $\geq$ 2 outpatient diagnoses at least two weeks apart during the follow-up.

Results: A total of 5,317 children were diagnosed with CP during the study period (292 exposed). Children exposed to maternal unintentional injury in-utero had a modest increase in the risk of CP, compared to those unexposed (Hazard ratio (HR) 1.33 (95% confidence interval (CI): 1.18, 150)) after adjusting for maternal sociodemographic and clinical factors). Injuries that resulted in hospitalization and delivery within a week from the injury conferred higher risks of CP (adjusted HR 2.18 (95% CI: 1.29, 3.68) and 3.40 (95% CI: 1.93, 6.00), respectively).

Conclusion: In this Canadian population-based birth cohort study, we found an increased risk of CP after exposure to maternal unintentional injury in-utero, with higher risk with severer injuries. These findings fill an important gap in knowledge about the long-term effect of maternal injury on children's neurodevelopment outcomes. Early monitoring and developmental assessment of children exposed to maternal injury in-utero would be warranted.

BACKGROUND

Injuries affect approximately 6–8% of pregnant women. [1,2] Most injuries are unintentional, with motor vehicle accidents and falls being the two most common (88–92%). [1-3] Injuries are the leading cause of non-obstetrical maternal mortality during pregnancy and are associated with complications in both the mother and the baby. [3-5] Maternal complications after injuries include uterine rupture, preterm delivery, premature rupture of membranes, placental abruption, and caesarean section delivery. [3-5] Maternal injuries are also linked to numerous fetal and neonatal complications, such as fetal hypoxia, fetal asphyxia, and neonatal respiratory distress syndrome. [3,5]

Several mechanisms may lead to brain injury in fetuses exposed in-utero to maternal injuries. [3-6] Maternal injury could cause shearing effects at the uteroplacental interface that may cause acute placental abruption with subsequent preterm birth [78] or may lead to chronic placental insufficiency, resulting in fetal growth restriction and oligohydramnios. [9] Placental abruptions, preterm delivery, and fetal growth restriction have all been linked to increased risk of CP. [6,10,11] Other potential mechanisms include direct injury to the fetus or placenta, fetal respiratory distress, fetal hypoxia resulting from maternal hypotension, and maternal response to acute severe stress. [12-15]

Although maternal and fetal complications have been reported after minor injuries, studies have shown that more severe injuries carry higher risks. [3,16] For example, researchers have found that one in three pregnant women hospitalized for injury would deliver during her hospitalization, and they have worse maternal and fetal outcomes than women who deliver after being discharged. [3,17] Motor vehicle accidents with high force impacts, or improper or lack of use of seat belts are also associated with poorer maternal and fetal outcomes. [9] Exposure to multiple motor vehicle accidents during pregnancy has also been linked to poorer pregnancy outcomes. [18]

Despite the common occurrence of unintentional injury during pregnancy, studies of its long-term effects on offspring's neurodevelopment are scarce. Few case series have reported an increased risk of poor neurodevelopmental outcomes following the in-utero exposure to injury. [19-21] To date, only one population-based study has examined associations between maternal

injuries (motor vehicle accidents) and CP and showed an increase in the risk of CP in children born preterm. [12]

In a large population-based cohort from the general population, therefore, we aimed to examine the effect of unintentional injuries during pregnancy on CP risk in offspring and explore the role of severity of the injury on the risk of CP.

Methods

Study Population

We created a retrospective birth cohort by linking several individual- and area-level administrative datasets at ICES (formerly known as Institute for Clinical Evaluative Sciences) that houses and maintains databases with health and demographic information of all users of the publicly-funded provincial health care system in Ontario, Canada. [22,23] The datasets were linked using unique encoded identifiers and analyzed at ICES. Eligible infant-mother dyads were identified from the Mother-Baby Database (MOMBABY) that deterministically links mother and delivery records with >98% linkage rate (see eTable 1 for details of data sources). We included all births who were born >20 weeks' gestation in Ontario hospitals between 1 April 2002 and 31 March 2017 and followed up until 31 March 2018. We excluded stillbirths, missing or invalid records, and births with missing or invalid birth characteristics (eFigure 1). [24] We received ethics approval from the Institutional Review Board of the Faculty of Medicine and Health Sciences at McGill University.

Exposure

Maternal unintentional injury during pregnancy was classified by any inpatient (from the Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD)) or emergency department (from the National Ambulatory Care Reporting System (NARCS) database) diagnosis of unintentional injury during the index pregnancy, using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision diagnostic codes (ICD-10-CA: V01–X59). [25] Further details are described in eTable 2. We excluded intentional injuries (e.g., suicidal attempts, domestic violence) as their effects may reflect

different processes of high levels of maternal stress, mental health disorders, or other psychosocial factors from that due to unintentional injuries. [26]

The severity of the identified injury was stratified into two categories: injuries treated in the emergency department with no in-hospital admission as the "non-severe" injury, and injuries treated as an inpatient as the "severe" injury. We also classified injuries according to the frequency of exposure to injury (one or ≥2), the timing of delivery relative to the injury (delivered within 7 days or >7 days of injury), and the timing of the injury (the first-, second-, and third-trimester).

Outcome

A diagnosis of cerebral palsy in children between birth and the age of up to 16 years was based on 1) a single inpatient hospitalization diagnosis from CIHI-DAD (ICD-10-CA codes: G80), or 2) two or more outpatient diagnoses, at least two weeks apart (code: 343), on physician billings claims (eTable 2). [12,22]

Covariates

We identified several sociodemographic and clinical factors that are potentially associated with both exposure and outcome based on the literature. [16,27,28] These factors included maternal age (<20, 20–24, 25–29, 30–34, 35–39, or ≥40 years), parity (0, 1, 2, 3, or ≥4 previous live births), maternal eligibility for the provincial drug benefits available for individuals with financial needs due to unemployment or disability [29] as a proxy for individual-level low socioeconomic status, the start of prenatal care (delayed if the first visit >13 weeks' gestation), [30] rural residence, [31] and area-based socioeconomic characteristics (neighborhood income, and the four Ontario marginalization indices, namely residential instability, material deprivation, economic dependency, and ethnic concentration) (details in eMethods). [32] We also included maternal diagnoses of substance (including smoking, alcohol, and drug) use disorder and obesity before or during pregnancy (details in eTable 2). We also included birth year to account for temporal changes in rates of exposure and outcome during the study period.

Data analysis

We estimated crude incidence rates of CP by exposure to maternal unintentional injury and crude and adjusted hazard ratios using Cox proportional hazards models. We followed each child from birth to the time of CP diagnosis, death, or the end of follow-up on March 31, 2018, whichever came first. Adjusted analyses included the a priori determined potential confounders in the following sequence: Model 1 adjusting for birth year; Model 2 adjusting for birth year and maternal sociodemographic characteristics (age, parity, and socioeconomic indicators); and Model 3 adjusting for all covariates in model 2 plus maternal substance use disorder or obesity, and delayed onset of prenatal care. We accounted for non-linear associations between birth year and the outcome, using restricted cubic splines [33,34] with 3 knots at 2003, 2010, 2016 years. We found no evidence of a violation of the proportional hazards assumption (tested graphically and statistically by the scaled Schoenfeld residuals for nonzero slope and the Chi-squared test of proportional hazards assumption) for all variables except for birth year. We, therefore, allowed the baseline hazard to vary by birth year (stratified Cox model) [35] because models with birth year as time-varying covariates did not converge. Clustered variance estimates were used in all models to account for clustering by mother using the clustered sandwich estimator (n=1,021,086 siblings born to 450,929 mothers).

Quantitative Bias Analysis

We conducted probabilistic bias analyses (record-level correction) to examine the robustness of our estimates against potential misclassification and confounding biases due to the administrative data-based observational nature of our study. [36,37] We first assessed impacts of outcome misclassification using sensitivity and specificity values of diagnostic codes of CP obtained from the literature. [38] We modeled the sensitivity and specificity of our CP definition using a beta distribution assuming a near-perfect specificity (~99%) and the sensitivity ranged between 40% and 80% (mode=60%). We then calculated positive and negative predicted values and created a bias-adjusted outcome variable defined according to these predicted probabilities and outcome and exposure status. The association of maternal injury with CP was then re-examined using the new "bias-adjusted" outcome. The entire process was repeated 1,500 times to get a distribution of the bias-adjusted hazard ratio (HR) and estimate confidence limits adjusted for systematic and random errors (further details in eMethods).

We also evaluated the effect of unmeasured confounding by maternal individual-level socioeconomic factors by simulating a dichotomous variable (U) representing maternal education (university graduate or not). We modeled the prevalence of U using a beta distribution assuming the prevalence of U (less than university graduate) to range between 0.48–0.88 (mode=0.68) in the exposed and 0.35–0.75 (mode=0.56) in the unexposed children with CP, and 0.45–0.85 (mode=0.64) in the exposed and 0.30–0.70 (mode=0.51) in the unexposed children without CP, based on the literature. [2,39] We then refitted the adjusted model while adjusting for measured confounders and the simulated confounder U (1,500 simulations). We also corrected for outcome misclassification and unmeasured confounding simultaneously, together with measured confounders, in the fully adjusted model (eMethods).

