

**INVESTIGATION OF THE EFFECT OF MATERNAL WEIGHT ON PEDIATRIC HEALTH
SERVICE UTILIZATION**

Lisa Currie, BSc, BScOT, MSc

A thesis submitted in partial fulfillment of the requirements for the Doctorate in Philosophy
degree in Epidemiology

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

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Supervisors

Primary Supervisor

Laura Gaudet, *University of Ottawa*

Co-Supervisors

Mark Walker, *University of Ottawa*

Beth Potter, *University of Ottawa*

Thesis Advisory Committee

Doug Coyle, *University of Ottawa*

Deshayne Fell, *University of Ottawa*

Steven Hawken, *University of Ottawa*

Shi Wu Wen, *University of Ottawa*

Dissertation Abstract

Introduction: Maternal weight during pregnancy has an important impact on multiple aspects of health for both mothers and their children. This dissertation investigated whether pre-pregnancy body mass index (BMI) and gestational weight gain (GWG) independently impact a child's health service utilization.

Methods: This dissertation included four studies. The study population for the first three studies was all women who delivered a singleton, live infant in Ontario between 2012-2014 and have information contained in the Better Outcomes Registry and Network (BORN) Ontario registry. Health service data in the first 24 months following birth were collected via health administrative databases housed at ICES. I investigated whether there was an association of pre-pregnancy BMI (Chapter 2) or GWG (Chapter 3) with pediatric health service use. I then investigated whether adverse birth outcomes, specifically small for gestational age (SGA) or preterm birth (PTB), mediated this relationship (Chapter 4). Finally, I developed a cost effectiveness evaluation framework for the implementation of a maternal weight intervention program to limit the impact on the child (Chapter 5).

Findings: Children born to women with pre-pregnancy obesity relative to normal weight experienced higher rates of hospitalization (adjusted incidence rate ratio [aIRR]: 1.20, 95% CI: 1.17,1.24), physician visits (aIRR: 1.05, 95% CI: 1.04,1.05) and emergency department (ED) visits (aIRR: 1.27, 95% CI: 1.25,1.29). Children born to normal weight (aIRR: 1.07, 95% CI: 1.05,1.09) or overweight (aIRR: 1.04, 95% CI: 1.01,1.07) mothers with above recommended (versus recommended) GWG had increased ED visits. Children born to underweight women with below recommended GWG had increased hospitalizations (aIRR: 1.31, 95% CI: 1.14,1.51) and physician visits (aIRR: 1.14, 95% CI: 1.10,1.17). PTB (56.74%), and SGA (6.83%)

mediated the relationship of below recommended GWG and pediatric hospitalizations only. A detailed cost effectiveness framework is outlined to investigate an intervention plan targeting GWG to limit adverse pediatric health outcomes.

Discussion: The findings of this dissertation indicate that below or above optimal maternal weight is associated with pediatric health service use. This dissertation serves as a call to action to better inform clinical practice and impact health service policy related to maternal weight via early intervention.

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Contributions of Authors

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I created the study protocol, planned the project, completed all aspects of the analysis, interpreted the findings, drafted, and edited the manuscript. L. Gaudet and M. Walker contributed to the development of the protocol, with input from D. Fell, S. Hawken, and S. Wen. L. Gaudet, D. Fell, B. Potter and S. Hawken assisted with the interpretation of the findings and all authors assisted with editing the document.

Manuscript 2 (Chapter 3):

Lisa Currie, Deshayne Fell, Steven Hawken, Beth Potter, Doug Coyle, Shi Wu Wen, Mark Walker, Laura Gaudet

Relationship between gestational weight gain and health service utilization in early childhood: A retrospective cohort study.

Journal of Obstetrics and Gynaecology Canada (submission pending)

I created the study protocol, planned the project, completed all aspects of the analysis, interpreted the findings, drafted, and edited the manuscript. L. Gaudet and M. Walker contributed to the development of the protocol, with input from D. Fell, S. Hawken, and S. Wen. L. Gaudet, D. Fell, B. Potter and S. Hawken assisted with the interpretation of the findings and all authors assisted in editing the document.

Manuscript 3 (Chapter 4):

Lisa Currie, Hilary Brown, Deshayne Fell, Beth Potter, Steven Hawken, Doug Coyle, Shi Wu Wen, Mark Walker and Laura Gaudet

Association between maternal weight and pediatric health service utilization: Mediating role of adverse birth outcomes.

Journal of Obstetrics and Gynaecology Canada (submission pending)

I created the study protocol with consultation from H. Brown. I completed all aspects of study execution including the analysis, interpretation of findings, drafted and edited the manuscript. H. Brown lent her subject matter expertise to refine the analyses, and D. Fell and B. Potter contributed to the interpretation of the results. All authors facilitated the development of the study protocol, contributed to the interpretation of the results, and edited the final manuscript.

Manuscript 4 (Chapter 5):

Lisa Currie, Doug Coyle, Mark Walker and Laura Gaudet

Framework for Assessing the Cost Effectiveness of Prenatal Intervention Programs Targeting
Gestational Weight Gain to Limit Macrosomia

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All authors assisted in the development of the study protocol. I completed all aspects of literature review, writing and editing the document, with assistance from D Coyle. All authors contributed to the interpretation of the results and edited the final manuscript.

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COVID-19 Pandemic Impact Statement

The World Health Organization declared COVID-19 a global pandemic on March 11, 2020. Following this declaration, in-person activities were suspended, including access to the University of Ottawa and limited access to the UOttawa ICES student offices. At this time, projects outlined in Chapters 2, 3 and 4 were nearing completion, and the project outlined in Chapter 5 was scheduled to commence. The original proposal for the project outlined in Chapter 5 was to complete an economic evaluation with ICES data of the pediatric health service costs associated with maternal weight. Due to the global pandemic, in order to meet timelines for thesis completion, the thesis advisory committee approved a modification to develop a framework for assessing the cost effectiveness of an intervention program targeting maternal weight to limit adverse pediatric outcomes. It was determined that this would be a valuable project as it would provide guidance for the future economic evaluation of an intervention program which in turn would have direct policy implications. As this framework outlines all necessary components for a future analysis, it can be leveraged and implemented for identified intervention programs.

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List of Acronyms and Abbreviations

aIRR: adjusted incidence rate ratio

AOR: Adjusted Odds Ratio

ARR: Adjusted Relative Risk

BMI: Body Mass Index

CI: confidence interval

CIHI: Canadian Institute for Health Information

DAD: Discharge Abstract Database

ED: Emergency Department

GWG: Gestational Weight Gain

ICD-10: International Classification of Disease version 10

IKN: ICES Key Number

IRR: unadjusted incidence rate ratios

kg: kilograms

lb: pounds

m: metres

MI: Multiple Imputation

NACRS: National Ambulatory Care Reporting System

NELIP: Nutrition and Exercise Lifestyle Intervention Program

NICU: Neonatal Intensive Care Unit

NS: not significant

OR: Odds Ratio

OHIP: Ontario Health Insurance Plan

PTB: preterm birth

PY: Person Years

QALY: quality adjusted life years

RPDB: Registered Persons Database

SD: Standard deviation

SGA: small for gestational age

WHO: World Health Organization

Chapter 1

Introduction

Maternal weight, including pre-pregnancy weight and weight gain during pregnancy, has a profound impact on the health of both mothers and their children. While the impact of maternal weight has been investigated regarding the short- and long-term clinical implications on the mother and the child, evidence regarding the impact on health system utilization of the child is scarce. This dissertation investigated the association of maternal weight, identified as both pre-pregnancy body mass index (BMI) and gestational weight gain (GWG), with pediatric health service utilization in the first twenty-four months following birth.

1.1 Terminology

The main exposure of interest in this dissertation is maternal weight. Classifications of the World Health Organization (WHO) were used to classify body mass index (BMI) as underweight, normal weight, overweight and obese (Table 1.1). While there is inherent stigma associated with such terminology, within this text, in order to align with established practice, it is identified as a categorization of weight and not a judgement. Therefore, throughout the text, mothers with above normal pre-pregnancy BMI will be identified as either *overweight* or *obese* depending on their pre-pregnancy BMI status, and those with weight below normal will be identified as underweight, to remain consistent with the WHO guidelines.

Additionally, this dissertation identifies the population as *mothers* with the specified weight category. It is acknowledged that this identifier refers to all genders and is not limited to only the

female pronoun. Also, *mother* is in reference to the person who has birthed the child, given the potential biological mechanism of the neonatal exposure to maternal weight.

1.2 Approvals

Research ethics approval for these studies was provided by the Research Ethics Boards of the Ottawa Hospital Science Network (20180245-01 H, 2018-04-10), Children's Hospital of Eastern Ontario Research Institute (18/02 PE, 2018-02-02), the University of Ottawa (H-05-18-727, 2018-06-04), and the ICES Privacy Office (2018-05-08).

1.3 Maternal Body Weight and Pregnancy

Existing research provides strong evidence of the health risks associated with obesity, particularly during pregnancy (1). Women living with obesity more often undergo induction of labour or caesarean section delivery to mitigate potential risks during childbirth that are associated with obesity (2), including a significantly elevated risk of infant mortality (Adjusted Odds Ratio (AOR): 2.44, 95% CI: 1.88, 3.17) (3). The neonatal risks associated with maternal obesity extend throughout the perinatal period, including elevated risks of pulmonary disorders and admission to the neonatal intensive care unit (NICU) (4). A meta-analysis suggested that GWG is associated with multiple adverse birth outcomes, including small for gestational age (OR: 1.53, 95% CI: 1.44, 1.64), and preterm birth (OR: 1.70, 95% CI: 1.32, 2.20), for those with below recommended GWG; and large for gestational age (OR: 1.85, 95% CI 1.76, 1.95), macrosomia (OR: 1.95, 95% CI: 1.79, 2.11), and caesarean section delivery (OR: 1.30, 95% CI: 1.25, 1.35) (5) for those with above recommended GWG. Children born to mothers with obesity (6), and those with excessive GWG (7) are at increased risk of obesity themselves, as well as associated disease states including diabetes and cardiovascular disease (8). They are also at

increased risk of other adverse conditions, such as developmental delay (9) and long term impairment extending into childhood and beyond (10–12).

1.4 Child Development

Research suggests that children born to mothers with pre-pregnancy obesity are at risk of their own morbidities, such as delays in psychosocial and cognitive development. For example, children born to mothers with elevated pre-pregnancy BMI had lower IQ scores (13) and poorer nonverbal skills ($\beta = -5.6$, $P=0.003$) (14). Additionally, these children have an increased risk of intellectual disability (15), autism spectrum disorder (AOR 3.13; 95% CI: 1.10, 8.94) and attention deficit/hyperactivity disorder (OR: 4.55; 95% CI: 1.80, 11.46) (14–22). Degree of cognitive impairment may have a dose response relationship to maternal weight (23,24).

Maternal weight is also associated with the child's emotional stability (AOR: 2.24, 95% CI: 1.27, 3.98), peer interactions (AOR: 2.07, 95% CI: 1.26, 3.40), overall psychosocial development (AOR: 2.17, 95% CI: 1.24, 3.77), and referral to psychological service (AOR: 2.27, 95% CI: 1.09, 4.73), speech language pathology (AOR: 1.93, 95% CI: 1.18, 3.15), and other high needs health services (AOR: 1.99, 95% CI: 1.33, 2.97). (22). Maternal obesity has an associated risk of pediatric congenital anomalies, such as neural tube defects (OR: 1.87; 95% CI: 1.62, 2.15), most notably spina bifida (OR: 2.24; 95% CI: 1.86, 2.69), as well as general cardiovascular anomalies (OR: 1.30; 95% CI: 1.12, 1.51) (25), and more specifically congenital heart defects (OR: 1.15, 95% CI: 1.07, 1.23) (26).

1.5 Impact on Health Service Utilization

There is a dearth of information pertaining to the association of maternal weight with health service use of Canadian children, in particular as it relates to health care expenditures. An

increase in negative health outcomes may not correspond to an increase in health service use or expenditure if a child is monitored at a similar frequency to non-affected children, or if the increase in service use is negligible. There are recent studies to suggest that children born to mothers with obesity have increased rates of hospitalization up to the age of five [Adjusted Relative Risk (ARR): 1.48, 95% CI: 1.10, 1.98] (27), related to infection, metabolic issues, perinatal complications, injuries, respiratory conditions and conditions affecting the central and peripheral nervous systems. Interestingly, children born to mothers who had low pre-pregnancy BMI also demonstrated increased risk of hospitalization (27) and higher overall service use for psychosocial or language issues (22). These findings highlight the importance of understanding health service utilization in children across all maternal weight categories.

Research suggests that infants born to mothers living with obesity have 72% greater health care costs (RR: 1.72, 95% CI: 1.71, 1.73), primarily associated with more frequent and longer hospitalizations and more physician office visits (28). A cost service analysis found that infants born to mothers living with obesity utilized £1138.11 (approximately \$1,868.33 CAD) more services than those born to normal weight mothers in the first year of life. From a policy perspective, the authors of the analysis suggested that pre-pregnancy weight loss and interventions costing less than £2310 (approximately \$3,791.96 CAD) per person would qualify as a cost saving measure (28).

1.6 Exposures and Outcomes

As discussed, maternal weight that is either below or above recommended values is associated with adverse outcomes for both the mother and the child. Further, it is known that children born to these mothers are at risk of long-term health consequences, either associated with biological or environmental factors, such as obesity and diabetes. However, it is unclear if maternal weight

below or above recommended values is associated with increased health service use following birth.

Traditional WHO BMI categories were used to categorize weight, as these cut points are routinely used by clinicians when counselling women prior to pregnancy (Table 1.1). For completeness, we opted to assess BMI as both categorical and continuous within Chapter 2, a process that yielded similar results under both conditions. Therefore, WHO categorizations were used for all subsequent analyses. GWG was categorized for all analyses, using clinically meaningful cut-points. Health Canada cut points were used to define below recommended and above recommended GWG given this is the point of reference for Canadian physicians providing prenatal counselling (Table 1.2).

Table 1.1: World Health Organization Body Mass Index Classifications (29)

BMI	Classification
< 18.5 kg/m ²	Underweight
18.5-24.9 kg/m ²	Normal weight
25.0-29.9 kg/m ²	Overweight
≥30.0 kg/m ²	Obese

Table 1.2. Health Canada gestational weight gain recommendations (30)

Pre-Pregnancy BMI	Recommended Total Weight Gain	
	Kg	lb
< 18.5 kg/m ²	12.5 - 18	28 - 40
18.5-24.9 kg/m ²	11.5 - 16	25 - 35
25.0-29.9 kg/m ²	7 - 11.5	15 - 25
≥30.0 kg/m ²	5 - 9	11 - 20

Despite different biological mechanisms, our studies included women with both below recommended and above recommended weight. This allowed us to understand the impact of any

abnormal weight and reflects the importance of attending to all categories, not just overweight and obese.

Pregnancies, not mothers, were used as the unit of analysis. There were very few mothers with multiple records within the dataset (n=6311, 2.45%). As infant health was the outcome of interest, all records were maintained. Generalized Estimating Equations (GEE) were used in preliminary analysis with the mother as the repeated measure, but did not impact the findings, hence all subsequent analyses were completed without GEE.

Primary areas of pediatric health service use assessed were hospitalizations, emergency department (ED) visits, and physician visits. Physician visits were sub-analyzed for Chapters 2-3 to ascertain type of physician visit: well baby, specialist, non-specialist. As physician visits may not be associated with adverse health, as is the case for well baby visits, it was important to explore this area further.

1.7 Overview of methods

The studies included in this dissertation in Chapters 2-4 were based on secondary data analyses that leveraged advanced data manipulation and analysis of large datasets housed at ICES. ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. The population of interest was all singleton children born in Ontario from April 2012 to March 2014. Fiscal year data (versus calendar year data) was chosen as maternal pre-pregnancy BMI and GWG data are not available prior to April 2012. As health service utilization was the main outcome of interest, all records

from April 2012 to March 2016 were included to determine service use in the child's first twenty-four months following birth.

Covariates were identified a priori, and included variables associated in the literature with both the exposure and the outcome and that were not hypothesized to be in the causal pathway. The covariates included infant sex (31), maternal age (32), maternal smoking status (33), pre-existing maternal medical conditions (i.e. diabetes (34), hypertension (35)), gestational medical conditions (i.e. diabetes (34), hypertension (35)) and neighbourhood income quintile (36). All covariates except neighbourhood income quintile [identified from the ICES Registered Persons Database (RPDB)] were identified from BORN. Pre-existing and gestational medical conditions are identified as a pick list within BORN and entered by personnel at the individual health organization. For pre-existing medical conditions, there were specific codes for diagnoses of Diabetes type 1, diabetes type 2 (insulin) and diabetes type 2 (no insulin). For cardiovascular disease, a broad diagnostic category of 'cardiovascular disease?' was used. For pregnancy-related conditions, distinct codes were used. For gestational hypertension, the code 'hypertensive disorders in pregnancy' was utilized. For diabetes isolated to pregnancy, the code 'gestational diabetes' was used. Income was only available at the neighbourhood level, and is obtained based on government sources of income (37).