Secondary Analyses

To examine if the risk of CP varies by injury mechanism, we estimated the associations by injury mechanism: transport-related accidents (V01–V99), falls (W00–W19), accidents related to mechanical forces (W20–W64), and other unintentional injuries (W65–X59). Time-to-event analyses may reflect the age of diagnosis rather than the onset of CP and may be influenced by factors that affect how soon a child is diagnosed with CP. Thus, we re-examined associations between maternal unintentional injury and CP using Poisson regression with follow-up time as the offset variable (rate ratios) and log-binomial regressions (risk ratios).

Children born preterm are at increased risk of CP [10] and have a shorter duration for the in-utero exposure to maternal injury than those born at term; thus, using "anytime-in-pregnancy" definitions may underestimate associations between injury and CP. We thus re-estimated associations for maternal injury separately for preterm and term births to examine whether associations varied by preterm birth status.

RESULTS

Of 2,227,286 identified births, 2,110,177 live births born to 1,277,024 mothers were included in the study (eFigure 1). Of those, 82,281 children were exposed in-utero to maternal unintentional injury. Young mothers, mothers with substance use disorder, recipients of provincial drug

benefits, and those living in rural areas or neighborhoods with low ethnic diversity, high material deprivation, or high economic dependency were more likely to experience unintentional injury during pregnancy (Table 6.1). The most common mechanisms of injury were falls, transport-related accidents, and accidents related to mechanical forces such as being struck by an object or another person (eTable 3). As shown in Table 2, ~8% of exposed women experienced more than one injury during pregnancy, and a minority were hospitalized after the injury (~3%) or delivered the baby within a week of injury (1.6%). The prevalence of live births exposed to unintentional injury has remained stable during the study period at approximately 4%, except for 2002 births (~2.5%) (eFigure 2). We only used NACRS and CIHI-DAD data from April 2002 onward; thus, the ascertainment of maternal injury was incomplete for those born in 2002.

The median follow-up was 8 years (interquartile range, 4–12 years). During this time, 5,317 children were diagnosed with CP; 292 of them were exposed to maternal unintentional injury (Table 6.1). The incidence rate was 2.99 (95% confidence interval (CI): 2.91, 3.07) per 10,000 child-year. Figure 6.1 illustrates the Kaplan-Meier plot of crude cumulative incidence of CP by exposure status. Average annual CP incidence rates were 4.36 (95% CI: 3.89, 4.89) and 2.93 (95% CI: 2.85, 3.02) per 10,000 child-year in the exposed and the unexposed to maternal injuries, respectively.

Table 6.2 shows crude and adjusted associations of maternal unintentional injuries with CP. Children exposed to maternal unintentional injury in-utero had a higher risk of CP (Hazard ratio (HR) 1.46 (95% CI: 1.30, 1.65)); adjustment for sociodemographic factors and clinically documented maternal substance use disorder and obesity attenuated these associations (adjusted HR 1.33 (95% CI: 1.18, 1.50)). Higher severity of injury may pose a higher risk of CP. For example, the adjusted HR for children exposed in-utero to injuries that resulted in hospitalization was 2.18 ((95% CI: 1.29, 3.68), *p*-value for the Wald test of equality of coefficients =0.06); the corresponding figure for children exposed to more than one injury was 1.77 ((95% CI: 1.26, 2.48), *p*-value for the Wald test=0.09). A higher risk of CP was also observed when delivery occurred shortly after the injury (adjusted HR 3.40 (95% CI: 1.93, 6.00), *p*-value=0.00). Injuries that occurred earlier in pregnancy tended to show higher risks for CP than those exposed in the

3rd-trimester, although the coefficients across timing of injury categories were not statistically heterogenous (*p*-value=0.16).

Results of quantitative bias analyses are presented in Table 6.3. Associations between maternal unintentional injury and CP slightly strengthened when we adjusted for the potential outcome misclassification (bias-adjusted HR 1.54 (95% simulated interval: 1.35, 1.76), accounting for systematic and random errors). Accounting for unmeasured confounding by maternal education did not influence the effect estimate (1.30 (1.16, 1.47)), while adjusted estimates corrected simultaneously for outcome misclassification and unmeasured confounding were slightly stronger (1.40 (1.23, 1.61)) than naïve estimates.

In our analysis stratified by the mechanism of the injury, the CP risk was increased for each type of injury, most notably transport-related injuries (eTable 4). Crude and adjusted effect estimates from Poisson regression (rate ratios) and log-binomial regression (risk ratios) were similar to HRs presented in the main results (eTables 5 and 6). When we separately analyzed preterm and term births, associations between maternal unintentional injury and CP in those born preterm were similar to main results, while estimates for term-born children were weaker, particularly after adjustment for potential confounders (eTable 7). Associations for 1st-trimester exposures were also comparable in children born preterm, whereas the association with 3rd-trimester injury was more pronounced in children born at term or later.

DISCUSSION

In this retrospective population-based study of about 2 million births, we found a modest increase in the risk of CP in children exposed in-utero to maternal unintentional injury. The risk of CP was higher among children exposed to maternal injuries that required hospital admission or resulted in the delivery shortly after the injury, or those exposed to injuries multiple times.

Limited evidence exists on long-term effects of maternal unintentional injuries during pregnancy on offspring. Consistent with our findings, a few case reports have described poor neurodevelopment in children exposed in-utero to injury. [19-21] Hayes and colleagues described ten cases of CP following maternal trauma in pregnancy. All cases had uneventful deliveries at

term with no sign of perinatal asphyxia but showed postnatal neuroimaging results consistent with prenatal brain damage. [21] Another report based on 529 CP cases from the Australian CP Register found a 1.4 times increase in CP risk in children of mothers exposed to injury requiring hospitalization, relative to those unexposed to injury. [40] However, their study was based on only two CP cases with maternal hospitalization due to injury. A Canadian population-based study has also found a small positive association between maternal motor vehicle accidents during pregnancy and CP, but only among preterm-born children. [12] This study was also based on a small number of CP cases (18 children with CP in the exposed) and only considered injuries related to motor vehicle crashes. [12]

Although we did not have direct information on injury severity, we have considered different characteristics related to the injury that may be linked to severity. Delivery within seven days of injury, in particular, posed a high risk for CP, consistent with others who have observed worse maternal and fetal outcomes in women delivered during the same hospitalizations for injury. [3,17,25] We also found that injuries that resulted in hospitalization tended to show stronger positive effects on CP risk than injuries treated in the emergency department. In the present study, approximately 8% of exposed women experienced more than one injury during pregnancy, and they showed slightly higher risks of CP in offspring than those exposed once. These results were consistent with Vladutiu et al., who found higher rates of adverse birth outcomes (e.g., preterm birth and placental abruption) in those involved in multiple motor vehicle crashes during pregnancy than those exposed to a single crash. [18]

Our analyses stratified by preterm birth status showed that associations among preterm-born children were almost identical to the main results while effect estimates in term-born children were attenuated. These results may suggest that preterm birth (either spontaneous or iatrogenic as a result of placental abruption) and its sequelae probably play important roles in explaining the increased risk of CP after exposure to injury. We observed higher rates of preterm birth in women exposed to injury than unexposed (9.7% vs 7.8%); preterm birth rates were especially high in women exposed in the 1st-trimester (12.9%), those admitted to hospitals (12.7%), those exposed to injury more than once (12.5%), and those delivered within a week of injury (12.9%).

Nevertheless, the stratified analysis results should be interpreted with caution as they are susceptible to collider-stratification bias, a phenomenon similar to the birth weight paradox. [41,42]

Trimester-specific associations showed slightly higher risks of CP in children of women injured in 1st and 2nd-trimesters, compared to 3rd-trimester. However, children born <28 weeks have no opportunity to be classified as 3rd-trimester-exposed; thus, 3rd-trimester associations may be underestimated as extreme prematurity (<28 weeks) is one of the strongest risk factors of CP. [10] Analyses restricted to term-born children showed that maternal unintentional injury increased the risk of CP in pregnancies that continue to term, although estimates were imprecise owing to the small number of exposed women and smaller in magnitude.

As reported by others, falls and transport-related accidents (mostly motor vehicle accidents) were the two most common mechanisms of injury during pregnancy. [1-3] Although the relationship is unclear for falls, transport-related accidents posed an increase in the risk of CP after adjusting for factors commonly related to vehicle accidents (e.g., young maternal age, low socioeconomic status). [16] Motor vehicle accidents are associated with the highest rates of maternal mortality and morbidities, as well as poor fetal outcome. [9,16] It is possible that injuries related to motor vehicle accidents are more severe (~5% of transport-related accidents in our study were hospitalized, compared to 2.7% for any injury) and may result in more damage to the placenta and fetus.

Strengths and Limitations

Our study population consisted of a population-based cohort of almost all live births occurring in Ontario—where a third of the Canadian population resides—over 16-year, reducing the potential selection bias and enhancing generalizability. The large sample also improved statistical precision and allowed for examining associations by more detailed characteristics of the injury. Our results, however, should be interpreted in light of several limitations. Misclassification of exposure and outcome is plausible and more likely to be non-differential. This was consistent with our results of quantitative bias analysis for outcome misclassification. We used injury codes developed by the international framework for injury surveillance by the Centre for Disease Control and Prevention [43] that were extensively used in various populations, including in pregnant women. [12,25,44] Although we did not conduct bias analysis for exposure

misclassification owing to lack of validation studies, we suspect that we captured most injuries in pregnancy that sought medical attention, which would be highly likely among pregnant women because of concerns about maternal and fetal well-being. We had information on neither individual-level maternal socioeconomic factors (e.g., education, income, race, and immigration status) nor other lifestyle factors than clinically diagnosed substance disorders and obesity during pregnancy or in the year before. Residual confounding by these factors is also a potential threat to the validity of our results; however, our quantitative bias analyses for unmeasured confounding with maternal education as an example only slightly attenuated observed associations. CP can only be diagnosed in live births that survive long enough to show the neurological manifestations of brain damage, and children with severe brain injury may die in-utero or shortly after birth. If in-utero or postnatal deaths of severe CP cases occur preferentially in those exposed in-utero to injury than the unexposed, associations between maternal injury and CP would be underestimated. [45] However, stillbirths and infant mortality rates are low in Canada (38.2 and 41.4 per 10 000 births respectively); [46] thus, we expect only a minor impact, if any, on our estimates.

Conclusion

This research is one of the first population-based studies to highlight the role of maternal injury during pregnancy on fetal neurodevelopment by showing an increased risk of cerebral palsy in children exposed to maternal unintentional injury in-utero that was consistently observed across several classifications according to the injury frequency, severity, and mechanism. Future studies that directly measure the severity of injury are needed to elucidate whether the risk of CP is linked to injury severity, as has been shown for other maternal and fetal outcomes. [3,9,17] Current guidelines of management of injury in pregnant patients focus only on monitoring the fetal condition immediately after the injury with little attention on its long-term effects on offspring. [8,47] Our results may indicate the need for monitoring of children exposed to maternal injury in-utero for early detection of adverse neurodevelopmental outcomes and thus for provision of optimal management and needed support. Emerging evidence suggests possible links between maternal injury with other neurodevelopmental outcomes; [8,48] thus, further work is needed to comprehensively evaluate the effects of maternal injuries on other neurodevelopmental disorders than CP.

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Table 6.1. Maternal and child characteristics (n (%)) by exposure to maternal unintentional injury during pregnancy in children born in Ontario, Canada in 2002–2017 (n=2,110,177)

	Exposure to unintentional injury during pregnancy	
Characteristics	**No (n=2,028,896)**	**Yes (n=81,281)**
Maternal age		
<20 years	60,818 (3.00)	5,546 (6.82)
20–24 years	246,627 (12.16)	16,313 (20.07)
25–29 years	562,286 (27.71)	23,284 (28.65)
30–34 years	713,102 (35.15)	23,000 (28.30)
35–39 years	367,699 (18.12)	10,775 (13.26)
≥40 years	78,364 (3.86)	2,363 (2.91)
Parity	907,287 (44.72)	37,600 (46.26)
0	721,911 (35.58)	26,216 (32.25)
1	264,764 (13.05)	11,035 (13.58)
2	80,298 (3.96)	3,758 (4.62)
3	54,636 (2.69)	2,672 (3.29)
≥4		
Neighborhood income quintile	336,246 (16.57)	11,075 (13.63)
Q1 (highest)	419,902 (20.70)	15,324 (18.85)
Q2	413,458 (20.38)	16,162 (19.88)
Q3	403,341 (19.88)	17,317 (21.31)
Q4	448,642 (22.11)	21,049 (25.90)
Q5 (lowest)	7307 (0.36)	354 (0.44)
Missing		
ON-Marg residential instability quintile [a]	402,937 (19.86)	12,472 (15.34)
Q1 (least marginalized)	401,903 (19.81)	15,158 (18.67)
Q2	358,897 (17.69)	15,258 (18.77)
Q3	380,411 (18.75)	17,611 (21.67)
Q4	450,431 (22.20)	18,968 (23.34)
Q5 (most marginalized)	34,317 (1.69)	1,814 (2.23)
Missing		

ON-Marg material deprivation quintile [a]		
Q1 (least marginalized)	488,055 (24.06)	14,637 (18.01)
Q2	368,920 (18.18)	13,395 (16.48)
Q3	360,808 (17.78)	14,467 (17.80)
Q4	351,350 (17.32)	15,684 (19.30)
Q5 (most marginalized)	425,446 (20.97)	21,284 (26.16)
Missing	34,317 (1.69)	1,814 (2.23)
ON-Marg economic dependency quintile [a]		
Q1 (least marginalized)	616,554 (30.39)	20,536 (25.27)
Q2	458,002 (22.57)	16,532 (20.34)
Q3	358,264 (17.66)	15,105 (18.58)
Q4	302,114 (14.89)	114,107 (17.63)
Q5 (most marginalized)	259,645 (12.80)	13,187 (16.22)
Missing	34,317 (1.69)	1,814 (2.23)
ON-Marg ethnic concentration quintile [a]		
Q1 (least marginalized)	248,452 (12.25)	14,132 (17.39)
Q2	288,474 (14.22)	14,427 (17.75)
Q3	333,711 (16.45)	14,925 (18.36)
Q4	440,666 (21.72)	15,999 (19.68)
Q5 (most marginalized)	683,276 (33.68)	19,984 (24.59)
Missing	34,317 (1.69)	1,814 (2.23)
Recipient of Ontario Drug Benefit	1,864,422 (91.89)	
No	164,474 (8.11)	58,371 (83.90)
Yes		11,921 (16.10)
Living in rural area	1,829,459 (90.17)	68,193 (83.10)
No	198,683 (9.79)	13,088 (16.85)
Yes	754 (0.04)	41 (0.05)
Missing		
Smoking, alcohol, or drug use disorder [b]	2,000,762 (98.61)	78,623 (96.73)
No	28,134 (1.39)	2,658 (3.27)
Yes		

Obesity [b]	1,983,282 (97.75)	78,700 (96.82)
No	45,614 (2.25)	2,581 (3.18)
Yes		
Start of prenatal care	1,803,491 (88.89)	73,740 (90.72)
≤ 13 weeks	225,405 (11.11)	7,541 (9.28)
> 13 weeks		
Cerebral palsy		
No	2,023,871 (99.75)	80,989 (99.64)
Yes	5,025 (0.25)	292 (0.36)

Notes

[a] ON-Marg – Ontario Marginalization Index

[b] Maternal substance use disorder and obesity were based on inpatient or outpatient diagnoses before or during pregnancy (up to 660 days before the delivery date)

Table 6.2. Hazard ratios (95% confidence interval) for the associations between maternal unintentional injury during pregnancy and cerebral palsy in offspring

Characteristic	**Crude**	**Model 1** [a] (birth year)	**Model 2** [b] (birth year and sociodemographic factors)	**Model 3** [c] (birth year, sociodemographic, and clinical factors)
Injury				
No (n=2,028,896)	Ref.	Ref.	Ref.	Ref.
Yes (n=81,281)	1.46 (1.30, 1.65)	1.45 (1.29, 1.64)	1.35 (1.19, 1.52)	1.33 (1.18, 1.50)
Treatment of injury				
No injury (n=2,028,896)	Ref.	Ref.	Ref.	Ref.
Emergency department only (n=79,123)	1.43 (1.27, 1.62)	1.42 (1.26, 1.61)	1.32 (1.17, 1.49)	1.31 (1.15, 1.48)
Hospitalization (n=2,158)	2.52 (1.49, 4.26)	2.45 (1.45, 4.14)	2.23 (1.32, 3.78)	2.18 (1.29, 3.68)
Frequency of injury				
No injury (n=2,028,896)	Ref.	Ref.	Ref.	Ref.
One injury (n=74,703)	1.40 (1.24, 1.59)	1.40 (1.23, 1.59)	1.30 (1.15, 1.48)	1.29 (1.14, 1.47)
Two or more (n=6,578)	2.11 (1.51, 2.96)	2.09 (1.48, 2.93)	1.80 (1.28, 2.54)	1.77 (1.26, 2.48)
Timing of delivery relative to injury				
No injury (n=2,028,896)	Ref.	Ref.	Ref.	Ref.
Delivered >7 days after injury (n=79,958)	1.42 (1.26, 1.61)	1.42 (1.25, 1.60)	1.31 (1.16, 1.48)	1.30 (1.15, 1.47)
Delivered ≤7 days after injury **(n=**1,323)	3.67 (2.08, 6.47)	3.67 (2.08, 6.46)	3.43 (1.94, 6.04)	3.40 (1.93, 6.00)
Timing of injury [d]				
No injury (n=2,028,896)	Ref.	Ref.	Ref.	Ref.
First trimester (0–12 weeks) (n=33,481)	1.68 (1.42, 1.99)	1.67 (1.41, 1.98)	1.52 (1.28, 1.80)	1.50 (1.26, 1.78)
Second trimester (13–27 weeks)	1.38 (1.13, 1.68)	1.37 (1.13, 1.67)	1.28 (1.05, 1.56)	1.27 (1.04, 1.55)
(n=29,999)	1.20 (0.91, 1.57)	1.19 (0.91, 1.56)	1.13 (0.86, 1.48)	1.12 (0.86, 1.47)
Third trimester (≥28 weeks) (n=17,801)				

Notes:

[a] Model 1 included birth year. Birth year was modeled using restricted cubic splines with 3 knots at 2003, 2010, 2016 years.