1.8 Methodological Issues

Several challenges exist with the study of the impact of maternal weight on pediatric health service utilization, primarily related to data access. There is a high degree of missingness in maternal weight variables. Sensitivity analyses were completed to ascertain differences between those with and without missing data, and multiple imputation was implemented as the primary

analysis, when possible. These steps were taken to overcome these challenges and produce the most accurate estimate of the association to pediatric health service utilization in Ontario based on these exposure variables available to date. Also, few databases capture maternal weight both as pre-pregnancy BMI and GWG within a population level registry. Maternal weight was first available in the BORN database as of 2012, hence a two-year cohort of 2012-2014 data was identified for inclusion in this analysis. Additionally, pre-pregnancy BMI is difficult to obtain in a study leveraging registry data, since it would require data capture prior to conception. Therefore, self report or measured weight and height at first prenatal visit was used as a proxy for this measurement. Research suggests that self-reported pregnancy related weight is a sufficient proxy, although direct estimate remains preferential (38). BORN implements a correction factor of subtracting 2 kilograms from the weight measurement at the first prenatal visit, to account for weight gained in the first trimester (personal communication, BORN). Additionally, GWG was ascertained using the last recorded weight in the registry. As weight is not captured at delivery, it is captured at the last prenatal visit prior to delivery. For women ≥ 37 weeks gestation, prenatal visits in Ontario are scheduled weekly (39), but there is variation in the duration of time between the last visit and delivery. Therefore, the precision of this measurement has inherent variability.

1.9 Research Questions

There are two primary research questions of this dissertation:

Research Question 1: Is maternal body weight, including both pre-pregnancy BMI and GWG, associated with pediatric health service utilization in the first twenty-four months following birth?

Research Question 2: Do adverse birth outcomes explain any increase in pediatric health service utilization by children born to mothers with below or above recommended pre-pregnancy BMI or GWG?

1.10 Research objectives

The overall aim of this dissertation was to investigate the role of maternal weight on pediatric health service utilization. Given the importance of both pre-pregnancy BMI and GWG, both exposures were investigated separately. Specifically, this dissertation had three specific objectives:

Objective 1: Determine if pre-pregnancy BMI (Chapter 2) and GWG (Chapter 3) is associated with health service utilization of Ontario children in the first 24 months following birth.

Objective 2: Investigate if increases in pediatric health service utilization associated with below or above optimal maternal weight is explained by indirect (mediational) effects of adverse birth outcomes, specifically small for gestational age (SGA) or preterm birth (PTB) (Chapter 4).

Objective 3: Develop a cost effectiveness framework addressing early intervention in pregnancy for women with above recommended maternal weight to mitigate the costs associated with lifetime health service use of the child (Chapter 5).

1.11 Dissertation Organization

This dissertation is composed of four substantive chapters, each formatted for publication. The conceptual framework guiding the thesis is presented in Figure 1.1. Maternal body weight has been shown to impact a variety of aspects of pediatric health, as previously discussed. While there is evidence that children born to mothers with both above and below recommended weight

have more health problems (8,9,11,12,40) it is unknown if this translates to greater health service utilization in a Canadian population. This is important because early intervention and promotion of healthy weight strategies have the potential to reduce the risk of non-ideal weight, which has outcomes on both the individual and their future offspring. Further, while previous studies tended to focus on the dichotomy of obesity versus normal weight, there is little research on both insufficient and excess weight.

Chapters 2 and 3 report studies investigating the impact of maternal pre-pregnancy BMI and GWG on health service use of children in Ontario (*Objective 1*). The hypothesis for these studies was that maternal body weight would be associated with health service utilization in the offspring. Specifically, for Chapter 2, it was hypothesized that there will be increased service use for those children whose mothers are overweight or living with obesity prior to pregnancy. For Chapter 3, it was hypothesized that there will be an increase in health service use for children born to mothers with above recommended GWG. It was further hypothesized that there will be an indiscriminate increase in health service use across all areas of care, and not limited to a specific health service for both the investigation of pre-pregnancy BMI and GWG.

Regarding Chapter 4, maternal weight may directly have an impact on health service utilization. However, it is also possible that there is an indirect effect of maternal weight, through the association of maternal weight with adverse birth outcomes, and the association of adverse birth outcomes with health service use. This study aimed to quantify the potential mediating role of adverse birth outcomes in the relationship between maternal weight and pediatric health service utilization (*Objective 2*). The hypotheses of this study were that: 1) infants born to mothers living with overweight or obesity will have a greater occurrence of adverse birth outcomes than those born to mothers with normal pre-pregnancy weight, 2) infants born to mothers with GWG higher

than the recommended range would be more likely to have adverse birth outcomes than those born to mothers with GWG within the recommended range and 3) any observed association of maternal pre-pregnancy weight or GWG with pediatric health care utilization would at least partially be explained by adverse birth outcomes.

Once health service utilization was ascertained in Chapter 2 and Chapter 3, and the role of mediating factors were ascertained in Chapter 4, from a health policy perspective we sought to investigate if the implementation of an intervention program has the potential to mitigate lifelong associated pediatric health service use associated with adverse events stemming from above recommended maternal weight (Chapter 5). A framework was developed that has the flexibility to be implemented with multiple intervention programs targeting maternal weight to ascertain the associated cost effectiveness for the implementation, thereby impacting health policy in the care of mothers with above recommended weight (*Objective 3*).

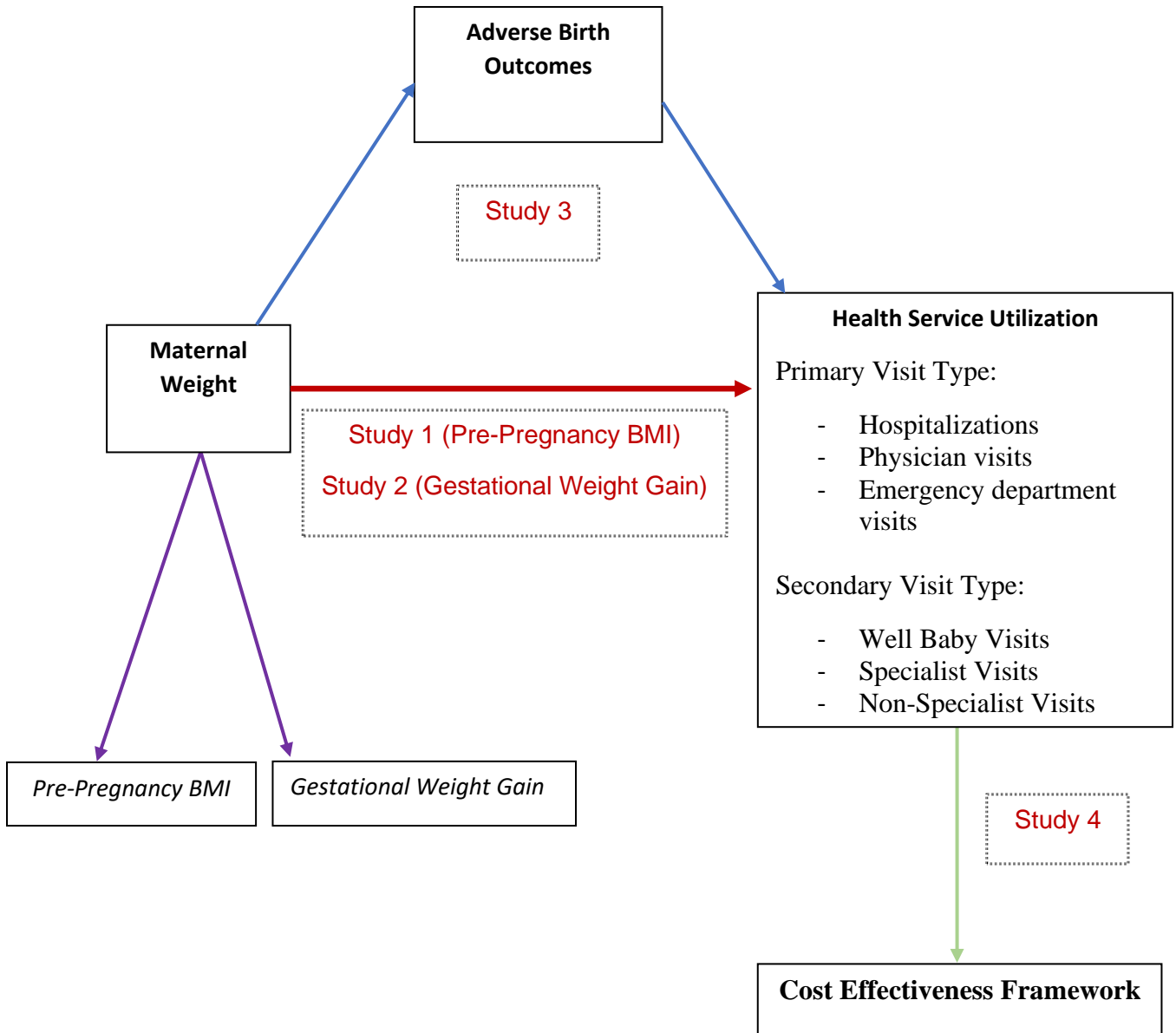
1.12 Summary

The findings of this study contribute to the epidemiological understanding of the impact of maternal weight on health service use of offspring and will inform clinical care decision making regarding appropriate surveillance and early intervention for at-risk children. This study could lead to a change in health policy and increase the uniformity of practice to improve the care provided to mothers and their children. Further, it provides valuable evidence on the long-term impact of maternal weight and assists with pre-pregnancy counselling of women living with obesity.

This dissertation provides a novel contribution to the study of perinatal epidemiology in the characterization of the effects of maternal BMI and GWG on child health service utilization in a

Canadian health care context thereby providing a nidus for Canadian policy change. This dissertation is a necessary contribution to the scientific literature and understanding of maternal weight as it extends the direct assessment of maternal to child health outcomes to assess the impact on overall health service utilization. It provides a comprehensive assessment of various aspects of health service utilization, but also an understanding of the indication for visits and an exploration of potential mediators to any associations. It investigates both below and above recommended maternal weight categories, providing a comprehensive overview of the impact. Finally, it provides an assessment at the population level within a Canadian context, thereby augmenting the applicability of the findings, as well as providing a framework to assess the cost effectiveness of an early intervention program targeting GWG, as explored within the final project of this dissertation. This comprehensive assessment of the impact of maternal weight on pediatric health service utilization provides important information on the contribution of a modifiable risk factor to long term child health service use.

Figure 1.1: Conceptual Framework



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Chapter 2

A retrospective cohort study investigating the impact of maternal pre-pregnancy body mass index on pediatric health service utilization

Authors: Lisa M. Currie, MSc ¹, Deshayne B. Fell, PhD ^{1,2,3}, Steven Hawken PhD ^{1,3,4}, Beth K. Potter PhD ^{1,3,4}, Doug Coyle PhD ^{1,4}, Shi Wu Wen PhD ^{1,4}, Mark Walker MD ^{1,4} and Laura Gaudet MD ^{1,5}

Affiliations:

1. School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada
2. Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada
3. ICES Ontario
4. Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
5. Kingston Health Sciences Centre, Kingston, Ontario, Canada

2.1 Preface

This published manuscript assessed the relationship between maternal pre-pregnancy BMI and pediatric health service utilization in the first 24 months following birth. It addressed the first research question of the dissertation: *is maternal body weight, including both pre-pregnancy BMI...associated with pediatric health service utilization and costs in the first twenty-four months following birth?* It also addressed the first objective of the dissertation, *to determine if GWG is associated with health service utilization of Ontario children in the first 24 months following birth.*

This project, alongside the project presented in Chapter 3, assessed the relationship between maternal weight and pediatric health service use, providing a foundation which was further explored in subsequent projects. LC, LG, and MW were involved in the conception of the project. LC, LG, MW, DF, SW, SH, and DC were involved in the planning of the project and carrying out of the project. LC, LG, DF, and SH were involved in the analysis and all authors were involved in the interpretation of the findings and contributed to the writing of the document. All authors reviewed and approved the final manuscript prior to submission.

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Ethics approval: Research ethics approval was provided by the Research Ethics Boards of the Ottawa Hospital Science Network (20180245-01 H, 2018-04-10), Children's Hospital of Eastern Ontario Research Institute (18/02 PE, 2018-02-02), the University of Ottawa (H-05-18-727, 2018-06-04), and the ICES Privacy Office (2018-05-08). These datasets were linked deterministically using unique encoded identifiers and analyzed at ICES.

2.2. Abstract

Objective: Maternal weight during pregnancy impacts the health of both mothers and their children. This project investigated how maternal pre-pregnancy body mass index (BMI) was associated with the child's health service utilization.

Methods: The study population consisted of all women who delivered a singleton, live infant in Ontario between 2012 and 2014, and was assembled from data contained in the provincial birth registry. Health service utilization over the first 24 months following birth was examined by linking data from the registry with other provincial health administrative databases housed at ICES.

Results: A total of 258 005 records were available for analysis. Following adjustment for baby's sex, maternal age, smoking status, neighbourhood income quintile, and pre-existing or gestational diabetes or hypertension, children born to mothers who were overweight or had obesity prior to pregnancy had increased rates of hospitalization (overweight adjusted incidence rate ratio [aIRR]: 1.09, 95% confidence interval [CI]: 1.06-1.12; obese aIRR: 1.20, 95% CI: 1.17-1.24), physician visits (overweight aIRR: 1.03, 95% CI: 1.03-1.04; obese aIRR: 1.05, 95% CI: 1.04-1.05) and emergency department (ED) visits (overweight aIRR: 1.12, 95% CI: 1.10-1.13; obese aIRR: 1.27, 95% CI: 1.25-1.29) compared to infants born to mothers with normal pre-pregnancy BMI.

Conclusion: Excess maternal weight was associated with greater pediatric health service utilization. Rates of health service utilization appeared to increase as maternal pre-pregnancy BMI increased. Future study of the reasons behind this increase may allow for early education, diagnosis, and intervention in this at-risk population.

Gestational Age Notation: Gestational age is reported as number of weeks gestation as reported within the BORN database, derived from medical records.

Key words: Pregnancy, Epidemiology, Health Services, Obesity

2.3 Introduction

Existing research provides strong evidence of health risks associated with obesity, including risks during pregnancy¹. Maternal pre-pregnancy weight has been associated with elevated risk of disease in the offspring, including diabetes, cardiovascular disease², congenital heart defects³, congenital anomalies⁴ and developmental delay in the child⁵. The impact of maternal obesity on pediatric physician visits and hospitalizations over an 18 year period was studied, showing slightly higher utilization in children born to mothers with pre-pregnancy obesity compared to children born to mothers with normal weight across all measured domains⁶. Further, children born to mothers with obesity had increased rates of hospitalization up to the age of five⁷, while children born to mothers with low pre-pregnancy BMI also have greater risk of hospitalization⁷. A US study identified higher overall service use for psychosocial or language issues among children born to mothers with low BMI by age six⁸. A Canadian study identified increased health service use of mental health services in children born to mothers with pre-pregnancy obesity compared to those born to mothers with normal weight⁹. These findings highlight the importance of understanding health service utilization in young children across all maternal weight categories.

The purpose of this study is to investigate child health service utilization in children born to mothers who were underweight, overweight, or had obesity prior to pregnancy across multiple health service areas. Understanding this relationship has the potential to better inform health care providers of the long-term impact of maternal weight on child health. The objective of this study was to investigate the relationship between pre-pregnancy maternal body mass index (BMI) and health service utilization among Ontario children in the first 24 months following birth.

2.4 Methods

2.4.1 Study design, population, and data sources

This population-based retrospective cohort study assessed health service utilization in the first 24 months of life for all live-born, singleton infants born in Ontario from April 1, 2012 to March 31, 2014, identified within the Better Outcomes Registry & Network (BORN) birth registry database (www.bornontario.com). BORN is a high quality, comprehensive registry with 100% coverage of all births within Ontario hospitals. It collects data from medical records and patient interviews, entered in a secure centralized electronic system. BORN data quality has been evaluated and demonstrated good agreement between the data elements and patient records, with 76% of categorical data elements demonstrating >90% agreement ⁹.

All data used in this study were accessed via ICES – an independent, non-profit research entity whose legal status under Ontario’s health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement (www.ices.on.ca). The BORN birth registry has been deterministically linked at ICES via maternal and newborn encrypted Ontario Health Insurance Plan (OHIP) numbers and other individual identifiers. Once linked, an ICES Key Number (IKN) was appended to allow each infant’s record to be linked with other health administrative databases. Episodes of hospitalization were acquired from the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD), which captures all hospitalizations recorded by Ontario institutions. OHIP billing records were used to quantify number of physician visits. Emergency department (ED) visits were captured from the CIHI National Ambulatory Care Reporting System (NACRS) database. The ICES Registered Persons Database (RPDB) provided information on follow-up and neighbourhood income quintile.