[b] model 2 included birth year maternal sociodemographic characteristics (age, parity, and socioeconomic indicators).

[c] Model 3 included all covariates in model 2 plus clinically documented maternal substance use disorder and obesity

[d] Timing of injury was calculated based on the gestational age at the time of injury. Women exposed to more than one injury were classified according to the gestational age at the *first* injury.

Table 6.3. Hazard ratios (95% simulated interval) for the associations between maternal unintentional injury during pregnancy and cerebral palsy in offspring corrected for outcome misclassification and unmeasured confounding

Crude analyses [a]			
	Naïve crude estimate	**Corrected for outcome misclassification [b]**	
Injury	1.46 (1.30, 1.65)	1.54 (1.35, 1.76)	
Adjusted analyses [c]			
	Naïve adjusted estimate	**Corrected for unmeasured confounding [b]**	**Corrected for outcome misclassification and unmeasured confounding [b]**
Injury	1.33 (1.18, 1.50)	1.30 (1.16, 1.47)	1.40 (1.23, 1.61)

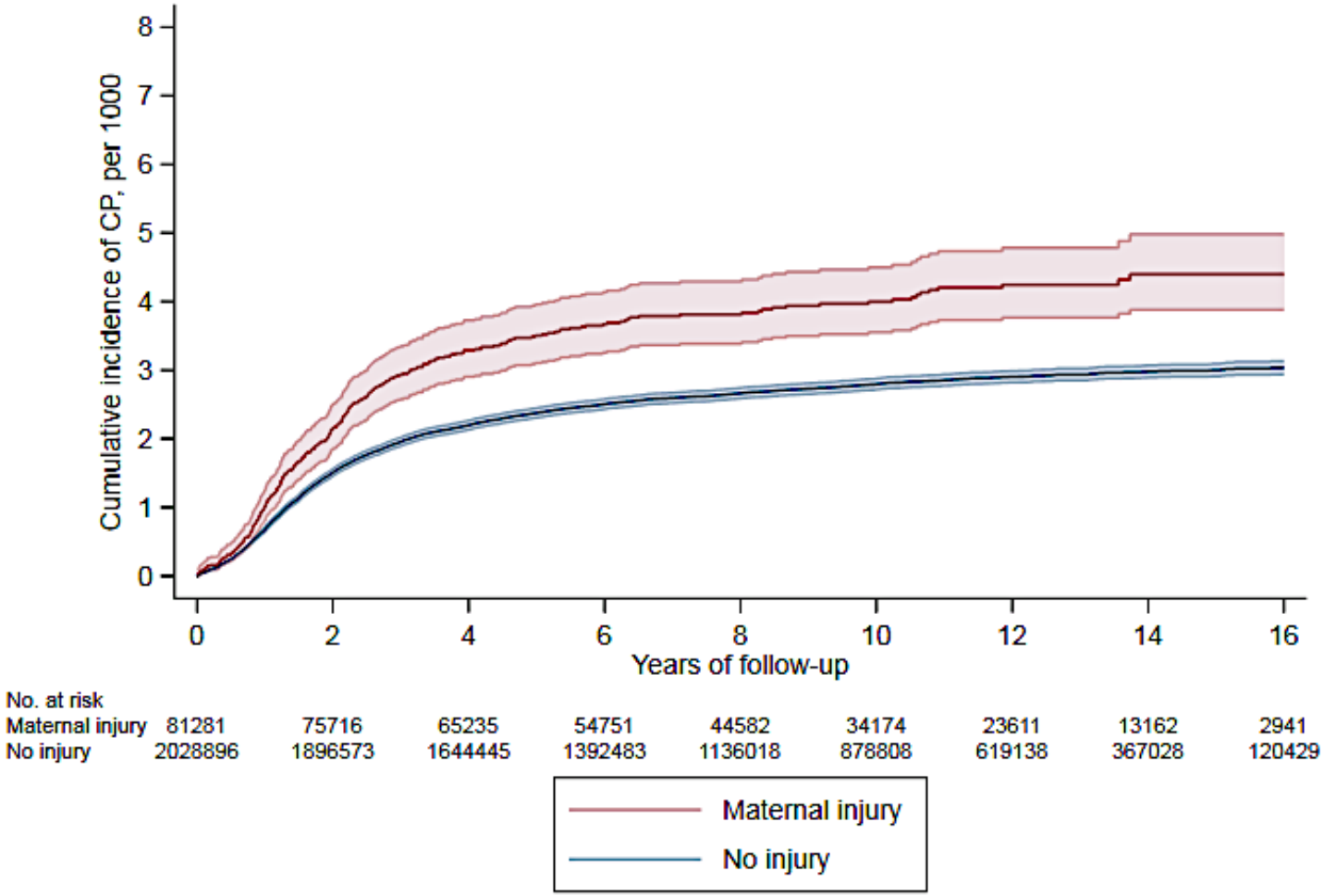
Notes

[a] Crude analyses only included maternal unintentional injury during pregnancy

[b] Adjusted for both systematic and random errors

[c] Adjusted analyses included birth year, birth year, maternal sociodemographic characteristics (age, parity, and socioeconomic indicators), clinically documented substance use disorder and ~~clinically documented~~ obesity

Figure 6.1. Unadjusted cumulative incidence of cerebral palsy by exposure to maternal unintentional injury during pregnancy



6.3. Supplementary Material-Manuscript 3

eMethods

Measures

Socioeconomic Indicators

We defined rural residence according to the Rurality Index of Ontario (RIO), which incorporates measures of population density and travel times to the nearest basic and advanced referral center. [1] We calculated RIO at the Census Subdivision (CSD) level (municipalities) using the version of RIO closest to the year of birth (RIO-2004 for 2002–2006 births and RIO-2008 for 2007–2017 births). Rural residence was defined as having RIO>45. [1]

Census data and maternal residential postal code at delivery were linked to measure area-based socioeconomic status. Data from the census year closest to birth year were used (2001 census for 2002–2003 births and 2006 census for 2004–2017 births). [2] Neighborhood income was used as quintiles from the highest (Q1) to the lowest (Q5) income. We used the four indices of the Ontario Marginalization (ON-Marg) indices, residential instability, material deprivation, economic dependency, and ethnic concentration, that were derived from 42 census questions using principal components analysis. [2] Residential instability measures the area-level concentration of individuals at risk of family and housing instability and includes the following: proportion of the population living alone; proportion of the population who are not youth (age 5–15); average number of persons per dwelling; proportion of dwellings that are apartment buildings; proportion of the population who are single/ divorced/widowed; proportion of dwellings that are not owned,; and proportion of the population who moved during the past 5 years). [2] Material deprivation includes the proportion of the population aged 20+ without a high-school diploma, the proportion of families who are lone parent families, the proportion of the income from government transfer payments, the proportion of the population aged 15+ who are unemployed, the proportion of the population considered low- income, and proportion of households living in dwellings that are in need of major repair. [2] Economic dependency measures the proportion of people with no income from employment (proportion of the population who are aged 65 and older; dependency ratio (total population 0–14 and 65+ /total population 15 to 64); and proportion of the population not participating in labor force (aged

15+)). [2] Ethnic concentration measures the proportion of recent immigrant (arrived in the past 5 years) and people who self-identify as a visible minority. [2] Each ON-Marg index was summarized as 5 quintiles from the least (Q1) to the most (Q5) marginalized neighborhood. [2] Both neighborhood income and ON-Marg indices were calculated at the dissemination area level (the smallest geographic unit for Canadian census with a population of 400–700 persons).

Quantitative Bias Analysis

Misclassification Bias

We conducted a probabilistic bias analysis with Monte Carlo sampling techniques to adjust for non-differential outcome misclassification. [3,4] We started by modeling the sensitivity and specificity of the CP definition using a beta distribution, informed by the validity of CP diagnostic codes obtained from the literature. [5] The shape of the beta distribution is determined by two parameters: α and β. We calculated α and β according to plausible minimum and maximum values and adjusted the values as needed so the mean of the beta distribution accurately reflected the sensitivity and specificity values obtained from published validation studies. [5] The minimum, maximum, and mode of the distribution of bias parameters were 40%, 80%, and 60% for sensitivity and 99.9%, 99.999%, and 99.99% for specificity of CP definition.