2.4.2 Exposure variable

The BORN birth registry was used to obtain information pertaining to maternal pre-pregnancy BMI. Maternal height and weight measures, captured at the first prenatal visit either via self-report or clinical measurement, were used to derive pre-pregnancy BMI in the BORN database using maternal weight (kilogram) divided by height squared (metre²). We categorized BMI according to World Health Organization (WHO) criteria ¹⁰, with underweight classified as BMI <18.5 kg/m², normal weight as 18.5-24.9 kg/m² (reference group), overweight as 25-29.9 kg/m², and obesity as ≥30 kg/m². We excluded records with maternal BMI values deemed to be implausible (i.e., pre-pregnancy BMI <10 kg/m² or >80 kg/m²) ¹¹, or with missing gestational age or birth weight. An algorithm was applied to identify and exclude records with implausible gestational age/birth weight combinations based on population normative values ^{12,13}.

2.4.3 Outcome measures

The outcomes were rates of hospitalizations, physician visits, and ED visits (15) among children during the first 24 months following birth, determined from the DAD, NACRS and OHIP databases, as previously described. We derived the total number of episodes of hospitalizations (excluding the birth event) that occurred over the two-year follow-up period. Physician visits included all billings for the same patient and same physician on a given calendar day to be part of a single visit, excluding physician visits associated only with lab billing codes. Separate analyses for well-baby visits (inclusive of visits coded for immunizations) and specialist (visits to any physician not identified as a general practitioner or pediatrician) and non-specialist visits were completed. For the total number of ED visits, we excluded NACRS records that were classified as non-urgent visits in the ED (e.g., children accessing a physician visit through the ED) or same day surgery visits. It is possible that a child would have multiple health service encounters for a single episode of care ¹⁵.

2.4.4 Statistical methods

Baseline characteristics are described of mothers and children using frequency distributions. Incidence rates of health service utilization during the first 24 months of life were calculated separately for each type of health service and reported as visits per 1000 person-years (PY). Incidence rate ratios (IRRs) for health service utilization across pre-pregnancy BMI categories were calculated to compare rates of infant health service utilization. Regression accounted for potential confounders ¹⁸ determined *a priori*, included infant sex, maternal age, smoking status during pregnancy, pre-existing medical conditions (i.e., diabetes, hypertension), gestational medical conditions (i.e., diabetes, hypertension) and neighbourhood income quintile. We employed negative binomial regression ^{16,17} to address overdispersion.

Given a high percentage of missing pre-pregnancy BMI data (20.9%), we decided *a priori* to use multiple imputation for the primary analyses¹⁹, using the Markov chain Monte Carlo method. Review of missing data patterns was completed prior to initiating the analyses to inform whether data could be considered missing at random. Twenty imputed datasets were generated from a model that included pre-pregnancy BMI as a continuous variable, all covariates and total number of health service visits^{20,21}. The mean of the estimate and the confidence intervals of the twenty imputed datasets generated from the *MI* procedure in SAS. Complete case analyses were completed as a secondary analysis to assess if there were meaningful differences in the two approaches.

Maternal weight was also stratified by deciles to further assess the impact of maternal weight without reliance on the WHO BMI categories. Rate differences were calculated by comparing maternal pre-pregnancy BMI decile relative to the first decile encompassing a normal BMI (reference BMI=20.61 kg/m²). These rate differences were plotted to demonstrate how frequency of offspring health service utilization changes across maternal BMI when compared to the reference.

We investigated the primary diagnoses from the health service visit to ascertain differences by maternal pre-pregnancy weight, stratified by age. Both the DAD and NACRS databases contain diagnosis codes classified by the International Classification of Disease version 10 (ICD-10) (<https://icd.who.int>). The top five diagnoses at the ICD category level are presented by categories of maternal weight.

All analyses were completed using SAS Enterprise Guide 7.1 (SAS Institute, Cary, North Carolina).

2.5 Results

258 833 birth records were identified in BORN from April 1, 2012 to March 31, 2014. Following exclusions, the final cohort included in the analysis consisted of 258 005 infants (Figure 1).

Characteristics of the study population are presented in Table 1. Mean maternal age was 30.5 years (SD: 5.41). The mean gestational age was 38.9 weeks (SD: 1.81) and mean birth weight was 3362.3 grams (SD: 547.9). A high proportion of records had missing data on pre-pregnancy BMI (20.9%). Among those with complete information, the median pre-pregnancy BMI was 23.9 kg/m² (mean: 25.5 kg/m², SD: 6.42).

Overall, children born to mothers with obesity experiencing a greater overall rate of hospitalizations compared to children born to mothers with normal pre-pregnancy BMI. This pattern was similarly observed in the overall rate of physician visits, with higher rates in children born to mothers who were underweight, overweight or had obesity. The rate of overall ED visits also was higher in children born to mothers who were overweight or had obesity prior to pregnancy (Table 2). Children born to underweight mothers experienced a lower overall rate of hospitalizations and ED visits compared to children born to mothers with normal pre-pregnancy BMI.

In adjusted analyses, children born to mothers who were underweight prior to pregnancy had a slightly higher rate of physician visits and lower rate of ED visits (compared to mothers with normal BMI. Children born to overweight mothers had a higher rate of hospitalizations, physician visits and ED visits compared to those born to mothers with normal BMI. Children born to mothers with obesity had an even further increased rate of hospitalizations, physician visits and ED visits (Table 2).

Compared to children born to mothers with normal BMI, children born to underweight mothers had a greater rate of non-specialist physician visits, while children born to overweight mothers had a higher rate of well-baby visits, specialist visits and non-specialist visits. Children born to mothers with obesity also had higher rates of well-baby visits, specialist visits and non-specialist physician visits (Table 3).

The plot of deciles for hospitalizations and physician visits suggests that, after adjustment, the rate difference increased as maternal pre-pregnancy BMI deviated from a normal weight status (< or > the second decile). The adjusted plot for pediatric ED visits suggested that rates increase compared to the reference value until approximately the eighth decile, then declined (Figure S1). Children born to mothers who were overweight or had obesity prior to pregnancy were more likely to be hospitalized for acute bronchiolitis compared to those born to normal weight mothers (Figures S2, S3, S4, S5, and S6). Most ED visits were attributed to acute upper respiratory infections, particularly for children 31-720 days old born to mothers who were overweight or had obesity prior to pregnancy (Figures S7, S8, S9, S10 and S11).

Complete case analyses that were completed as sensitivity analyses generated comparable results to those from the multiple imputation models (Table S1 and S2).

2.6 Discussion

Our results suggest that elevated maternal pre-pregnancy weight is associated with greater health service utilization in children in the first twenty-four following birth. The findings are corroborated by additional analyses of maternal weight by deciles. Our results are consistent with a previous study which found elevated health service utilization in children up to age 18 born to mothers who were overweight or had obesity ⁶. Results of supplementary analyses are suggestive that increased health service utilization associated with maternal pre-pregnancy weight may be attributable to increased visits associated with bronchitis and acute respiratory infections, which is consistent with previous findings ²³.

Our findings are suggestive of a dose response relationship – when pre-pregnancy maternal BMI increases, so does the rate of health service utilization. A dose response relationship in maternal weight and rate of congenital heart defects has previously been demonstrated ³, however, research to demonstrate a similar finding with respect to pediatric health service utilization has not yet been conducted. The increase in rate of specialist visits, as well as hospitalizations, which may be less sensitive to factors such as care-seeking behaviour and health care access, point to poorer health status among children born to mothers with excessive pre-pregnancy weight as an explanation for the findings.

A strength of this study is the unique ability to link maternal weight and height to pediatric health service utilization within the available datasets, given that maternal weight and height rarely appears in medical records. A key limitation was the high proportion of missing data on maternal pre-pregnancy BMI. The results of the analyses following multiple imputation are consistent with the findings presented for the complete case analyses, which aligns with previous studies ²². Given the nature of the data analysis, preterm/unwell infants would not have had the

same opportunity to access health services due to prolonged hospitalization at birth, potentially underestimating total health service utilization. Additionally, neither congenital anomalies nor NICU admissions were included as covariates in the analysis given the high proportion of missing data on anomalies within the dataset (98.07%) and that most children did not experience a NICU event (88.91%). It is likely that these variables would significantly impact health service utilization but is unable to be assessed given the missing data. Further, neither Caesarean section delivery nor breastfeeding were included as covariates, which may have impacted the findings given associations between these variables and both the exposure and outcome. Finally, the weight at the first prenatal visit, captured either via measurement or self report, was used as a proxy for pre-pregnancy BMI, and may be inaccurate as mothers may have already commenced pregnancy related weight gain.

The findings of this study have implications for the pre-conception care of women. The results suggest that maternal weight can impact a child's health service utilization. High pre-pregnancy BMI is not typically an acute event, and clinicians should consider this evidence to promote population level system changes that improve diet and physical activity to prevent high BMI. Improvements to the health of a population have long standing impacts²³. Early intervention and education have the potential to decrease health service utilization and can impact health service resources and expenditures²⁴, as well as long term health outcomes^{25,26} although this requires further investigation in light of recent evidence²⁷.

2.7 Conclusion

Maternal pre-pregnancy BMI was associated with health service utilization in the child in the first 24 months of life, with higher rates of health care use among children born to mothers considered overweight or had obesity, relative to those with normal pre-pregnancy BMI, in a

dose-dependent manner. This study highlights the importance of addressing maternal weight to potentially improve the health of children in the first years of life and reduce associated health service utilization.

2.8 Table and Figures

Table 1: Maternal and infant characteristics of the study population

Characteristics	N	%
All births	258005	100
Maternal age (years)		
<20	7012	2.7
20-24	29983	11.6
25-29	71571	27.7
30-34	92040	35.7
35-40	50852	19.7
≥41	6528	2.5
Missing	19	0
Smoking during pregnancy		
No	229007	88.7
Yes	21326	8.3
Missing	7672	3
Neighbourhood income quintile		
1 (lowest)	55701	21.6
2	51333	19.9
3	51866	20.1
4	54961	21.3
5 (highest)	41856	16.2
Missing	2288	0.9
Pre-pregnancy BMI (kg/m²)		
<18.5 (underweight)	10901	4.2
18.5-24.9 (normal)	108170	41.9
25-29.9 (overweight)	48141	18.7
≥30 (obese)	36950	14.3
Missing	53843	20.9
Infant sex		
Male	132231	51.3
Female	125629	48.7
Missing	145	0
Gestational age at birth (weeks)		
<37	15211	5.9
≥37	242794	94.1
Birth weight (grams)		
<2500	11762	4.6
≥2500	246243	95.4

Table 2: Incidence rates per 1000 person-years and incidence rate ratios (IRR) of health service utilization outcomes by maternal pre-pregnancy BMI

	Hospitalizations			Physician Visits			ED Visits		
	108.01			11524.17			803.87		
	Overall Incidence Rate								
	Incidence Rate	IRR (95% CI)		Incidence Rate	IRR (95% CI)		Incidence Rate	IRR (95% CI)	
		Unadjusted	Adjusted*		Unadjusted	Adjusted*		Unadjusted	Adjusted*
Underweight	100.70	0.98 (0.93-1.02)	0.96 (0.92-1.00)	11244.41	1.02 (1.01-1.03)	1.02 (1.02-1.03)	799.44	0.99 (0.97-1.01)	0.93 (0.91-0.95)
Normal weight (ref)	101.12	1.0	1.0	11190.27	1.0	1.0	752.22	1.0	1.0
Overweight	111.61	1.10 (1.07-1.13)	1.09 (1.06-1.12)	11501.29	1.04 (1.03-1.04)	1.03 (1.03-1.04)	842.82	1.10 (1.09-1.12)	1.12 (1.10-1.13)
Obese	125.73	1.23 (1.19-1.26)	1.20 (1.17-1.24)	11686.42	1.06 (1.06-1.07)	1.05 (1.04-1.05)	984.11	1.27 (1.26-1.29)	1.27 (1.25-1.29)

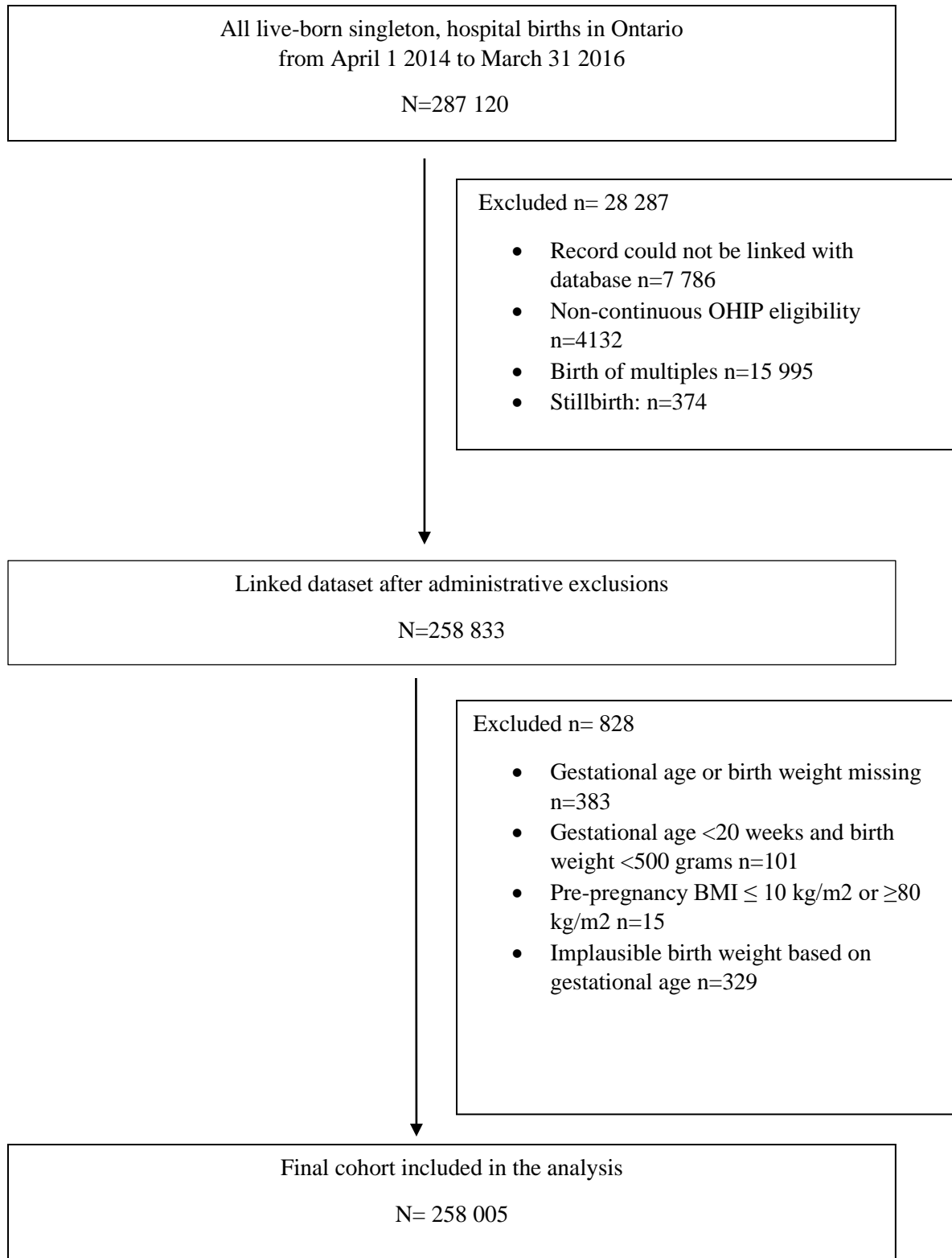
*Adjusted for infant sex, maternal age, smoking status, maternal pre-existing medical conditions (i.e., diabetes, hypertension), gestational medical conditions (i.e., diabetes, hypertension) and neighbourhood income quintile

Table 3: Incidence rates per 1000 person-years and incidence rate ratios (IRR) of well-baby visits, specialist, and non-specialist physician visits by maternal pre-pregnancy BMI.

		Well Baby Visits		Specialist Physician Visits		Non-Specialist Physician Visits			
Overall Incidence Rate		3837.17		1203.48		10320.63			
	Incidence Rate	IRR (95% CI)		Incidence Rate	IRR (95% CI)		Incidence Rate	IRR (95% CI)	
		Unadjusted	Adjusted*		Unadjusted	Adjusted*		Unadjusted	Adjusted*
Underweight	3750.58	1.00 (0.99-1.01)	1.01 (1.00-1.02)	1161.97	1.00 (0.97-1.02)	0.98 (0.96-1.01)	10082.45	1.02 (1.01-1.03)	1.03 (1.02-1.04)
Normal weight (ref)	3783.06	1.0	1.0	1144.95	1.0	1.0	10045.32	1.0	1.0
Overweight	3880.57	1.02 (1.02-1.03)	1.02 (1.01-1.03)	1270.20	1.11 (1.09-1.13)	1.11 (1.09-1.13)	10231.10	1.03 (1.02-1.03)	1.02 (1.01-1.03)
Obese	3834.92	1.02 (1.01-1.02)	1.01 (1.01-1.02)	1370.17	1.22 (1.20-1.24)	1.21 (1.19-1.23)	10316.26	1.04 (1.03-1.05)	1.01 (1.01-1.02)

*Adjusted for infant sex, maternal age, smoking status, maternal pre-existing medical conditions (i.e., diabetes, hypertension), gestational medical conditions (i.e., diabetes, hypertension) and neighbourhood income quintile

Figure 1: Study Flow Diagram



2.9 Declarations

Funding

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Acknowledgements

This study is based in part on data provided by Better Outcomes Registry and Network (“BORN”), part of the Children’s Hospital of Eastern Ontario. The interpretation and conclusions contained herein do not necessarily represent those of BORN Ontario. Part of this material are based on data and/or information compiled and provided by CIHI. However, the analyses, conclusions, opinions, and statements expressed in the material are those of the author(s) and not necessarily those of CIHI. This study was supported by a CIHR research grant awarded to Laura Gaudet (MFM 146444). ICES is supported by an annual grant from the Ontario Ministry of Health and Long-Term Care.

Disclosure of Interests

None of the authors in this study have any competing interests to disclose.

2.10 Supplemental Information

2.10.1 Missing data

Patterns of missingness were explored across several variables, including maternal smoking, infant sex, large for gestational age (>90th percentile), small for gestational age (<10th percentile), birth presentation, maternal age, birth weight, gestational age, infant death, or birth year. When data were missing for the maternal weight variable, they were also more likely to be missing for other variables. Otherwise, the characteristics across the identified variables were similar, suggesting that the missing pattern could be considered as ‘missing at random’. We also assessed whether specific institutions accounted for a high number of records with missing data. Even with omission of institutions with records having $\geq 90\%$ missing information on maternal pre-pregnancy weight, 16% of the overall cohort still had missing weight data. Therefore, deletion of institutions with a high amount of missing BMI data would not have an impact on the high proportion of missing BMI data in our study population. In summary, the results at both the individual and the institution level indicate no clear patterns to the missingness of data. In this situation, multiple imputation was deemed appropriate.

2.10.2 Supplemental Figures

Figure S1: Rate difference of maternal pre-pregnancy BMI by decile for pediatric health service utilization, adjusted for maternal age, maternal smoking status, infant sex, maternal pre-existing medical conditions (diabetes, hypertension), gestational medical conditions (diabetes, hypertension) and neighbourhood income quintile. A) hospitalizations; B) physician visits; C) ED visits; D) well baby physician visits; E) specialist physician visits; F) non-specialist physician visits

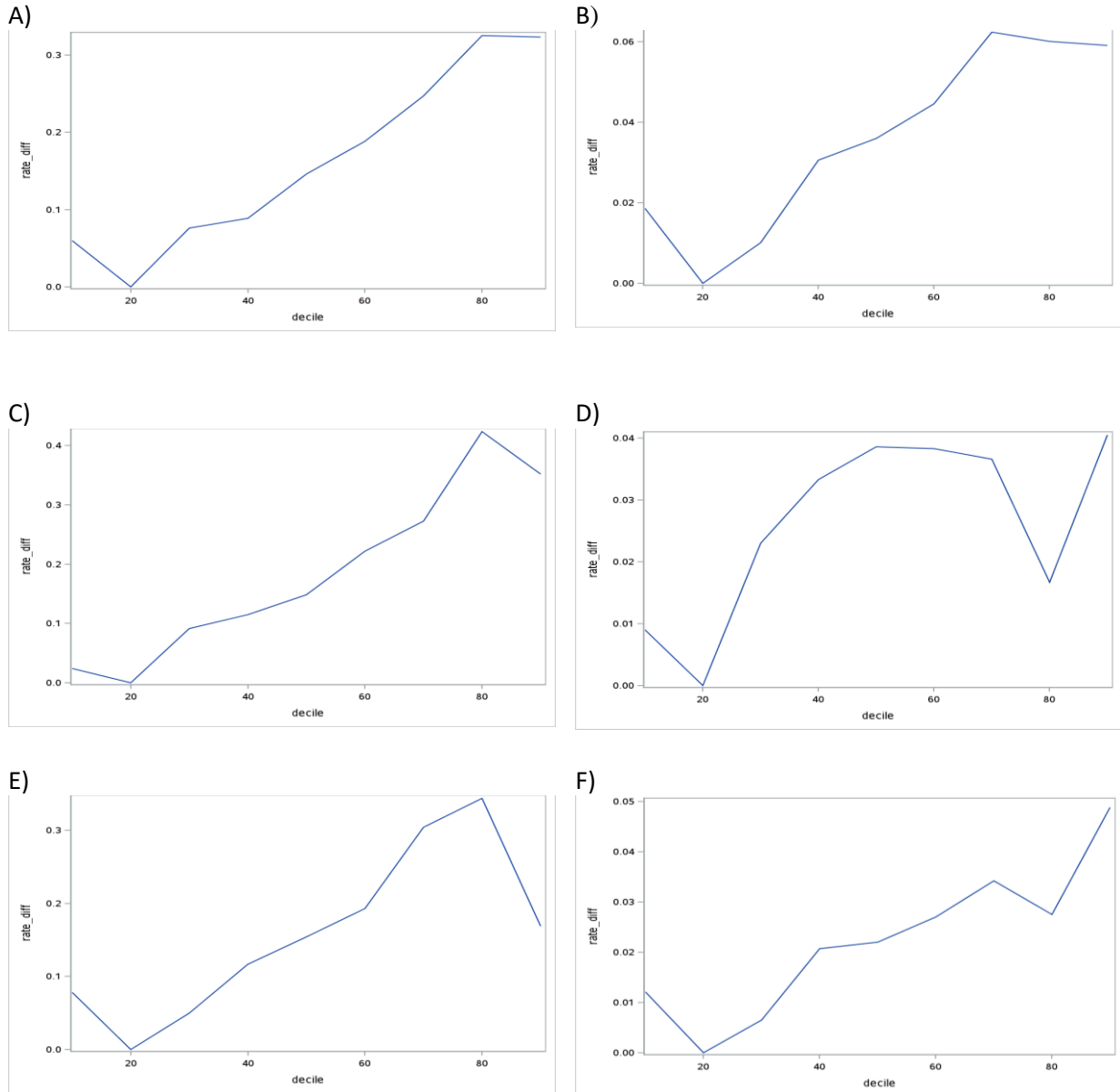


Figure S2: Most frequent diagnoses for hospitalizations by maternal pre-pregnancy BMI

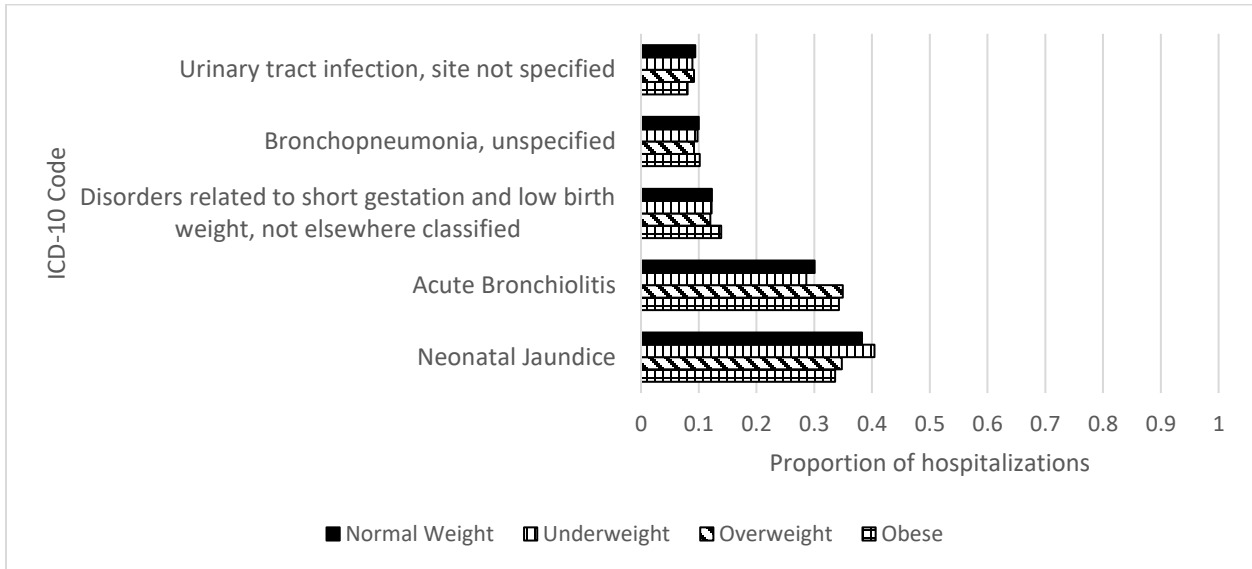


Figure S3: Most frequent diagnoses for hospitalizations by maternal pre-pregnancy BMI for children 0-30 days old

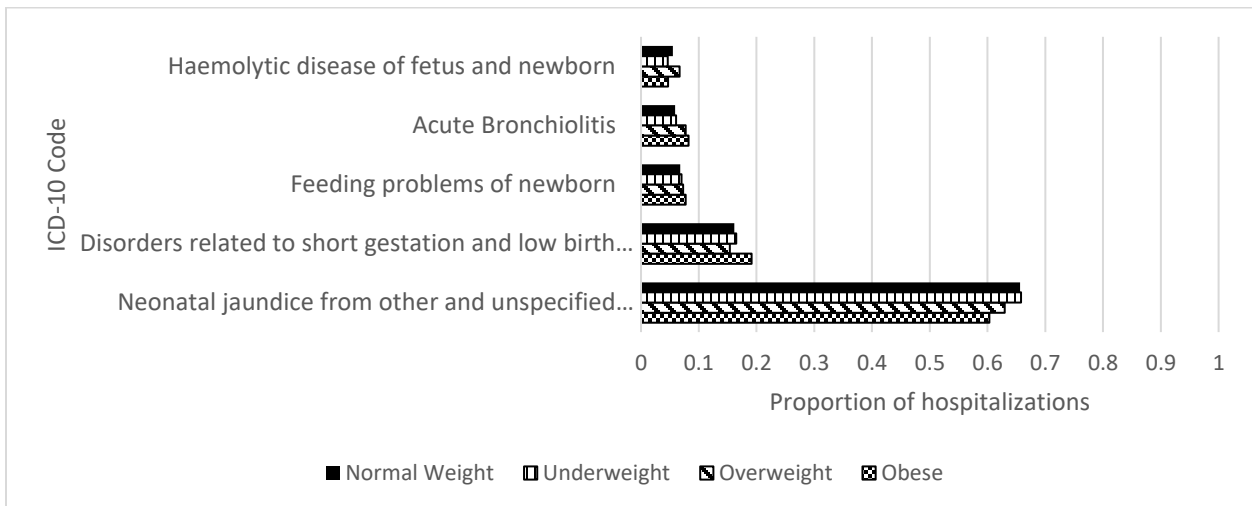


Figure S4: Most frequent diagnoses for hospitalizations by maternal pre-pregnancy BMI for children 31-180 days old

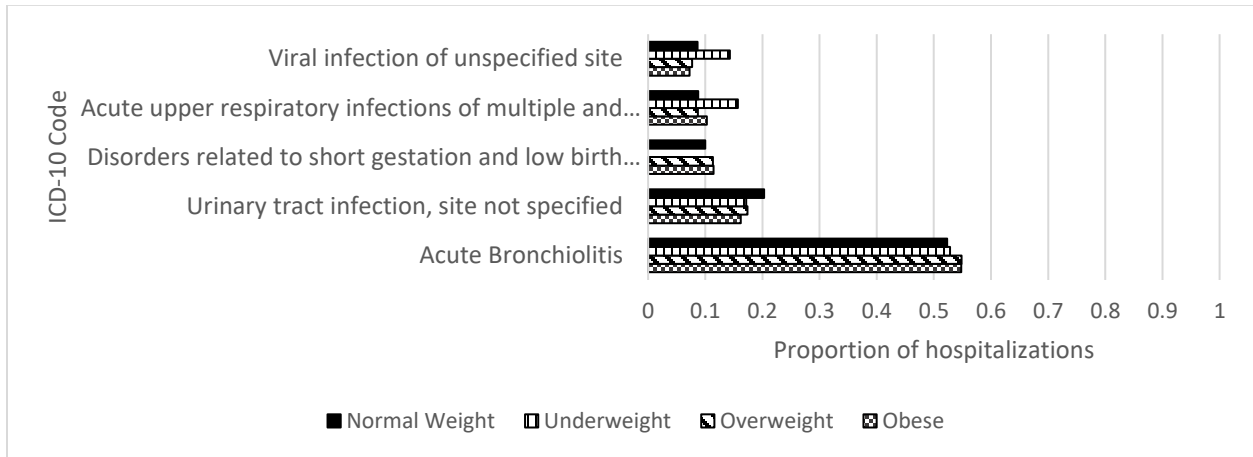


Figure S5: Most frequent diagnoses for hospitalizations by maternal pre-pregnancy BMI for children 181-365 days old

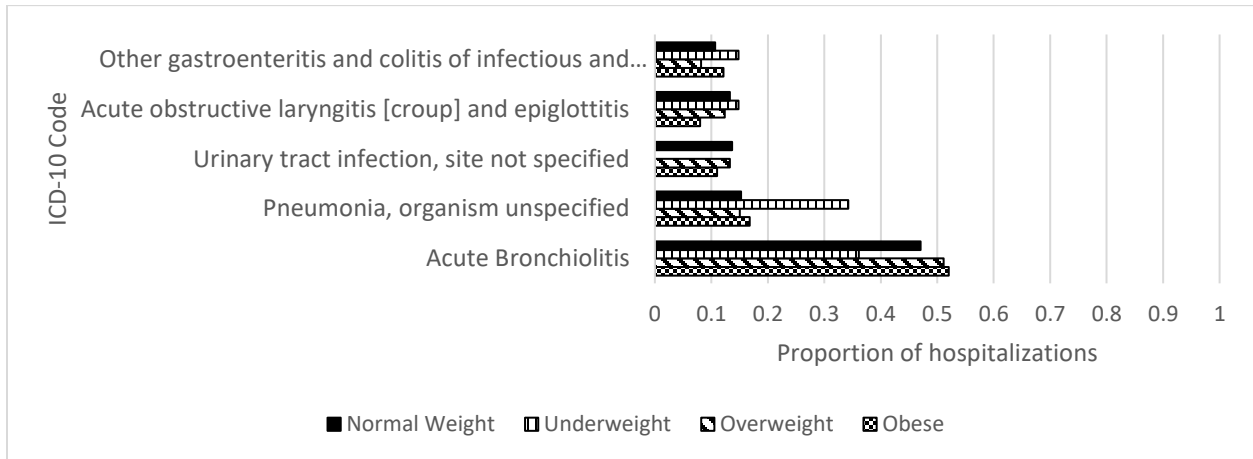


Figure S6: Most frequent diagnoses for hospitalizations by maternal pre-pregnancy BMI for children 366-720 days old