We then used these bias parameters to calculate the positive and negative predicted values based on observed data and exposure and outcome status. [3,4] These predicted values were then applied to each record in the dataset to check whether the outcome status for each individual was correctly classified using a Bernoulli trial with a probability equal to the relevant predicted probability. [3,4] The result of this trial was used as the bias-adjusted outcome variable. Using the bias-adjusted dataset, we then used a Cox proportional hazards model to estimate the association between the exposure and CP, adjusted for misclassification. The entire process was repeated 1,500 times to generate a distribution of bias-adjusted estimates. [3,4] The bias-adjusted effect estimate is the 50^{th} percentile of the distribution and the 2.5^{th} and 97.5^{th} percentiles of the distribution provide a 95% simulation interval that only accounts for systematic error. [3,4] We then estimated total error (systematic plus random error) by subtracting the conventional standard error (i.e. those calculated from main analyses) and a random normal deviate from each of the bias-adjusted estimates. [3,4]

Unmeasured Confounding

We also assessed the effect of unmeasured confounding by maternal individual-level socioeconomic factors by simulating a dichotomous variable (U) representing maternal education (university degree vs not). We guessed the value of U for each child, based on their exposure and outcome status. [6,7] We modeled the prevalence of U using a beta distribution and assumed the prevalence of U (no university degree) to range between 0.48–0.88 (mode=0.68) in children of mothers with unintentional injury during pregnancy who have CP, 0.35–0.75 (mode=0.56) in children of mothers with no unintentional injury during pregnancy who have CP, 0.45–0.85 (mode=0.64) in children of mothers with unintentional injury during pregnancy who do not have CP, and 0.30–0.70 (mode=0.51) in children of mothers with no unintentional injury during pregnancy who do not have CP, based on information from the literature. [6,7]

We then conducted a Bernoulli trial to determine if each subject has the dichotomous confounder, based on the assigned probability according to their exposure and outcome status. [3] We then estimated the effect of maternal unintentional injury on CP, adjusted for measured confounders and the new confounder using the Cox proportional hazards models. [3] The entire process was then repeated 1,500 to create a distribution of bias-adjusted estimates and effect estimates with 95% limits corrected for systematic and random errors. [3]

eReferences

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eTable 1. Description of different datasets at ICES and the relevant study variables

DATASET	Description	Relevant study variables
MOMBABY	Records of delivering mothers and newborns in all hospital births in Ontario (ON) since 2002	• Birth characteristics (birth weight, gestational age at birth) • Child characteristics (birth plurality, infant's sex) • Maternal characteristics (age and parity)
CIHI-DAD (The Canadian Institute for Health Information Discharge Abstract Database)	Administrative, clinical (diagnoses and procedures), and demographic information of all hospital admissions	• Inpatient diagnosis of cerebral palsy • Inpatient diagnosis of maternal unintentional injury • Inpatient diagnosis of maternal substance use disorder • Inpatient diagnosis of maternal obesity
NACRS-National Ambulatory Care Reporting System	Provides data about both hospital- and community-based ambulatory care, including emergency department visits.	• Maternal unintentional injury
OHIP (The Ontario Health Insurance Plan)	Outpatient physician service information	• Outpatient diagnoses of cerebral palsy • Maternal use of prenatal care services • Outpatient diagnosis of maternal substance use disorder • Outpatient diagnosis of maternal obesity
ON-Marg (Ontario Marginalization Index)	Marginalization index for geographic locations in ON	• The four ON-Marg indices: material deprivation, dependency, ethnic diversity, and residential instability
Census-data	Links postal code of the mothers to a range of socioeconomic indicators by geographic region.	• Home location (urban, rural) • Neighborhood income
ODB (Ontario Drug Benefit Claims)	Prescription medication claims for those covered under the provincial drug program	• Eligibility to receive ODB benefits as a proxy for receiving social assistance

eTable 2. Diagnostic codes used to define study variables

Variable	ICD-10-CA	OHIP code	Observation window
Cerebral palsy	G80	343	From birth to death or end of follow-up
Maternal unintentional injury			
Land transport accident	V01–V89	-	294 days before the index delivery date
Water transport accident	V90–V94	-	294 days before the index delivery date
Air and space transport accident	V95–V97	-	294 days before the index delivery date
Other and unspecified transport accidents	V98–V99	-	294 days before the index delivery date
Falls	W00–W19	-	294 days before the index delivery date
Burns	X00–X19	-	294 days before the index delivery date
Drowning/submersion	W65–W74	-	294 days before the index delivery date
Unintentional Poisoning	X40–X49	-	294 days before the index delivery date
Other accidental threats to breathing	W75–W84	-	294 days before the index delivery date
Exposure to electric current, radiation and extreme ambient air temperature and pressure	W85–W99	-	294 days before the index delivery date
Contact with venomous animals and plants	X20–X29	-	294 days before the index delivery date
Exposure to forces of nature	X30–X39	-	294 days before the index delivery date
Exposure to inanimate or animate mechanical forces	W20–W64	-	294 days before the index delivery date
Overexertion, travel and privation	X50–X57	-	294 days before the index delivery date
Accidental exposure to other and unspecified factors	X58–X59	-	294 days before the index delivery date
Maternal substance use disorder	F10–F19	303–305	660 days before the index delivery date
Maternal obesity	E66	278	660 days before the index delivery date

eTable 3. Number of children exposed to maternal unintentional injury according to the mechanism of injury.

Characteristic	N (%)
Fall	
No	2,088,208 (98.96)
Yes	21,969 (1.04)
Exposure to mechanical forces [a]	
No	2,086,452 (98.88)
Yes	23,725 (1.12)
Transport-related accidents [b]	
No	2,095,905 (99.32)
Yes, includes	14,272 (0.68)
• Land transport accidents (n= 14,206)	
• Water transport accidents (n=45)	
• Air or space transport accidents (n=3)	
• Other and unspecified transport accidents (n=18)	
Other accidental causes of external injury	
No	2,088,465 (98.97)
Yes, includes:	21,712 (1.03)
• Accidental drowning and submersion (n=5)	
• Other accidental threats to breathing (n=23)	
• Exposure to electric current, radiation and extreme ambient air temperature (n=423)	
• Burns (n= 1,944)	
• Contact with venomous animals and plants (n=782)	
• Exposure to forces of nature (n=184)	
• Accidental poisoning by and exposure to noxious substances (n=1,826)	
• Overexertion, travel and privation (n= 7,545)	
• Accidental exposure to other and unspecified factors (n=9,003)	

Notes:

[a] included accidents related a heterogenous group of animate mechanical force (e.g., struck by an animal or another person in sport) or inanimate mechanical forces (e.g., struck by an object)

[b] Most transport-related accidents were related to motor vehicle accidents (V40–V49)

eTable 4. Hazard ratios of the association between maternal unintentional injury during pregnancy and cerebral palsy in offspring according to the mechanism of injury.

Characteristic	**Crude**	**Model 1** [a] (birth year)	**Model 2** [b] (birth year and sociodemographic factors)	**Model 3** [c] (birth year, sociodemographic, and clinical factors)
Falls				
No (n=2,088,208)	Ref.	Ref.	Ref.	Ref.
Yes (n=21,969)	1.27 (1.01, 1.61)	1.26 (1.00, 1.60)	1.16 (0.91, 1.47)	1.15 (0.90, 1.45)
Transport-related accidents				
No (n=2,095,905)	Ref.	Ref.	Ref.	Ref.
Yes (n=14,272)	1.66 (1.29, 2.15)	1.65 (1.28, 2.13)	1.58 (1.23, 2.04)	1.57 (1.22, 2.02)
Exposure to mechanical forces [d]				
No (n=2,086,452)	Ref.	Ref.	Ref.	Ref.
Ye (n=23,725)	1.54 (1.25, 1.89)	1.52 (1.24, 1.88)	1.39 (1.13, 1.72)	1.38 (1.11, 1.70)
Other external injury [e]				
No (n=2,088,465)	Ref.	Ref.	Ref.	Ref.
Yes (n=21,712)	1.35 (1.07, 1.70)	1.36 (1.08, 1.71)	1.25 (1.00, 1.58)	1.24 (0.98, 1.56)

Notes:

[a] Model 1 included birth year. Birth year was modeled using restricted cubic splines with 3 knots at 2003, 2010, 2016 years.

[b] model 2 included birth year maternal sociodemographic characteristics (age, parity, and socioeconomic indicators).

[c] Model 3 included all covariates in model 2 plus clinically documented maternal substance use disorder and obesity

[d] included accidents related a heterogenous group of animate mechanical force (e.g., struck by an animal or another person in sport) or inanimate mechanical forces (e.g., struck by an object)

[e] included injuries related to a heterogenous group of exposures, such as burns and accidental poisoning.

eTable 5. Rate ratios for the associations between maternal unintentional injury during pregnancy and cerebral palsy in offspring, calculated using Poisson regression models.