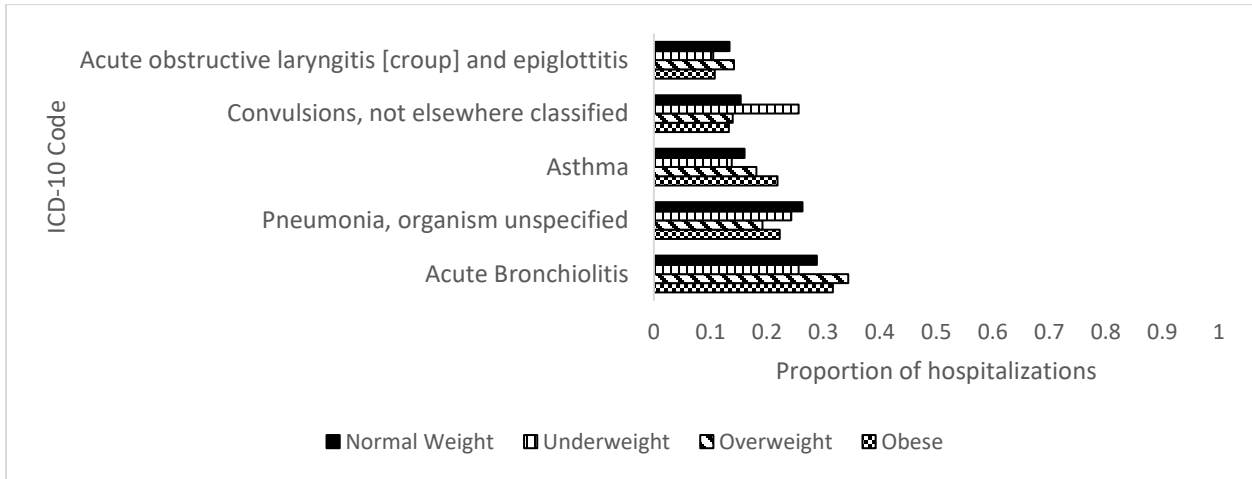


Figure S7: Most frequent diagnoses for ED visits by maternal pre-pregnancy BMI

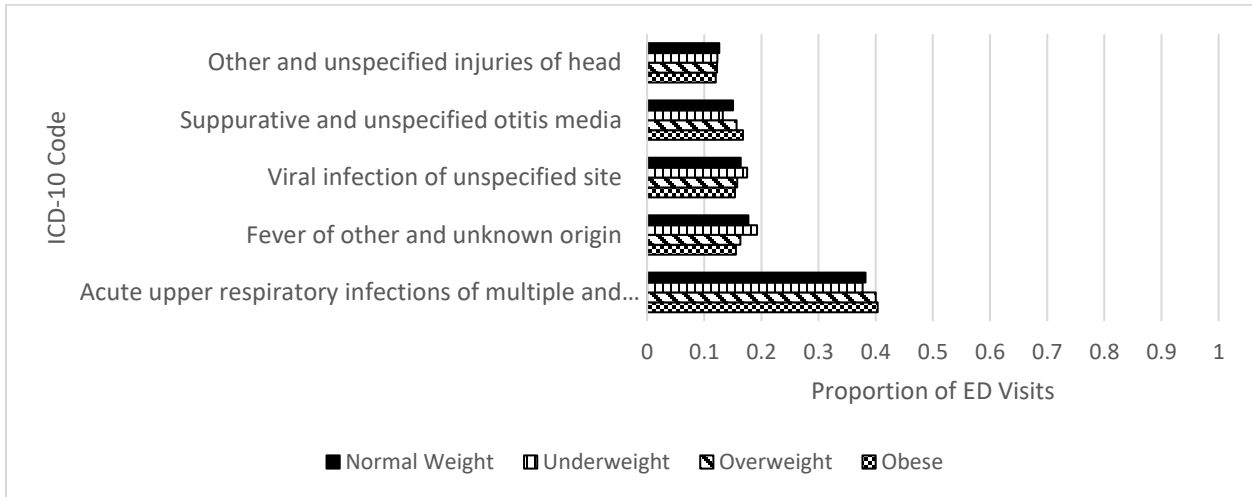


Figure S8: Most frequent diagnoses for ED visits by maternal pre-pregnancy BMI for children 0-30 days old

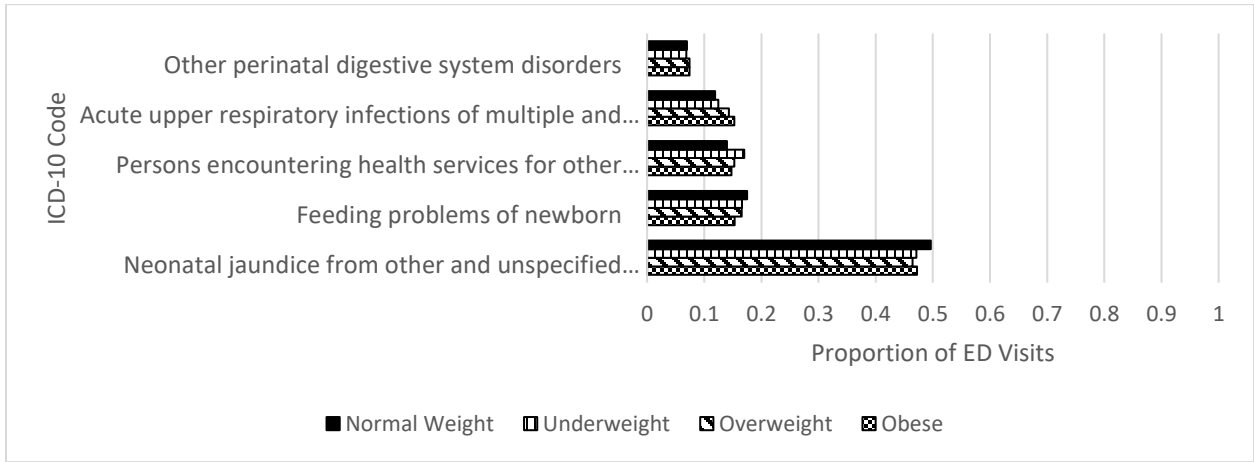


Figure S9: Most frequent diagnoses for ED visits by maternal pre-pregnancy BMI for children 31-180 days old

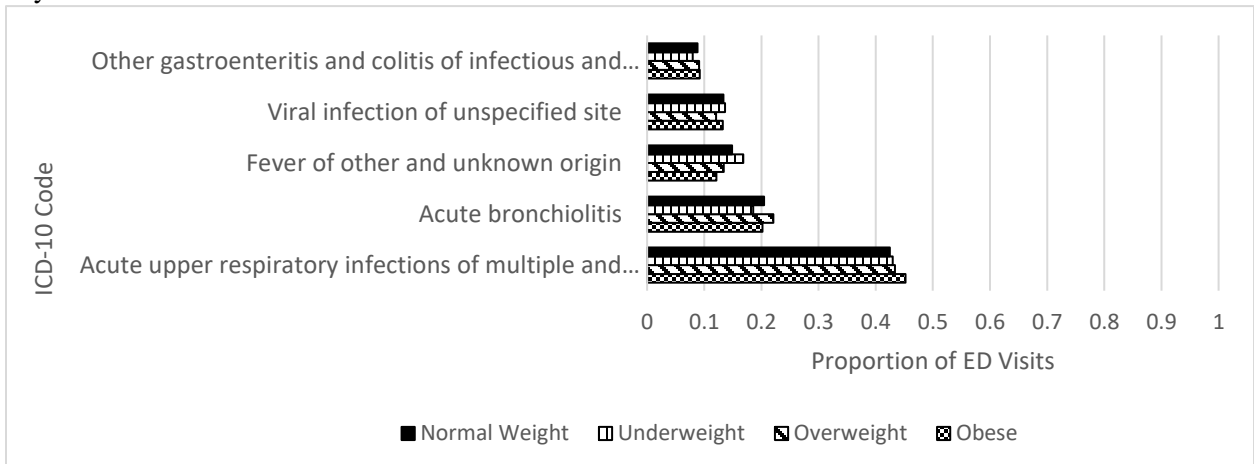


Figure S10: Most frequent diagnoses for ED visits by maternal pre-pregnancy BMI for children 181-365 days old

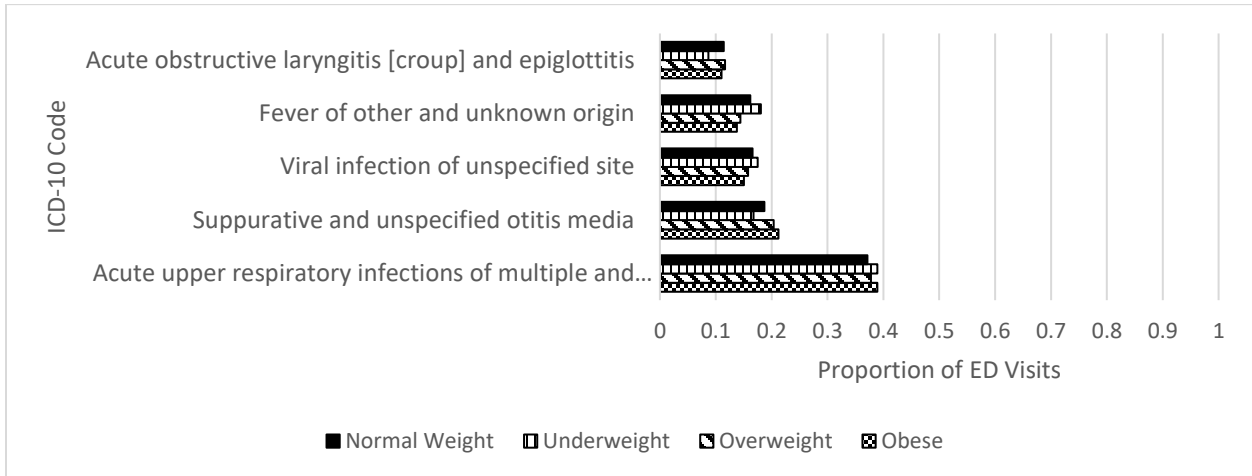


Figure S11: Most frequent diagnoses for ED visits by maternal pre-pregnancy BMI for children 366-720 days old

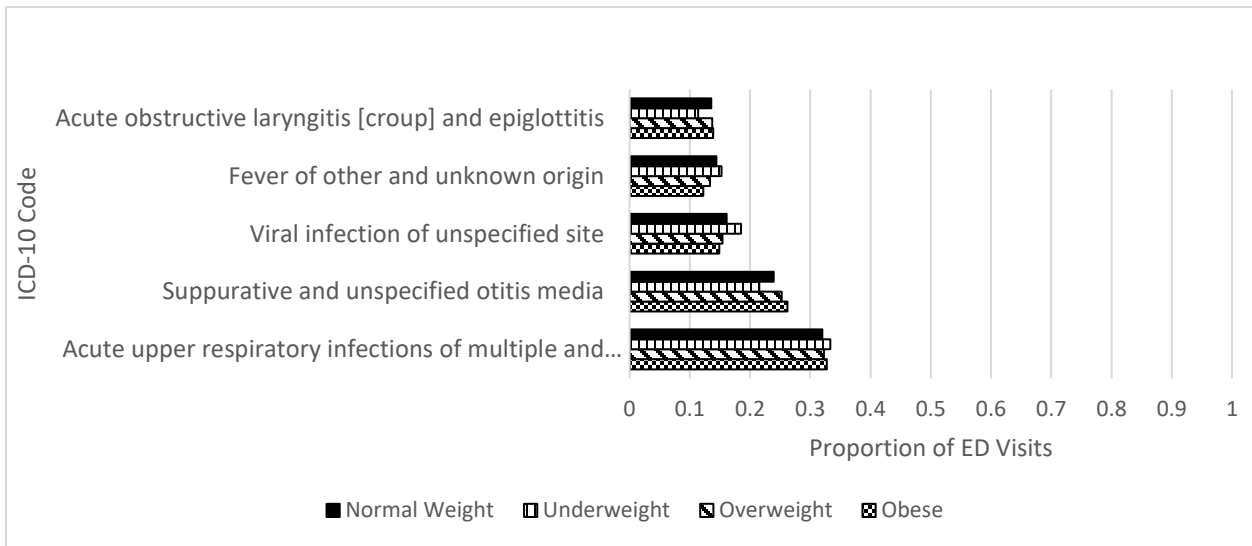


Table S1: Sensitivity Analyses of Factors by Missing BMI Data

Variable	BMI Standardized Difference	
Maternal smoking	Non-Smoker	-0.17
	Smoker	-0.05
	Missing	0.54
Gender	Male	0.00
	Female	0.00
	missing	0.03
LGA ($\geq 90^{\text{th}}$ percentile)	No	0.04
	Yes	-0.04
	missing	-0.01
SGA $\leq 10^{\text{th}}$ percentile)	No	-0.28
	Yes	0.02
	missing	0.45
Presentation	Breech	-0.02
	Cephalic	-0.57
	Transverse	0.00
	missing	0.65
Maternal Age (years)	<20	-0.01
	20-24	-0.03
	25-29	-0.05
	30-34	0.01
	35-40	0.05
	≥ 41	0.05
	missing	0.09
Birth weight (grams)	<2500	0.07
	≥ 2500	-0.07
Gestational Age (weeks)	<37	0.07
	≥ 37	-0.07
Time to Death	≤ 42	0.00
	42-365	0.00
	365-730	0.00
	missing	0.00

Birth Year		
	2012	0.14
	2013	-0.09
	2014	-0.07

Table S2: Incidence rates per 1000 person-years and incidence rate ratios (IRR) of health service utilization outcomes by maternal pre-pregnancy BMI, complete case analysis

	Hospitalizations			Physician Visits			ED Visits		
Overall Incidence Rate	108.01			11524.17			803.87		
	Incidence Rate	IRR (95% CI)		Incidence Rate	IRR (95% CI)		Incidence Rate	IRR (95% CI)	
		Unadjusted	Adjusted*		Unadjusted	Adjusted*		Unadjusted	Adjusted*
Underweight	100.70	1.00 (0.94-1.05)	0.96 (0.91-1.02)	11244.41	1.01 (1.00-1.02)	1.02 (1.01-1.03)	799.44	1.06 (1.03-1.09)	0.96 (0.93-0.99)
Normal weight (ref)	101.12	1.0	1.0	11190.27	1.0	1.0	752.22	1.0	1.0
Overweight	111.61	1.10 (1.07-1.14)	1.10 (1.06-1.13)	11501.29	1.03 (1.03-1.04)	1.03 (1.02-1.03)	842.82	1.12 (1.10-1.14)	1.13 (1.11-1.15)
Obese	125.73	1.24 (1.21-1.29)	1.22 (1.18-1.26)	11686.42	1.06 (1.05-1.06)	1.04 (1.04-1.05)	984.11	1.31 (1.29-1.33)	1.29 (1.27-1.31)

* Adjusted for maternal age, maternal smoking status, infant sex, maternal pre-existing medical conditions (diabetes, hypertension), gestational medical conditions (diabetes, hypertension) and neighbourhood income quintile.

A Retrospective Cohort Study Investigating the Impact of Maternal Pre-Pregnancy Body Mass Index on Pediatric Health Service Utilization



L. Currie

Lisa M. Currie, MSc;¹ Deshayne Fell, PhD;^{1,2,3} Steven Hawken, PhD;^{1,2,4}
Beth Potter, PhD;^{1,2,4} Doug Coyle, PhD;^{1,4} Shi Wu Wen, PhD;^{1,4} Mark Walker, MD;^{1,4}
Laura Gaudet, MD^{1,4,5,6}

¹School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON

²ICES Ontario

³Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada

⁴Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

⁵Kingston Health Sciences Centre, Kingston, Ontario, Canada

⁶Queen's University, Kingston, Ontario, Canada

ABSTRACT

Objective: Maternal weight during pregnancy impacts the health of both mother and baby. This project investigated associations between maternal pre-pregnancy body mass index (BMI) and the child's future health service utilization.

Methods: The study population comprised all women who delivered a singleton, live infant in Ontario between 2012 and 2014, and was assembled from data contained in the provincial birth registry. Health service utilization in the 24 months following birth was examined by linking data from the registry with other provincial health administrative databases housed at ICES.

Results: A total of 258 005 records were available for analysis. After adjusting for infant sex and maternal age, smoking status, income quintile, and pre-existing or gestational diabetes or hypertension, children born to mothers who were overweight or had obesity prior to

pregnancy had increased rates of hospitalization (overweight adjusted incidence rate ratio [aIRR] 1.09, 95% confidence interval [CI] 1.06–1.12; obesity aIRR 1.20, 95% CI 1.17–1.24), physician visits (overweight aIRR 1.03, 95% CI 1.03–1.04; obesity aIRR 1.05, 95% CI 1.04–1.05) and emergency department visits (overweight aIRR 1.12, 95% CI 1.10–1.13; obesity aIRR 1.27, 95% CI 1.25–1.29) than infants born to mothers with normal pre-pregnancy BMI.

Conclusion: Excess maternal weight was associated with greater pediatric health service utilization. Rates of health service utilization appeared to increase with maternal pre-pregnancy BMI. Future study of the reasons behind this increase may allow for early education, diagnosis, and intervention in this at-risk population.

RÉSUMÉ

Objectif : Le poids maternel pendant la grossesse a une influence sur la santé de la mère et du bébé. Ce projet a examiné l'association entre l'indice de masse corporelle (IMC) maternel avant la grossesse et l'utilisation future des services de santé par l'enfant.

Méthodologie : La population étudiée se compose de toutes les Ontariennes ayant accouché entre 2012 et 2014 d'un nourrisson vivant issu d'une grossesse monofœtale. Cette population a été constituée à partir des données du registre des naissances provincial. L'utilisation des services de santé dans les 24 mois suivant la naissance a été examinée en reliant les données du registre à celles d'autres bases de données administratives provinciales sur la santé hébergées à l'ICES.