Characteristic	**Crude**	**Model 1** [a] (birth year)	**Model 2** [b] (birth year and sociodemographic factors)	**Model 3** [c] (birth year, sociodemographic, and clinical factors)
Injury				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.49 (1.32, 1.67)	1.47 (1.30, 1.65)	1.36 (1.20, 1.53)	1.34 (1.19, 1.51)

Notes:
[a] Model 1 included birth year. Birth year was modeled using restricted cubic splines with 3 knots at 2003, 2010, 2016 years.
[b] model 2 included birth year maternal sociodemographic characteristics (age, parity, and socioeconomic indicators).
[c] Model 3 included all covariates in model 2 plus clinically documented maternal substance use disorder and obesity

eTable 6. Risk ratios for the associations between maternal unintentional injury during pregnancy and cerebral palsy in offspring, calculated using Log-binomial regression models.

Characteristic	**Crude**	**Model 1** [a] (birth year)	**Model 2** [b] (birth year and sociodemographic factors)	**Model 3** [c] (birth year, sociodemographic, and clinical factors)
Injury				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.45 (1.29, 1.63)	1.46 (1.30, 1.65)	1.35 (1.20, 1.53)	1.34 (1.19, 1.51)

Notes:
[a] Model 1 included birth year. Birth year was modeled using restricted cubic splines with 3 knots at 2003, 2010, 2016 years.
[b] model 2 included birth year maternal sociodemographic characteristics (age, parity, and socioeconomic indicators).
[c] Model 3 included all covariates in model 2 plus clinically documented maternal substance use disorder and obesity

eTable 7. Hazard ratios of the association between maternal unintentional injury during pregnancy and cerebral palsy in offspring stratified by preterm birth

Children born at term or after (≥37 weeks), n=1,944,932				
Characteristic	**Crude**	**Model 1** [a] (birth year)	**Model 2** [b] (birth year and sociodemographic factors)	**Model 3** [c] (birth year, sociodemographic, and clinical factors)
Injury				
No (n=1,871,562)	Ref.	Ref.	Ref.	Ref.
Yes (n=73,370)	1.26 (1.07, 1.48)	1.26 (1.07, 1.48)	1.17 (0.99, 1.38)	1.16 (0.99, 1.37)
Timing of injury				
No injury (n=1,871,562)	Ref.	Ref.	Ref.	Ref.
First (0–12) (n=29,151)	1.12 (0.86, 1.47)	1.12 (0.86, 1.46)	1.02 (0.78, 1.33)	1.01 (0.77, 1.32)
Second (13–27) (n=27,390)	1.29 (1.00, 1.66)	1.29 (1.00, 1.67)	1.21 (0.94, 1.56)	1.20 (0.93, 1.56)
Third (28+) (n=16,829)	1.45 (1.07, 1.97)	1.45 (1.07, 1.96)	1.38 (1.01, 1.87)	1.37 (1.01, 1.86)
Children born preterm (<37 weeks), n=165,245				
Characteristic	**Crude**	**Model 1** [a] (birth year)	**Model 2** [b] (birth year and sociodemographic factors)	**Model 3** [c] (birth year, sociodemographic, and clinical factors)
Injury				
No (n=157,334)	Ref.	Ref.	Ref.	Ref.
Yes (n=7,911)	1.48 (1.25, 1.77)	1.47 (1.24, 1.76)	1.37 (1.15, 1.64)	1.36 (1.14, 1.63)
Timing of injury [d]				
No injury (n=157,334)	Ref.	Ref.	Ref.	Ref.
First (0–12) (n=4,330)	1.66 (1.33, 2.07)	1.69 (1.35, 2.10)	1.55 (1.24, 1.94)	1.54 (1.23, 1.92)
Second (13–27) (n=2609)	1.39 (1.03, 1.89)	1.33 (0.97, 1.83)	1.25 (0.91, 1.72)	1.25 (0.91, 1.71)
Third (28+) (n=972)	0.97 (0.53, 1.75)	0.96 (0.53, 1.74)	0.91 (0.50, 1.65)	0.91 (0.50, 1.64)

Notes:

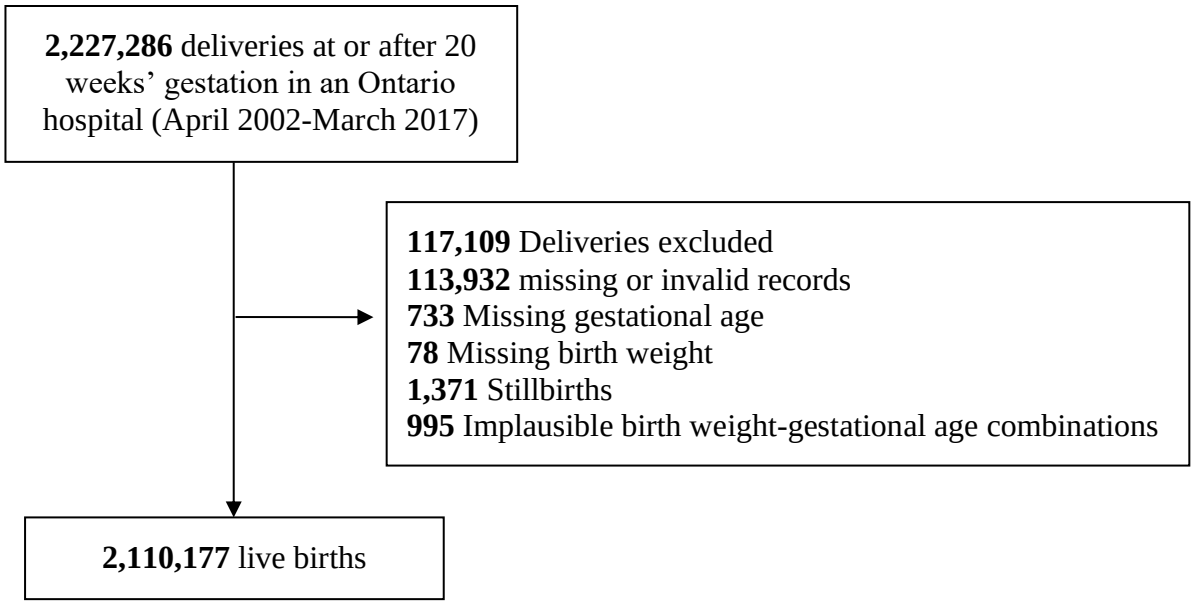
[a] Model 1 included birth year. Birth year was modeled using restricted cubic splines with 3 knots at 2003, 2010, 2016 years.

[b] model 2 included birth year maternal sociodemographic characteristics (age, parity, and socioeconomic indicators).

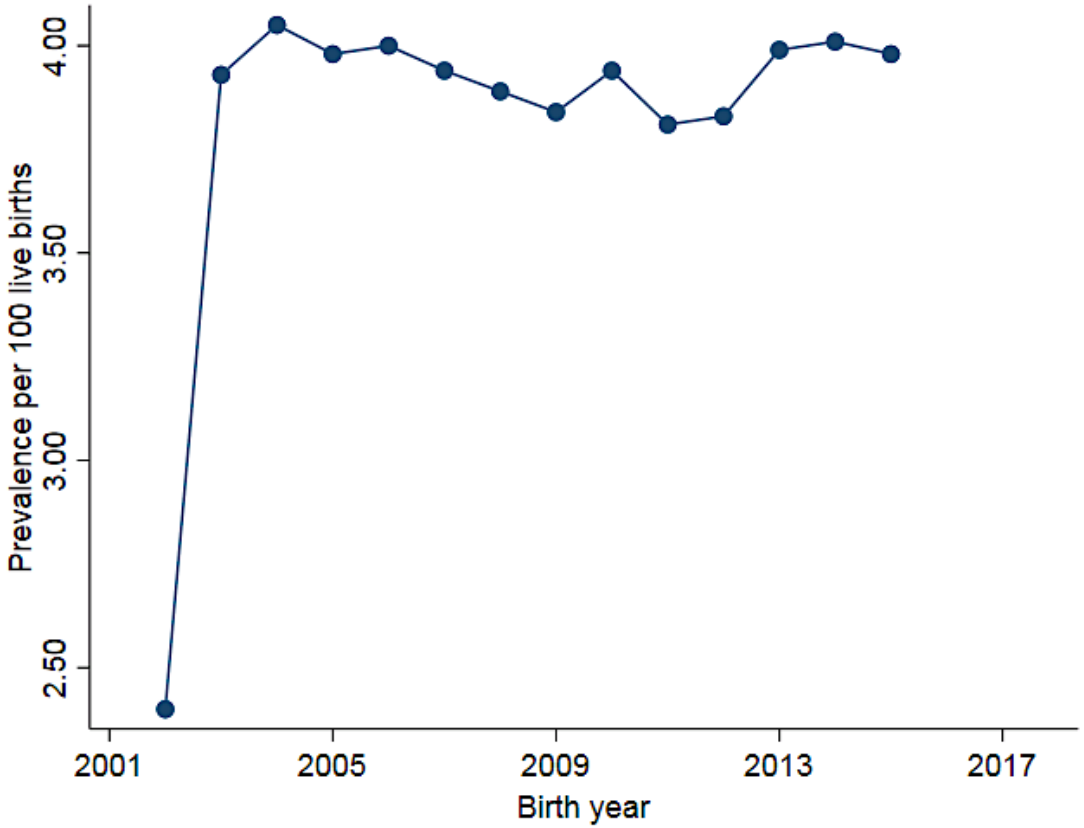
[c] Model 3 included all covariates in model 2 plus clinically documented maternal substance use disorder and obesity

[d] Timing of injury was calculated based on the gestational age at the time of injury. Women exposed to more than one injury were classified according to the gestational age at the *first* injury.

eFigure 1. Flowchart illustrating the formation of the study cohorts



eFigure 2. Crude prevalence of maternal exposure to unintentional injury during pregnancy by year of birth.



Chapter 7. Discussion and Conclusions

7.1. Summary of Findings

The overarching aim of this thesis was to advance our knowledge about the burden and etiology of CP. The motivation for the first manuscript was the scarce data on CP prevalence in Canada, particularly secular trends, and the limited understanding of changes in CP rates by key sociodemographic characteristics over time. In this manuscript, I aimed to describe the burden of CP in the Canadian context by estimating the prevalence and temporal trends of CP overall and in subgroups identified by important population characteristics. To address this question, I conducted a population-based retrospective cohort study of all live hospital births born in the province of Ontario, Canada between 2002–2017 using administrative health data. Overall CP prevalence among children aged 0–16 years was 2.52 (95% CI: 2.45, 2.59) per 1000 live births, consistent with estimates from other developed countries. [2] However, CP rates showed changes over time. CP rates in children ages 0–4 years peaked at 2.86 (95% CI: 2.73, 2.95) in those born in 2007 and steadily declined afterward to 1.94 (95% CI: 1.78, 2.11) per 1000 live births in those born in 2013. CP prevalence and temporal trends differed by the child and maternal characteristics. CP rates over time were higher in children born preterm and small-for-gestational-age, but rates in these categories were stable between 2002–2007 and decreased after 2007. CP rates were also higher in boys, multiples, children with congenital malformations, and in children born to young (<20 years), old (≥40 years), primiparous, or grand multiparous (≥4) mothers, or mothers with inadequate prenatal care or who delivered by caesarean section; though, the gaps by these characteristics had narrowed in recent births (after 2007). Socioeconomic disparities in CP were also evident over the study period, and they persisted and remained relatively stable over time.

In the second and third manuscripts, my focus shifted towards understanding the role of prenatal factors in the etiology of CP. I was motivated by the limited evidence of the role of two common and important prenatal exposures in the etiology of CP—maternal diabetes and unintentional injuries. The objective of the second manuscript was to examine the effects of maternal pre-gestational and gestational diabetes on CP, and whether increased fetal size explained some of these effects. I found that children of mothers with PGDM had an increased risk of CP (HR 1.84

(95% CI: 1.59, 2.14)) after adjusting for maternal sociodemographic and pre-existing factors; the risk of CP increased with the duration of PGDM (adjusted HR 2.49 (95% CI: 1.76, 3.54) for PGDM>10 years**)**. No similar associations were found for GDM (adjusted HR 0.91 (95% CI: 0.77, 1.06)). The positive associations between PGDM and CP were robust to a wide range of sensitivity analyses that accounted for exposure and outcome misclassifications and unmeasured confounding. Large for gestational age did not explain most of the effect of PGDM on CP (explained only ~12%). Overall, the results of this study suggested an important role of PGDM in the etiology of CP with a limited contribution of increased fetal size in explaining these associations. These results also suggested that GDM may not affect the risk of CP in offspring. These findings were consistent with two prior population-based studies that found a higher risk of CP in offspring of mothers with PGDM but no associations for GDM. [26,27] It is possible that children of mothers with PGDM may have been exposed to more prolonged and severe hyperglycemia, particularly during critical windows for brain development in early pregnancy. Differences in fetal metabolic and vasculopathic sequelae and placental changes between PGDM and GDM may also explain their different associations with CP. [198]

In the third manuscript, I focused on the effect of another maternal exposure during pregnancy—unintentional injury. Despite the plausible link, I noticed the scarcity of evidence of the long-term effects of maternal injuries on offspring's neurodevelopment. I, therefore, conducted a study that aimed to examine the effect of maternal unintentional injury on the risk of CP in offspring and whether the effect differed by the severity of the injury. My results showed a modest increase in the risk of CP in children exposed *in-utero* to maternal unintentional injury (HR 1.33 (95% CI: 1.18, 150) after adjusting for maternal sociodemographic and lifestyle factors). These results were robust in several sensitivity analyses that accounted for outcome misclassifications and unmeasured confounding and were consistent across different injury mechanisms. My findings also suggested a higher risk of CP among children exposed to maternal injuries that required hospital admission or resulted in the delivery shortly after the injury, or those exposed to injuries multiple times. These findings were consistent with a few existing case reports and one population-based study that showed possible links between maternal injuries and CP. [28,170-172] My findings that severer injuries might be linked to a higher

risk of CP were also in line with reports that showed worse maternal and fetal outcomes with increased severity of injuries. [158,161,199]

7.2. Strengths and Limitations

Results of manuscripts enclosed in this thesis generated high-quality evidence on the effect of two important and common maternal exposures during pregnancy on the risk of CP in offspring. In addition, I conducted the first population-based Canadian study that specifically examined the prevalence and temporal trends of CP over time, overall and across a wide range of child, maternal and sociodemographic characteristics. This thesis used data from ~2 million live births within a single-payer health system, reducing the possibility of selection bias and enhancing generalizability. With a rare outcome like CP, it is essential to have a large sample in order to improve our inference and examine associations according to detailed characteristics of each exposure and potential causal pathways.

Several specific limitations were noted throughout the three manuscripts enclosed in this thesis. I highlight a few overarching limitations that are important to consider in this chapter. First, outcome misclassification is plausible as I relied on administrative data to ascertain CP. [200] Under-ascertainment of CP is possible in children born in more recent years where the follow-up time was short, particularly for milder cases that might only be diagnosed at a later age. Furthermore, my outcome data were obtained from administrative health databases; thus, only cases presented for medical care were identified. On the other hand, given the complexity of CP diagnosis and the existence of several differential diagnoses and comorbidities, [29,30,36] some children labeled as having CP might not be true cases. I attempted to protect against outcome misclassifications in several ways. First, I defined CP based on at least a single inpatient diagnosis or 2 or more outpatient diagnoses at least 2 weeks apart, assuming that inpatient diagnoses are more accurate as they are mostly made by pediatric specialists (e.g., pediatric neurologists). I developed this outcome definition in consultation with Dr. Rosella, a knowledgeable researcher of the Ontario administrative databases at ICES, and Dr. Oskoui, a pediatric neurologist with extensive clinical and research experience with CP. This definition was also used by other researchers who used ICES data with CP as the outcome. [28,108] I also used an alternative definition of CP in manuscript 1 and found a consistent trend overall and across

population characteristics. In manuscripts 2 and 3, I suspected that outcome misclassification was likely non-differential that would underestimate the true associations. This was consistent with the results of the quantitative bias analysis for outcome misclassification using bias parameters from a validation study of CP diagnostic codes in administrative health databases in Quebec. [201] Exposure misclassification in both manuscripts 2 and 3 was possible, although it was also likely non-differential and thus would underestimate the observed associations. In manuscript 2, I conducted quantitative bias analyses for the potential misclassification of PGDM and GDM according to validation data from the ICES databases [184,202] and found that PGDM estimates became slightly stronger after correcting for exposure misclassification while GDM results remained close to the null. For exposure to injury in manuscript 3, I used injury classifications developed by the international framework for injury surveillance developed by the Centre for Disease Control and Prevention using ICD-10-CA External Cause of Injury Codes. [203] These codes have been extensively used in different populations, including in pregnant women. [28,199,204] I, however, did not conduct bias analysis for exposure misclassification of injury because of a lack of validation data in the literature. Nevertheless, injuries captured in my data have likely included all injuries during pregnancy requiring medical attention because of the general concerns about maternal and fetal well-being.

Given the observational nature of this thesis, residual confounding is also a potential threat to validity in manuscripts 2 and 3. Although we adjusted for multiple covariates available using multiple databases, we could not rule out the possibility of residual confounding by individual-level maternal characteristics, such as maternal education, income, and immigration status, that would explain the observed associations. [108,110] Nevertheless, our estimates in manuscripts 2 and 3 only shifted slightly when we simulated the effect of unmeasured confounding by maternal education as an example using probabilistic bias analyses.