Résultats : Au total, 258 005 dossiers ont été obtenus pour analyse. Après ajustement en fonction du sexe du nourrisson et de l'âge de la mère, du tabagisme, du quintile de revenu et du diabète ou de l'hypertension gestationnels ou préexistants, les enfants nés de mères en surpoids ou atteintes d'obésité avant la grossesse présentent une augmentation du taux d'hospitalisation (rapport du taux d'incidence ajusté pour le surpoids [RTIa] : 1,09; intervalle de confiance [IC] à 95 % : 1,06-1,12; RTIa pour l'obésité : 1,20; IC à 95 % : 1,17-1,24), des consultations chez le médecin (RTIa pour le

Keywords: pregnancy; epidemiology; health services; obesity

Corresponding author: Lisa Currie

Disclosures: This study is based in part on data provided by Better Outcomes Registry and Network ("BORN"), part of the Children's Hospital of Eastern Ontario. The interpretation and conclusions contained herein do not necessarily represent those of BORN Ontario. Part of this material are based on data and/or information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed in the material are those of the author(s) and not necessarily those of CIHI. This study was supported by a CIHR research grant awarded to Laura Gaudet (MFM 146444). ICES is supported by an annual grant from the Ontario Ministry of Health and Long-Term Care.

All authors have indicated they meet the journal's requirements for authorship.

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2.11 Citations

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Chapter 3

Relationship between gestational weight gain and health service utilization in early childhood: A retrospective cohort study

Authors: Lisa M. Currie, MSc ¹, Deshayne B. Fell, PhD ^{1,2,3}, Steven Hawken PhD ^{1,3,4}, Beth K. Potter PhD ^{1,3,4}, Doug Coyle PhD ^{1,4}, Shi Wu Wen PhD ^{1,4}, Mark Walker MD ^{1,4}, and Laura Gaudet MD ^{1,5}

Affiliations:

1. School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada
2. Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada
3. ICES Ontario
4. Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
5. Kingston Health Sciences Centre, Kingston, Ontario, Canada

3.1 Preface

This manuscript assessed the relationship between maternal GWG and pediatric health service utilization in the first 24 months following birth. It addressed the first research question of the dissertation: *is maternal body weight, including both pre-pregnancy BMI and GWG, associated with pediatric health service utilization and costs in the first twenty-four months following birth?* It also addressed the first objective of the dissertation, *to determine if GWG is associated with health service utilization of Ontario children in the first 24 months following birth.* This project, alongside the project presented in Chapter 2, were foundational for the dissertation, as it assessed the main relationship between maternal weight and pediatric health service use, which was further explored in subsequent projects. LC, LG, and MW were involved in the conception of the project. All authors were involved in the planning of the project. LC was responsible for project execution, and received guidance from LG, DF, and SH for the analysis. All authors were involved in the interpretation of the findings and contributed to the writing of the document. All authors reviewed and approved the final manuscript prior to submission.

Manuscript status: Pending submission as a brief communication to the *Journal of Obstetrics and Gynaecology Canada*

Ethics approval: Research ethics approval was provided by the Research Ethics Boards of the Ottawa Hospital Science Network (20180245-01 H, 2018-04-10), Children's Hospital of Eastern Ontario Research Institute (18/02 PE, 2018-02-02), the University of Ottawa (H-05-18-727, 2018-06-04), and the ICES Privacy Office (2018-05-08). These datasets were linked deterministically using unique encoded identifiers and analyzed at ICES.

3.2 Abstract

Gestational weight gain (GWG) outside recommended ranges can negatively impact both the mother and child. The long-term effects of below recommended or above recommended GWG on the child are unclear. This retrospective cohort study used a population-based birth registry to evaluate the impact of maternal GWG on pediatric health service use. The results suggest below recommended GWG in underweight women in particular is associated with an increased rate of hospitalizations and specialist visits in the first 24 months. Findings indicate that GWG may impact pediatric outcomes in ways that depend on pre-pregnancy BMI.

Key Words: Pregnancy, Epidemiology, Health Services, Gestational Weight Gain, Pediatrics

3.3 Introduction

Maternal pre-pregnancy obesity is associated with numerous health risks to the child, such as diabetes, cardiovascular disease (1) and developmental delay (2). A recent meta-analysis suggests that women with below recommended gestational weight gain (GWG) had a higher risk of neonatal complications, including small-for-gestational-age birth, preterm birth (3), low birth weight and failure to initiate breast feeding (4). However, the potential impact of GWG as it relates to pediatric health in the first years of life, is largely unknown. Research suggests that overweight or obesity during pregnancy is associated with increased hospitalizations, but GWG was not explored (5). The objective of this study was to investigate whether GWG is associated with rates of health service utilization of Ontario children in the first 24 months following birth. It was hypothesized that above recommended GWG would be associated with increased health service utilization.

3.4 Methods

This study extends earlier work (6). In brief, this population-based retrospective cohort study assessed health service utilization in the first 24 months after birth for all live-born, singleton infants born in Ontario from April 1, 2012 to March 31, 2014, identified using the Better Outcomes Registry & Network (BORN) birth registry database (7). All data used in this study were accessed via ICES - an independent, non-profit research entity whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement (www.ices.on.ca). The BORN birth registry has been linked deterministically at ICES via maternal and newborn encrypted unique Ontario Health Insurance Plan (OHIP) numbers and

other individual identifiers. Once linked, an ICES Key Number (IKN) was appended to allow each infant's record to be linked with other health administrative databases.

The exposure, GWG, was captured as a continuous measure within the BORN database calculated as the difference between weight at time of delivery and pre-pregnancy weight based on self report or measured at first prenatal visit. We used the GWG variable from BORN and then categorized continuous GWG according to Health Canada recommendations (8) as below recommended weight gain, recommended, or above recommended weight gain. An algorithm which provided an alternative measure GWG based on gestation length (personal communication, M Guo) was tested to determine the impact on classification of cases compared to the categorization derived directly from the continuous BORN variable. No differences were identified between the two methods, therefore the existing variable from BORN was utilized to categorize GWG for all analyses. GWG categories were analyzed in strata defined by maternal body mass index (BMI), for which World Health Organization categories were used (underweight, normal weight, overweight and obese).

Pediatric health service utilization included: hospitalizations, captured from the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD); physician visits (total visits, specialist visits, non-specialist visits and well-baby visits, determined from OHIP billing records); and emergency department (ED) visits, determined from the CIHI National Ambulatory Care Reporting System (NACRS) database. The ICES Registered Persons Database (RPDB) provided information on neighbourhood income quintile. Due to overdispersion, negative binomial regression was used to estimate incidence rate ratios (IRR) reflecting the association between GWG and rates of health services use. Models were adjusted for infant sex, maternal age, smoking status, maternal pre-existing medical conditions (i.e., diabetes,

hypertension), gestational medical conditions (i.e., diabetes, hypertension) and neighbourhood income quintile. Given a high percentage of missing GWG data (33.7%), we implemented multiple imputation using the *MI* procedure in SAS to generate the twenty datasets using the Markov chain Monte-Carlo method and took the mean of the estimate and the confidence intervals of the twenty imputed datasets. Complete case analyses were completed as a secondary analysis.

Research ethics approval was provided by the Research Ethics Boards of the Ottawa Hospital Science Network (20180245-01H, 2018-04-10), Children's Hospital of Eastern Ontario Research Institute (18/02PE, 2018-02-02), the University of Ottawa (H-05-18-727, 2018-06-04), and the ICES Privacy Office (2018-05-08).

3.5 Results

258 833 birth records were identified from April 1, 2012 to March 31, 2014. Following exclusions, the final analyzed cohort included 258,005 infants. Women who delivered a live born, singleton baby had a mean age of 30.5 years (SD: 5.41). Most babies were born at term (94%; mean gestational age: 38.87, SD: 1.81) with a mean birth weight of 3362.3 grams (SD: 547.94). The median pre-pregnancy BMI was 23.9 kg/m² (mean: 25.5 kg/m², SD: 6.42), and the median GWG was 14.0 kg (mean: 14.96 kg, SD: 13.29). Few infants in the cohort died before the end of the follow-up period (n=501, 0.23%).

Overall, the rate of hospitalizations was 108.01 per 1000 person-years (PY), the rate of physician visits was 11524.17 per 1000 PY and the rate of ED visits was 803.87 per 1000 PY during the first 24 months following birth. The overall rate of well baby visits was 3837.17 per 1000 PY, 1203.48 per 1000 PY for specialist visits and 10320.63 per 1000 for non-specialist visits.

Children born to mothers with below recommended GWG had increased physician visits and hospitalizations regardless of pre-pregnancy BMI category compared with children born to mothers with recommended GWG (Figure 1). This association was strongest among children born to mothers who were underweight prior to pregnancy: those who had below recommended GWG had increased rates of hospitalization (adjusted IRR [aIRR]: 1.31, 95% CI: 1.14, 1.51) and physician visits (aIRR: 1.14, 95% CI: 1.10, 1.17), compared to those born to underweight mothers with recommended GWG (Figure 1). Rates of specialist visits (aIRR: 1.27, 95% CI: 1.16, 1.38) and non-specialist visits (aIRR: 1.11, 95% CI: 1.08, 1.14) were also increased among infants born to underweight mothers with below recommended GWG, compared to infants born to underweight mothers with recommended GWG (Figure 2).

Children born to mothers who were overweight prior to pregnancy but had below recommended GWG had an increased incidence of hospitalizations (aIRR: 1.17, 95% CI: 1.08, 1.27) and physician visits [aIRR: 1.08, 95% CI: 1.06, 1.10; which included increases in specialist (aIRR: 1.27, 95% CI: 1.20, 1.33) and non-specialist visits (aIRR: 1.05, 95% CI: 1.04, 1.07)] and ED visits (aIRR: 1.07, 95% CI: 1.03, 1.11), but a slightly reduced rate of well-baby visits (aIRR: 0.96, 95% CI: 0.94, 0.98) relative to children born to mothers who were overweight but experienced recommended GWG. Children born to mothers who were obese prior to pregnancy and had below recommended GWG had a small increase in physician visits (aIRR: 1.07, 95% CI: 1.05, 1.09), compared with mothers who were obese but had recommended GWG. Complete case analyses that were completed as sensitivity analyses generated comparable results to those from the main analyses.

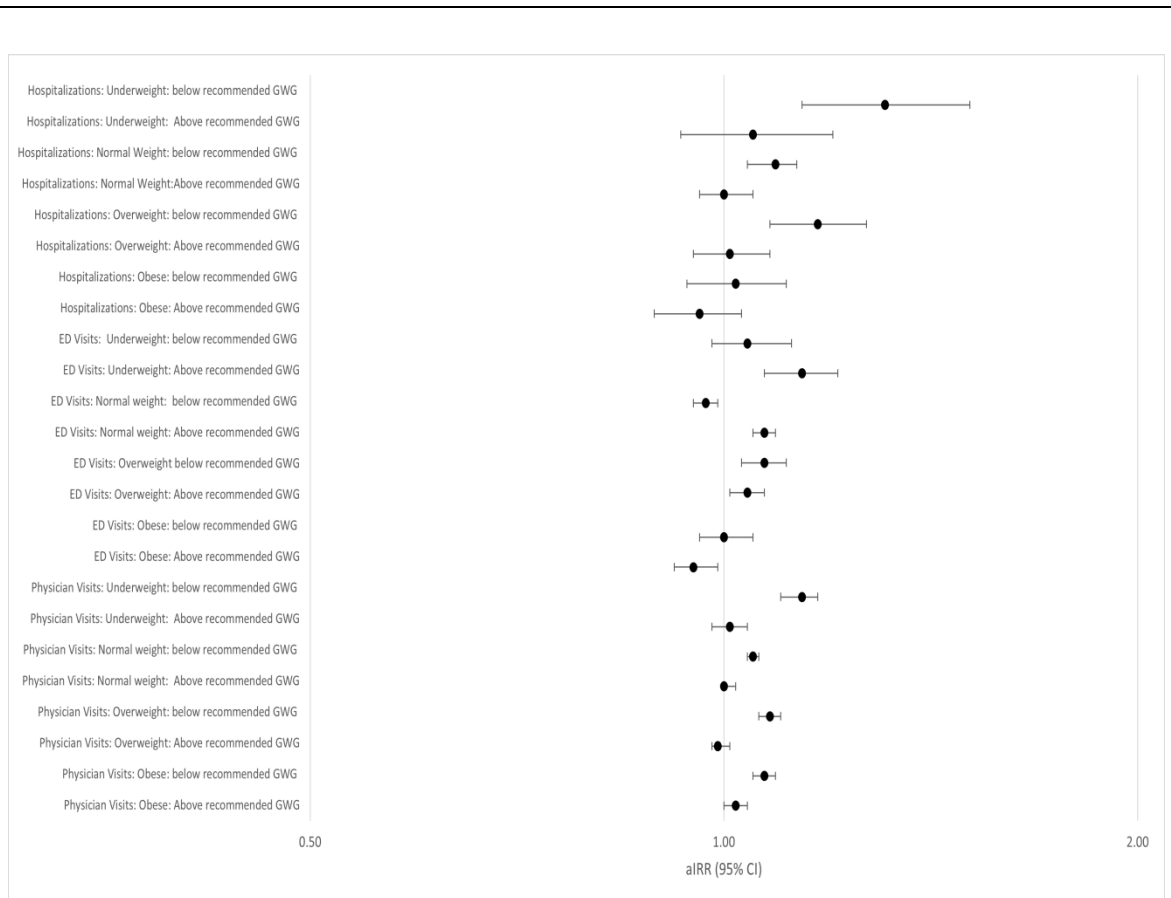
3.6 Discussion

We found small increases in rates of hospitalizations and physician visits in the first twenty-four months following birth of children born to mothers with below recommended GWG, regardless of maternal pre- pregnancy BMI. The largest relative increase in health service utilization was observed among children born to mothers who were underweight prior to pregnancy and had below recommended GWG, particularly for hospitalizations and specialist visits. There may be biological mechanisms at play in which some underweight mothers are unable to gain sufficient weight during pregnancy, perhaps due to insufficient diet quality (9), and therefore impacting the child's long term development (10). A strength of this study was the ability to link maternal GWG information to pediatric health service utilization. However, it is limited by the amount of missing data on GWG which may have introduced bias. There are also limitations to the maternal weight measurement, including when in pregnancy measurements were obtained and whether they were self reported, which could impact the accuracy of the exposure variable. While this study contributes to a more comprehensive understanding of the impact of GWG on long-term pediatric outcomes, further research is required to ascertain the impact of other factors that may be indirectly influencing this relationship.

3.7 Figures and Tables

Figure 1. Incidence rates per 1000 person years (PY), with unadjusted and adjusted incidence rate ratios (95% CI) demonstrating the association of below recommended or above recommended GWG relative to recommended GWG, stratified by pre-pregnancy BMI for hospitalizations, ED visits and physician visits.

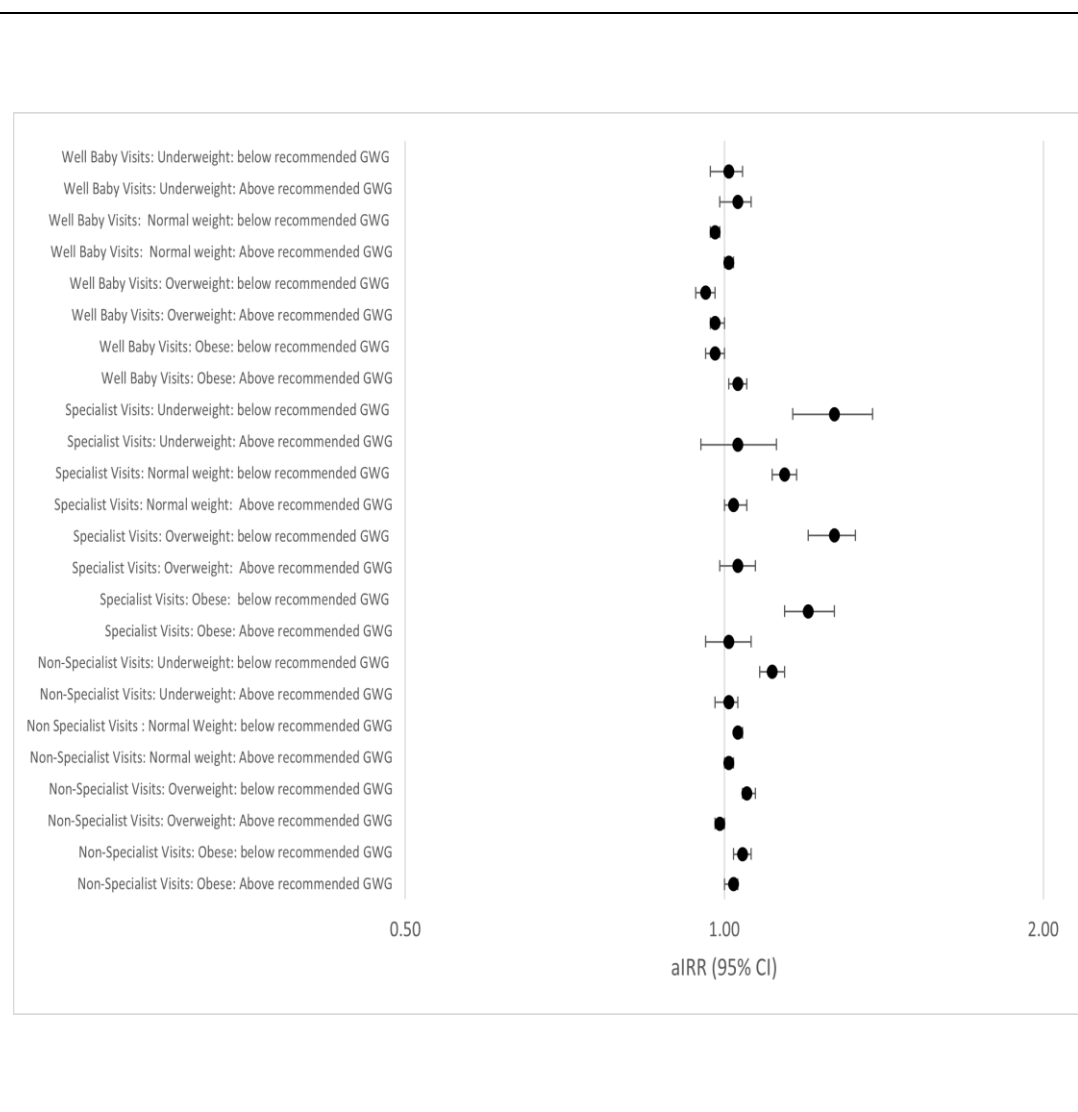
	IR /1000 PY	UA IRR (95% CI)	aIRR (95% CI)
Hospitalizations	108.01		
<i>Underweight</i>	100.70		
Below recommended GWG	116.50	1.32 (1.15,1.52)	1.31 (1.14,1.51)
Recommended GWG (ref)	88.97	1.00	1.00
Above recommended GWG	94.70	1.09 (0.96,1.24)	1.05 (0.93,1.20)
<i>Normal weight</i>	101.12		
Below recommended GWG	105.95	1.08 (1.04,1.13)	1.09 (1.04,1.13)
Recommended GWG (ref)	96.87	1.00	1.00
Above recommended GWG	98.03	1.02 (0.97,1.06)	1.00 (0.96,1.05)
<i>Overweight</i>	111.61		
Below recommended GWG	12.29	1.17(1.08,1.27)	1.17 (1.08,1.27)
Recommended GWG (ref)	106.07	1.00	1.00
Above recommended GWG	107.81	1.01 (0.95,1.08)	1.01 (0.95,1.08)
<i>Obese</i>	125.73		
Below recommended GWG	129.54	1.02 (0.94,1.11)	1.02 (0.94,1.11)
Recommended GWG (ref)	128.62	1.00	1.00
Above recommended GWG	122.51	0.96 (0.89,1.03)	0.96 (0.89,1.03)
ED Visits	803.87		
<i>Underweight</i>	799.44		
Below recommended GWG	776.36	1.05 (0.98,1.12)	1.04 (0.98,1.12)
Recommended GWG (ref)	729.22	1.00	1.00
Above recommended GWG	885.51	1.20 (1.13,1.27)	1.14 (1.07,1.21)
<i>Normal weight</i>	752.22		
Below recommended GWG	721.78	0.97 (0.95,0.99)	0.97 (0.95,0.99)
Recommended GWG (ref)	735.18	1.00	1.00
Above recommended GWG	832.85	1.11 (1.08,1.13)	1.07 (1.05,1.09)
<i>Overweight</i>	842.82		
Below recommended GWG	853.11	1.09 (1.05,1.13)	1.07 (1.03,1.11)
Recommended GWG (ref)	796.96	1.00	1.00
Above recommended GWG	854.72	1.06 (1.03,1.10)	1.04 (1.01,1.07)



<i>Obese</i>	984.11		
Below recommended GWG	1002.99	1.02 (0.97,1.06)	1.00 (0.96,1.05)
Recommended GWG (ref)	1000.83	1.00	1.00
Above recommended GWG	967.40	0.97 (0.94,1.00)	0.95 (0.92,0.99)
Physician Visits	11524.17		
<i>Underweight</i>	11244.41		
Below recommended GWG	11968.03	1.14 (1.11,1.18)	1.14 (1.10,1.17)
Recommended GWG (ref)	10841.54	1.00	1.00
Above recommended GWG	10850.76	1.01 (0.99,1.04)	1.01 (0.98,1.04)
<i>Normal weight</i>	11190.27		
Below recommended GWG	11509.00	1.05 (1.04-1.06)	1.05 (1.04-1.06)
Recommended GWG (ref)	10912.57	1.0	1.0
Above recommended GWG	10981.45	1.01 (1.00-1.02)	1.01 (1.00-1.02)
<i>Overweight</i>	11501.29		
Below recommended GWG	12270.59	1.08 (1.06-1.10)	1.08 (1.06-1.10)
Recommended GWG (ref)	11321.57	1.00	1.00
Above recommended GWG	11182.48	0.99 (0.98-1.01)	0.99 (0.98-1.01)
<i>Obese</i>	11686.42		
Below recommended GWG	12184.76	1.07 (1.04-1.09)	1.07 (1.05-1.09)
Recommended GWG (ref)	11379.30	1.00	1.00
Above recommended GWG	11483.30	1.02 (1.00-1.04)	1.02 (1.00-1.04)

Figure 2. Incidence rates per 1000 person years (PY), with unadjusted and adjusted incidence rate ratios (95% CI) demonstrating the association of below recommended or above recommended GWG relative to recommended GWG, stratified by pre-pregnancy BMI for well baby visits, specialist visits and non-specialist visits.

	IR /1000 PY	UA IRR (95% CI)	aIRR (95% CI)
Well Baby Visits	3837.17		
<i>Underweight</i>	3750.58		
Below recommended GWG	3673.41	1.01 (0.97,1.04)	1.01 (0.97,1.04)
Recommended GWG (ref)	3722.15	1.00	1.00
Above recommended GWG	3855.72	1.02 (0.99,1.05)	1.03 (0.99,1.06)
<i>Normal weight</i>	3783.06		
Below recommended GWG	3666.61	0.98 (0.97,0.99)	0.98 (0.97,0.99)
Recommended GWG (ref)	3828.85	1.00	1.00
Above recommended GWG	3936.94	1.01(1.00,1.02)	1.01 (1.00,1.02)
<i>Overweight</i>	3880.57		
Below recommended GWG	3718.96	0.96 (0.94,0.98)	0.96 (0.94,0.98)
Recommended GWG (ref)	3985.06	1.00	1.00
Above recommended GWG	3822.72	0.98 (0.96,0.99)	0.98 (0.97,1.00)
<i>Obese</i>	3834.92		
Below recommended GWG	3692.28	0.98 (0.95,1.00)	0.98 (0.96,1.00)
Recommended GWG (ref)	3785.20	1.00	1.00
Above recommended GWG	3936.82	1.03 (1.01,1.05)	1.03(1.01,1.05)
Specialist Visits	1203.48		
<i>Underweight</i>	1161.97		
Below recommended GWG	1353.93	1.29 (1.18,1.41)	1.27 (1.16,1.38)
Recommended GWG (ref)	1069.46	1.00	1.00
Above recommended GWG	1044.83	1.06 (0.98,1.14)	1.03 (0.95,1.12)
<i>Normal weight</i>	1144.95		
Below recommended GWG	1238.44	1.14 (1.10,1.17)	1.14 (1.11,1.17)
Recommended GWG (ref)	1069.03	1.00	1.00
Above recommended GWG	1076.00	1.03 (1.00,1.05)	1.02 (1.00, 1.05)
<i>Overweight</i>	1270.20		
Below recommended GWG	1532.49	1.26 (1.20,1.33)	1.27(1.20,1.33)
Recommended GWG (ref)	1146.13	1.00	1.00
Above recommended GWG	1184.86	1.04 (1.00,1.08)	1.03 (0.99,1.07)
<i>Obese</i>	1370.17		
Below recommended GWG	1564.86	1.21 (1.14,1.28)	1.20 (1.14,1.27)
Recommended GWG (ref)	1303.49	1.00	1.00
Above recommended GWG	1273.86	1.02 (0.97,1.07)	1.01 (0.96,1.06)



Non-Specialist Visits	10320.63		
<i>Underweight</i>	10082.45		
Below recommended GWG	10614.10	1.11 (1.08,1.14)	1.11 (1.08,1.14)
Recommended GWG (ref)	9772.08	1.00	1.00
Above recommended GWG	9805.93	1.01 (0.98,1.03)	1.01 (0.98,1.03)
<i>Normal weight</i>	10045.32		
Below recommended GWG	10270.56	1.04 (1.03,1.04)	1.03 (1.03,1.04)
Recommended GWG (ref)	9843.54	1.00	1.00
Above recommended GWG	9905.45	1.01 (1.00,1.02)	1.01 (1.00,1.02)
<i>Overweight</i>	10231.10		
Below recommended GWG	10738.10	1.05 (1.04,1.07)	1.05 (1.04,1.07)
Recommended GWG (ref)	10175.44	1.00	1.00
Above recommended GWG	9997.63	0.99 (0.98,1.00)	0.99 (0.98,1.00)
<i>Obese</i>	10316.26		
Below recommended GWG	10619.90	1.04 (1.02,1.06)	1.04 (1.02,1.06)
Recommended GWG (ref)	10075.81	1.00	1.00
Above recommended GWG	10209.44	1.02 (1.00,1.03)	1.02 (1.00,1.03)

3.8 Declarations

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Disclosure of Interests

None of the authors in this study have any competing interests to disclose.

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Chapter 4

Association Between Maternal Weight and Pediatric Health Service Utilization: Mediating Role of Adverse Birth Outcomes

Authors: Lisa M. Currie¹, Hilary K. Brown^{2,3}, Deshayne B. Fell^{1,2,4}, Beth K. Potter^{1,5}, Steven Hawken^{1,2,5}, Doug Coyle^{1,5}, Shi Wu Wen^{1,5}, Mark Walker^{1,5} and Laura Gaudet^{1,6,7}

Affiliations:

1. School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada
2. ICES Ontario
3. University of Toronto, Toronto, Ontario, Canada
4. Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada
5. Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
6. Kingston Health Sciences Centre, Kingston, Ontario, Canada
7. Queen's University, Kingston, Ontario, Canada

4.1 Preface

This manuscript assessed the separate mediating roles of two common and relevant adverse birth outcomes, small for gestational age and preterm birth, in the relationship between maternal weight and pediatric health service utilization. The relationship of these adverse birth outcomes with both the exposure (maternal weight) and outcome (pediatric health service use) have previously been documented. Further, as illustrated in Chapter 2 and Chapter 3, elevated maternal weight is associated with increased pediatric health service use. This study aimed to determine if the relationship may be attributed at least in part to adverse birth outcomes, assessed using mediation analysis. It addressed the second research question of the dissertation: *do adverse birth outcomes explain any increase in pediatric health service utilization by children born to mothers with below or above recommended pre-pregnancy BMI or GWG?*

It also addressed the second objective of the dissertation: *Investigate if an increase in pediatric health service utilization associated with below or above optimal maternal weight is explained by indirect (mediational) effects of adverse birth outcomes.* LC, LG, MW and HB were involved in the conception of the project. All authors were involved in the planning of the project and LC and HB were involved in project execution, with assistance from DF and BP. LC and HB were involved in the analysis and all authors contributed to the interpretation of the findings and writing of the document. All authors reviewed and approved the final manuscript prior to submission.

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Ethics approval: Research ethics approval was provided by the Research Ethics Boards of the Ottawa Hospital Science Network (20180245-01 H, 2018-04-10), Children's Hospital of Eastern Ontario Research Institute (18/02 PE, 2018-02-02), the University of Ottawa (H-05-18-727,

2018-06-04), and the ICES Privacy Office (2018-05-08). These datasets were linked deterministically using unique encoded identifiers and analyzed at ICES.

4.2 Abstract

Objective: Maternal pre-pregnancy body mass index (BMI) and gestational weight gain (GWG) above or below recommendations have been associated with increased pediatric health service utilization as well as increased risk of adverse birth outcomes. This study aimed to assess if small for gestational age (SGA) or preterm birth (PTB) partially explain the association between maternal weight and pediatric health service utilization.

Methods: The study population consisted of all women who delivered a singleton, live infant in Ontario, Canada, between 2012 and 2014. Health service utilization, defined as hospitalization, emergency department use or physician visit, over the first 24 months following birth was examined by linking data from the provincial birth registry with other provincial health administrative databases. The mediating roles of PTB and SGA were assessed using the Baron-Kenny method and causal mediation analysis.

Results: A total of 204162 infants were included in the analysis of maternal pre-pregnancy BMI and 171127 infants were included in the GWG analysis. The magnitude of association between maternal BMI and pediatric health service utilization was relatively small, impacting the ability to estimate the indirect effect of maternal BMI through adverse birth outcomes. Upon analysis using the Baron-Kenny method and causal mediation, PTB (56.74%) and SGA (6.83%) appeared to be contributing factors to increased hospitalizations in children born to mothers with below recommended GWG due to the percentage of the relationship mediated by these variables.

Conclusion: Pediatric hospitalizations are slightly attributable to PTB and SGA in children born to mothers with below recommended GWG, given that the magnitude of the association between maternal weight and health service utilization was small. However, maternal weight also appears to be related to increased pediatric health service utilization independent of PTB and SGA.

4.3 Introduction

Elevated maternal pre-pregnancy body mass index (BMI) and gestational weight gain (GWG) outside of the recommended range are associated with adverse birth outcomes, including small for gestational age (SGA) and preterm birth (PTB) (1,2). SGA and PTB are associated with numerous adverse health outcomes in the child, including delayed growth, motor and cognitive impairment (3–5). In a previous study, we observed that maternal pre-pregnancy BMI was associated with increased health service utilization in the child in the first 24 months of life, with higher rates of health care use among children born to mothers considered overweight or obese, relative to those with normal pre-pregnancy BMI, in a dose-dependent manner (6). Further, GWG outside the recommended range for BMI, particularly below recommended GWG, was associated with increased pediatric health service utilization, regardless of maternal pre-pregnancy BMI (7).

It is possible that any association between maternal weight and pediatric health outcomes may be partly explained by adverse birth outcomes. Cameron et al. previously investigated the relationship between maternal pre-pregnancy BMI and child hospital admissions and noted that birth weight and gestational age were on the causal pathway of this relationship (1). We aimed to quantify the potential mediating role of adverse birth outcomes in the relationship between maternal weight and pediatric health service utilization in the first 24 months of life. We hypothesized any observed increase in pediatric health care utilization associated with pre-pregnancy overweight/obesity or with GWG outside the recommended range would be at least partially mediated by the increased risk of adverse birth outcomes in infants born to women with below or above recommended pre-pregnancy BMI and GWG.

4.4 Methodology

4.4.1 Study design, population, and data sources

This population-based retrospective cohort study assessed health service utilization in the first 24 months of life for all live-born, singleton infants born in Ontario from April 1, 2012 to March 31, 2014, identified within the Better Outcomes Registry & Network (BORN) birth registry database (www.bornontario.com). BORN is a high-quality, comprehensive registry with 100% coverage of all births in Ontario. It collects data from medical records and patient interviews, which are then entered in a secure centralized electronic system. BORN data quality has been evaluated and demonstrated good agreement between the data elements and patient records, with 76% of categorical data elements demonstrating >90% agreement (8).

All data used in this study were accessed via ICES, an independent, non-profit research entity whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement (www.ices.on.ca). Datasets were linked using unique encoded identifiers and analyzed at ICES. The BORN birth registry has been linked deterministically at ICES via maternal and newborn encrypted Ontario Health Insurance Plan (OHIP) numbers and other individual identifiers. Once linked, an ICES Key Number (IKN) was appended to allow each infant's record to be linked with other health administrative databases. Episodes of hospitalization were acquired from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), which captures all hospitalizations recorded by Ontario institutions. OHIP billing records were used to quantify number of physician visits. Emergency department (ED) visits were captured from the CIHI National Ambulatory Care Reporting

System (NACRS) database. The ICES Registered Persons Database (RPDB) provided information on death and neighbourhood income quintile.