While ICES administrative databases provide a wealth of information on different aspects of clinical and sociodemographic factors on all users of the Ontario health care system, some limitations of these administrative databases should be noted. These datasets lacked information on several important individual-level socioeconomic and behavioral characteristics, as well as race and immigration status. Access to data on immigrants and refugees to Ontario (available at

ICES through the Immigration, Refugees and Citizenship Canada, Permanent Residents database) was restricted to individuals working in-person at one of ICES locations but was not possible with the virtual access option through IDAVE. [180] Furthermore, diagnostic codes in outpatient databases (OHIP) were only limited to major disease categories rather than specific diagnoses (the first three numbers of ICD-9 codes). [180] Thus, I was unable to examine CP prevalence and temporal trends in manuscript 1 by CP subtype, or associations by CP subtype in manuscripts 2 and 3. I was also only able to assess the effect of PGDM as a combined group of type 1 and 2 diabetes.

Selection bias may also have impacted our findings. It is possible that children with severe brain injury may die, either in-utero or postnatally, before being diagnosed with CP. Thus, reported associations may be underestimated if in-utero or postnatal deaths of severe CP cases occur preferentially in those exposed to diabetes or maternal injury than the unexposed. [205] Nevertheless, CP can only be diagnosed postnatally; thus, it would not be possible to identify stillbirths who might have a brain injury that would lead to CP. Also, given the small number of children who died during the study follow-up, I suspect a minimal impact on our findings, if any. I also did not consider information on the migration of the included births out of the province. Some children with CP possibly moved out of the province before getting a diagnosis of CP. However, I expect negligible migration rates among children included in our cohort as the rates of migration out of Ontario province to other Canadian provinces were minimal during the study period (<0.5%). [206] I also believe that immigration out of the province would be non-differential with respect to study outcome and exposure given the availability of good-quality health and educational services in Ontario for children with disabilities and the similarity of the health care system between Ontario and other provinces. [207,208]

7.3. Implications of Findings

Overall, the findings of this thesis provide an important addition to the body of literature about the burden of CP in the Canadian context and the etiology of CP. To our knowledge, manuscript 1 was the first study to assess temporal trends of CP rates stratified by key sociodemographic characteristics and the first in Canada on secular trends. Given the substantial economic burden of CP on the health care system, educational services, and affected families, [4] it is important to

have accurate estimates of the disease prevalence for optimal service planning and provision. My results showed a comprehensive description of the disease burden in Canada to better guide planning and providing adequate services that meet the complex needs of children with CP and their families. It is encouraging that I found declines in CP rates in more recent births, consistent with results from Europe and Australia. [15-18,21,47,48,209] Declines in CP rates across gestational age and birth weight categories—despite improvements in neonatal survival in preterm/LBW infants—are encouraging and may provide real-world evidence for the potential positive impact of advances in perinatal care and neuroprotective strategies. These results support the need for continued surveillance of CP rates over time to assess if these trends are continuing. My findings highlighted population subgroups with a persistently high prevalence of CP over time, which would help inform targeted public health programs for active surveillance and monitoring of young children at risk of CP.

Results of this thesis add to our understanding of the potential importance of maternal pre-conception and pregnancy exposures in the etiology of CP. These findings are relevant to epidemiologists, clinicians, and public health practitioners interested in gaining a better understanding of the underlying causes of CP. My findings showed a persistent and relatively robust positive effect of PGDM on the risk of CP in offspring that was stronger with a longer duration of diabetes. My research emphasizes the need for increased attention to the group of children exposed to maternal diabetes who should be monitored closely for early neurological manifestations of cerebral palsy to ensure early diagnosis and treatment, as early interventions have been linked to improved prognosis and neurological outcomes. [210] It was reassuring that CP rates have declined after 2007, despite the alarming increase of maternal diabetes rates over the study period. The decrease of CP rate is possibly caused by changes in other factors, such as sociodemographic factors and advances in obstetric and perinatal care. Findings of this research also filled important gaps in knowledge about the long-term effects of unintentional injuries experienced by pregnant women on children's neurodevelopment. The current clinical management guidelines of trauma among pregnant patients focus on monitoring the fetal condition immediately after the injury with little attention on long-term sequelae of trauma on fetal and children outcomes, [211] which enables the detection of short-term complications only. [212] Results of this study showed potential harmful long-term effects of maternal injuries on children.

Clinicians may consider advising pregnant women about the potential long-term effects of unintentional injury during pregnancy on children's developing brain. These results may also indicate the need for monitoring of children exposed to maternal injury in-utero to ensure early detection and management of children showing neurodevelopmental abnormalities. By providing further evidence of potential harmful effects of exposure to injuries during pregnancy, these results emphasize the importance of effective preventative interventions and monitoring to improve the safety of pregnant women on the road, at the workplace, and at home.

7.4. Avenues for Future Research

Results of manuscript 1 showed a comprehensive analysis of CP prevalence and temporal trends over a 16-year period overall and across population characteristics. However, I did not have data on CP subtypes based on motor impairment or functional status. Previous research has shown that certain motor subtypes are more prevalent in specific population subgroups (e.g., diplegic CP is mostly seen in preterm infants). [33] Thus, future studies that examine CP prevalence and temporal trends—overall and by characteristics—by CP motor subtype would shed further light on subgroups at risk specific of certain motor subtypes. Further studies on CP prevalence and secular changes according to the degree of functional limitation (GMFCS classification) [35] would also provide a better understanding of the disease burden and better inform service planning and provision. I showed declining trends in CP overall and across population subgroups, but further work is still needed to understand factors that may explain the downward trends of CP relative to concurrent changes in CP risk factors in the population.

Although this thesis filled an important gap with respect to the effect of PGDM on CP, I did not have information about the type of PGDM. Type 1 and 2 diabetes share many clinical features, but they have distinct pathophysiology and epidemiological profiles. [122,123] For example, type 1 diabetes is an autoimmune disease that typically starts during childhood or adolescence whereas type 2 diabetes is mostly linked to obesity and is usually found at a later age. [122,123] Studies have also shown different effects of type 1 and 2 diabetes on birth outcomes. [213] Thus, additional research is required to examine if the effects of type 1 and 2 diabetes on CP differ. Previous research has documented better perinatal outcomes in children of women with well-managed diabetes (e.g., lower risks of perinatal death, fetal overgrowth, and traumatic deliveries). [214,215]

Thus, future work that investigates whether stringent glycemic control would alleviate the impact of maternal PGDM is also needed for a better understanding of the effect of PGDM on the risk of CP in children.

In manuscript 3, I did not have a direct measure of the severity of injury but only used several characteristics of the maternal injury as an indirect measure. Future studies that directly measure the severity of injury would highlight whether a higher risk of CP would be seen after severer injuries, similar to what has been documented for other maternal and fetal outcomes. [158,160,161] Currently, there is limited information on the long-term effects of maternal injuries on children's outcomes; thus, further well-conducted studies are needed to comprehensively evaluate the long-term effect of maternal injuries on other neurodevelopment outcomes than CP, as evidence on possible links has emerged in the literature. [211,216] These studies would provide important additional evidence on the effects of maternal injury and may guide a more comprehensive approach to monitoring children exposed in-utero to maternal injuries. My results showed a high risk of CP after maternal transport-related accidents; however, I did not have information about important characteristics of the accidents that are linked to poorer fetal outcomes, such as the lack of seatbelt use, high speed, and use of alcohol or drugs. [160] Seat belt use has been linked to a reduced risk of adverse maternal and fetal outcomes in several large population-based studies. [217,218] Thus, studies that aim to understand the role of these characteristics in the effect of maternal injury on CP would be beneficial to inform interventions that promote the importance of proper seat belt use to protect the woman and her child.

7.5. Conclusions

Overall, this thesis provides an important addition to our knowledge about the burden of CP and its underlying causes. Specifically, findings from this thesis suggested that despite the decreasing trend of CP rates overall, CP rates varied by the child and maternal characteristics over time. The declines of CP rates in recent years were consistent with studies in other developed nations, and further work is needed to monitor if these trends continue and to identify factors that contribute to these downward trends. The evidence accumulated from this thesis indicated the importance of prenatal exposures in the etiology of CP. I documented that maternal PGDM but not GDM was associated with increased risk of CP. I also provided the first evidence of the effects of

diabetes duration and the potential role of increased fetal size in explaining these effects by showing that the risk of CP increased with the disease duration and that LGA did not substantially mediate the effect of PGDM on CP. This thesis also encompasses one of the first population-based studies to highlight the role of maternal injury during pregnancy on fetal neurodevelopment by showing an increased risk of cerebral palsy in children exposed to maternal unintentional injury in-utero. Taken together, findings of this thesis underscore the essential role of the in-utero environment and further support the accumulating evidence that the brain damage that leads to CP occurs before birth in most cases. Overall, these results not only lead to a better appreciation of the magnitude of the CP burden in Canada but also offer key insights on potential causal mechanisms of CP. Ultimately, this work will contribute to developing preventative strategies to reduce the risk of this disabling disorder in Canada and elsewhere.

8. References

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