4.4.2 Exposure variable

The BORN registry was used to obtain information pertaining to maternal pre-pregnancy BMI. Maternal height and weight measures, captured at the first prenatal visit either via self-report or clinical measurement, were used to derive pre-pregnancy BMI in the BORN database using maternal weight (kilograms) divided by height squared (metres²). We categorized BMI according to World Health Organization (WHO) criteria (9), with underweight classified as BMI <18.5 kg/m², normal weight as 18.5-24.9 kg/m², overweight as 25-29.9 kg/m², and obese as ≥30 kg/m². We excluded records with maternal BMI values deemed to be implausible (i.e., pre-pregnancy BMI <10 kg/m² or >80 kg/m²) (10). Gestational weight gain (GWG) was captured as a continuous measure within the BORN database based on maternal pre-pregnancy weight subtracted from maternal weight at delivery. We categorized GWG as below recommended (below recommended weight gain), recommended, or above recommended (above recommended weight gain), based on Health Canada recommendations (11). We did not adjust for gestational length, as previous analyses within this cohort demonstrated that it did not impact results.

4.4.3 Outcome measures

The outcomes were measures of pediatric health service utilization, including rates of hospitalizations, ED visits, and physician visits (12) in children during the first 24 months following birth, assessed using data from the DAD, NACRS and OHIP databases, respectively. We derived the total number of hospitalization episodes (excluding the birth hospitalization) that

occurred over the two-year follow-up period, which is inclusive of any hospitalization regardless of duration, but did not include day surgery visits. For the total number of ED visits, we did not count those records in NACRS that were classified as non-urgent visits in the ED (e.g., children accessing a routine physician visit through the ED) or same day surgery visits. It is possible that a child would have multiple health service encounters for a single episode of care (13). For physician visits, we considered all billings for the same patient on a given calendar day with the same physician to be part of a single visit since the OHIP database is organized by billing codes rather than discrete visits (i.e., there may be more than one billing associated with a single encounter between patient and physician). We also excluded physician visits associated only with lab billing codes from the total count of physician visits.

4.4.4 Covariates

Potential confounders of the relationship between maternal pre-pregnancy BMI and infant health service utilization (14) were identified *a priori* and included infant sex, maternal age, maternal smoking status, pre-existing maternal medical conditions (i.e., diabetes, hypertension), and neighbourhood income quintile. The same covariates were used for the GWG analysis.

4.4.5 Mediators

The following mediators were included in the analysis: gestational age <37 weeks (PTB) and SGA (<10th percentile), informed by previous research (1). We excluded all records with missing gestational age or birth weight. An algorithm was applied to identify and exclude records with implausible gestational age/birth weight combinations based on population normative values greater or less than five standard deviations from this value (15,16).

4.4.6 Statistical Analyses

We first described baseline characteristics of mothers and children using frequency distributions. Rates of health service utilization during the first 24 months of life were calculated separately for each type of health service. The total number of visits was divided by the total person-time of follow-up and reported as visits per 1000 person-years.

To compare rates of infant health service utilization by maternal pre-pregnancy BMI and by GWG, we first reported unadjusted incidence rate ratios (IRRs) for health service utilization across BMI/GWG categories. We then used multivariable regression analysis to adjust for potential confounders. Due to over-dispersion, we used negative binomial regression (17) in two separate models (one for pre-pregnancy BMI and one for GWG). (8,18). A graphical representation of the mediation assessment of the relationship between the exposures and pediatric health service utilization is presented in Figure 1.

4.4.7 Mediation Analysis

The Baron-Kenny approach was used to identify potential mediation. The possible mediation of the relationship between maternal pre-pregnancy BMI or GWG (separately) and pediatric health service utilization, by PTB and small for gestational age (19), was assessed. This four-step approach included: step 1. the IRR for the exposure–outcome relationship (as described above); step 2. the IRR for the relationship of the exposure to the mediators; step 3. the IRR for the relationship of the mediators to the outcome; step 4. the IRRs for the relationship of the exposure and mediators to the outcome.

In this mediation analysis approach, each step must demonstrate a significant relationship (either positive or negative) in order to proceed to the next step (19). However, no formal criterion has been established as best practice for determining cut points for progression through each step, beyond the need for a significant relationship. A conservative criterion of $0.90 > \text{adjusted IRR}$

[aIRR] <1.10 was chosen for this analysis to identify results with effect sizes small enough to be considered non-meaningful. A relationship was removed from subsequent steps when it did not meet this criterion for mediation (Figures 3 and 4).

SAS PROC CAUSALMED was used to ascertain the total, natural direct, and natural indirect effects to estimate the effect decomposition (20) and percent mediated for each relationship of maternal weight to outcome, addressing each mediator independently (21). All analyses were completed using SAS Enterprise Guide 7.1 (SAS Institute, Cary, North Carolina).

4.5 Results

258833 birth records were identified in BORN from April 1, 2012 to March 31, 2014. Following exclusions (Figure 2), 258005 infants were eligible for inclusion in the analysis. Of these records, there were 53843 with missing BMI data. As only complete cases were analyzed in this study, 204162 records were included in the analysis of maternal pre-pregnancy BMI. There were 86878 records with missing GWG information. Therefore, 171127 records were included in the GWG analysis.

Characteristics of the entire study population are presented in Table 1 and stratified by maternal pre-pregnancy BMI (Supplemental Table 1A) and GWG (Supplemental Table 1B). Overall mean maternal age was 30.5 years (SD: 5.41). The mean gestational age at birth was 38.9 weeks (SD: 1.81) and mean birth weight was 3362.3 grams (SD: 547.9). As described above, a high proportion of records had missing data for pre-pregnancy BMI (20.9%) and GWG (33.7%). We reviewed missing data patterns prior to analyses to compare characteristics of records with and without complete maternal BMI data. An absolute standardized difference of >10% was considered indicative of a different distribution between the two groups to inform whether data could be considered missing at random (Supplemental Table 2). There were few differences in

perinatal outcomes in those with complete versus missing weight information. Women with missing BMI data were more likely to have missing SGA and birth presentation and were less likely to be a non-smoker. Women with missing GWG data were more likely to have missing smoking and birth presentation data. Women with complete BMI and complete GWG data had increased cephalic birth presentations compared to those with missing data. Among those with complete information, the median pre-pregnancy BMI was 23.9 kg/m² (mean: 25.5 kg/m², SD: 6.42) and 21% had recommended GWG.

4.5.1 Mediation analysis results for pre-pregnancy BMI

Pertaining to pre-pregnancy BMI, *Step 1* assessed the relationship between the exposure and the outcome (Supplemental Table 3). The results suggested an increased rate of hospitalizations (overweight: aIRR 1.10, 95% CI: 1.07,1.13; obese: aIRR: 1.23, 95% CI: 1.19, 1.27) and ED visits (overweight: aIRR 1.13, 95% CI: 1.11, 1.15; obese: aIRR: 1.30, 95% CI: 1.28, 1.32) for children born to overweight and obese women compared to those born to normal weight women. However, none of the other associations between pre-pregnancy BMI and pediatric health service use were strong enough to meet criteria for continuation to step 2.

In the assessment of the relationship between the exposure and the mediator (*step 2*), the results suggested that children born to mothers who were overweight (aIRR: 0.73, 95% CI: 0.70, 0.76) or obese (aIRR: 0.63, 95% CI: 0.60,0.66) prior to pregnancy had lower rates of SGA (Supplemental Table 4) relative to children born to normal weight women. PTB demonstrated a nonsignificant positive relationship with pre-pregnancy BMI in the overweight (aIRR: 1.04, 95% CI: 0.99, 1.09) or obese (aIRR: 1.07, 95% CI: 1.02, 1.13) categories. As the magnitude of these IRRs were smaller than the range previously specified for inclusion, PTB was removed from subsequent mediation analyses related to maternal pre-pregnancy weight.

Step 3 assessed the relationship between the mediator and the outcome. Results suggested that children born SGA had an increased rate of hospitalizations (aIRR: 1.26, 95% CI: 1.21,1.31) and a small decrease in the rate of ED visits (aIRR: 0.97, 95% CI: 0.95, 0.99) compared to children who were not born SGA (Supplemental Table 5).

Steps 1-3 in the adjusted analyses had thus suggested that SGA may partially explain the relationship between maternal weight and pediatric hospitalization. However, the decreased rate of SGA among children born to mothers who were overweight or obese prior to pregnancy (*step 2*) limited the potential for a causal mediation interpretation given that the direction of association was opposite to what would be expected for a causal mediator. When SGA was included in the full model (*step 4*), children born to women who were overweight (aIRR: 1.11, 95% CI: 1.08, 1.14) or obese (aIRR: 1.24, 95% CI: 1.20, 1.28) still had increased rates of hospitalization compared to children born to mothers with normal pre-pregnancy BMI (Supplemental Table 6), with effect estimates that were comparable to the Step 1 findings. Causal mediation analyses to assess the role of SGA in the association between maternal pre-pregnancy BMI and hospitalizations (Table 2) did not demonstrate any mediation by SGA: the percent of the effect mediated through SGA was minimal and most of the association was due to the direct effect of maternal weight on pediatric hospitalizations.

4.5.2 Mediation analysis results for GWG

Pertaining to GWG, the results from Step 1 of the Baron-Kenny method suggested an increased rate of hospitalizations for children born to women with below recommended GWG (aIRR: 1.10, 95% CI: 1.06,1.14). Further, children born to mothers with above recommended GWG had an increased rate of ED visits compared to those born to mothers with recommended GWG (aIRR:

1.10, 95% CI: 1.09,1.12). However, all other associations were small or nonsignificant and removed from all subsequent analyses (Supplemental Table 7).

Step 2 assessed the relationship between the exposure and the mediator. Results suggested that children born to mothers with below recommended GWG had an increased rate of PTB (aIRR: 1.77, 95% CI: 1.69, 1.84) and SGA (aIRR: 1.82, 95% CI: 1.76, 1.88), compared to children born to mothers with recommended GWG. Children born to mothers with above recommended GWG were not measurable in this model due to a Hessian error, likely attributed to low cell sizes and lack of variation within the matrix. The model for above recommended GWG was unable to achieve an estimate after adjustment for number of iterations and was thus omitted from subsequent analyses (Supplemental Table 8).

Step 3 assessed the relationship between the mediator and the outcome. Children born preterm (aIRR: 3.01, 95% CI 2.90, 3.12) and those with SGA (aIRR: 1.26, 95% CI: 1.22, 1.31) had increased rates of hospitalizations (Supplemental Table 9).

As a result of Steps 1-3 in the adjusted analyses, it was suggestive that PTB and SGA may be mediators in the relationship between below recommended GWG and infant hospitalizations. In *step 4*, the association of below recommended GWG with increased hospitalizations was diminished and non-significant after controlling for PTB (aIRR: 1.01, 95% CI: 0.98, 1.04) and was diminished after controlling for SGA (aIRR: 1.06, 95% CI: 1.02, 1.09) (Supplemental Table 10).

Causal mediation analyses were completed to assess the roles of SGA and PTB in the association between below recommended GWG and infant hospitalizations (Table 3). As shown in Table 3, PTB appeared to be responsible for a majority of the association between below recommended

GWG and infant hospitalizations, as 56.74% of the small association was mediated by PTB. SGA only mediated 6.83% of the relationship between below recommended GWG and hospitalizations (Table 3). However, given the small magnitude of all the associations, the percentages mediated should be interpreted with caution.

4.6 Discussion

The purpose of this study was to determine if adverse birth outcomes mediated the association between maternal weight and pediatric health service use. The results of the study suggested that PTB (particularly) and SGA (to a small degree) may be contributing factors to increased hospitalizations in children born to mothers with below recommended GWG. However, the magnitude of association between maternal weight and pediatric health service utilization was relatively small, impacting the ability to estimate the indirect effect of maternal weight through adverse birth outcomes.

The results of this study regarding pre-pregnancy BMI are suggestive of inconsistent mediation. When a relationship within the causal pathway has a different direction of association compared to the other effects, it can result in suppression of the total effect (22). Within this study, increased maternal pre-pregnancy BMI was associated with increased health service utilization. However, increased pre-pregnancy BMI was associated with decreased rates of SGA. Since the directionality of the effects opposite, the resulting suppression of the total effect limits the interpretation of the findings.

SGA and PTB appeared to partially explain the observed higher rates of child hospitalizations in the first 24 months of life among children born to mothers with below recommended maternal GWG, compared to children born to mothers with recommended GWG, but was not associated with pre-pregnancy BMI. PTB and SGA are associated with longstanding health implications

(23). The results of these analyses suggest that PTB and SGA lie on the causal pathway but have a small contribution to the increase in hospitalizations of children born to women with below recommended GWG within the first twenty-four months following birth.

Our findings are consistent with other studies in that children born to overweight or obese mothers have increased health service utilization (24). Children born to obese mothers (25), and those with above recommended GWG (26) are at increased risk of obesity themselves, as well as associated disease states including diabetes and cardiovascular disease (27). They are also at increased risk of other adverse conditions, such as developmental delay (28) and impaired neurodevelopment extending into childhood (29). Research suggests that normal pre-pregnancy BMI and recommended GWG are associated with a decreased risk of PTB (30), thereby limiting the potential consequences on long-term outcomes (31).

A strength of this study is availability of maternal weight and height information, linked with pediatric health service utilization in a large population, given the scarcity of maternal weight and height in electronic databases. Population-based information from a birth registry augments the generalizability of the findings to other populations with similar characteristics. A key limitation was the high proportion of missing data on maternal pre-pregnancy BMI and GWG. Self reported pre-pregnancy weight should be interpreted with caution given the potential for reporting bias. Research suggests that women tend to under report pre-pregnancy weight, but the magnitude is typically small and in previous studies reporting bias did not have a large impact on findings (32). Additionally, there may be other factors not explored that may explain the relationship between maternal weight and health service utilization. Finally, GWG is impacted by gestational length, which can be shortened by PTB. Preterm deliveries were included in this analysis as only 6% of deliveries in this cohort were preterm. Sensitivity analyses support that

those with preterm birth were more likely to have below recommended GWG (Supplemental Table 11). Despite the small proportion of preterm births within the cohort, this is an important limitation within this study, given that it may inflate the perceived role of PTB as a mediator in the relationship of maternal GWG to pediatric hospitalizations.

4.7 Conclusion

In conclusion, PTB is attributed to the increased hospitalizations in children born to mothers with below recommended GWG. Increased pediatric health service utilization in children born to mothers who were overweight or living with obesity prior to pregnancy does not appear to be related to SGA or PTB, suggesting that it is due to either maternal weight status alone or due to other unmeasured mediators. These findings are important as they indicate that future studies are needed to ascertain if there are other mediators, beyond those identified in this study, that may be contributing to this relationship.

4.8 Figures and Tables

Figure 1a: Graphical representation of the mediation assessment of the relationship between pre-pregnancy BMI and pediatric health service utilization.

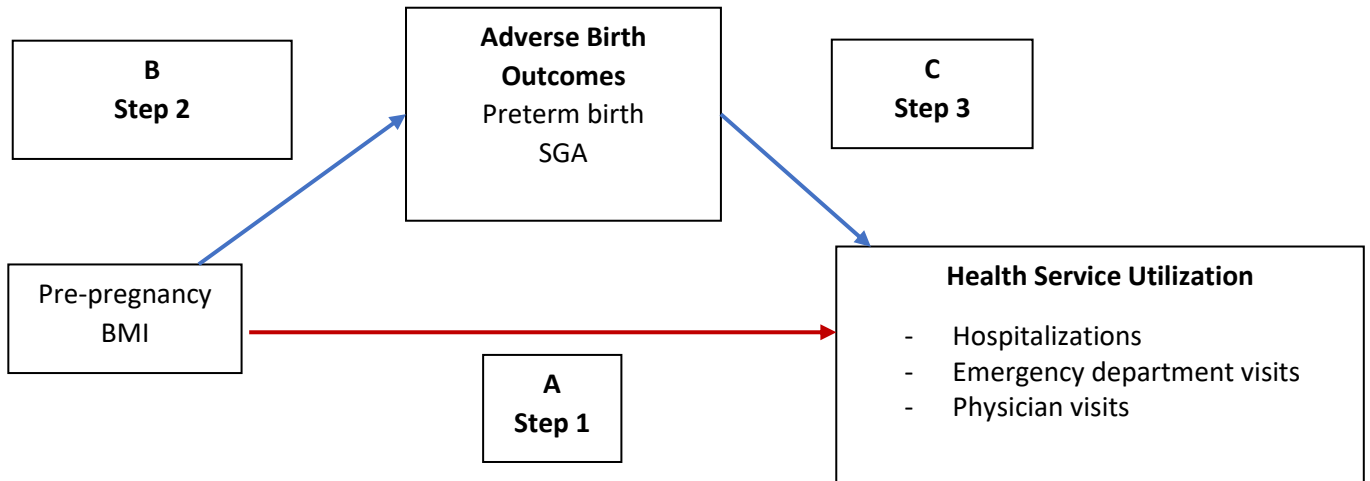


Figure 1b: Graphical representation of the mediation assessment of the relationship between gestational weight gain and pediatric health service utilization.

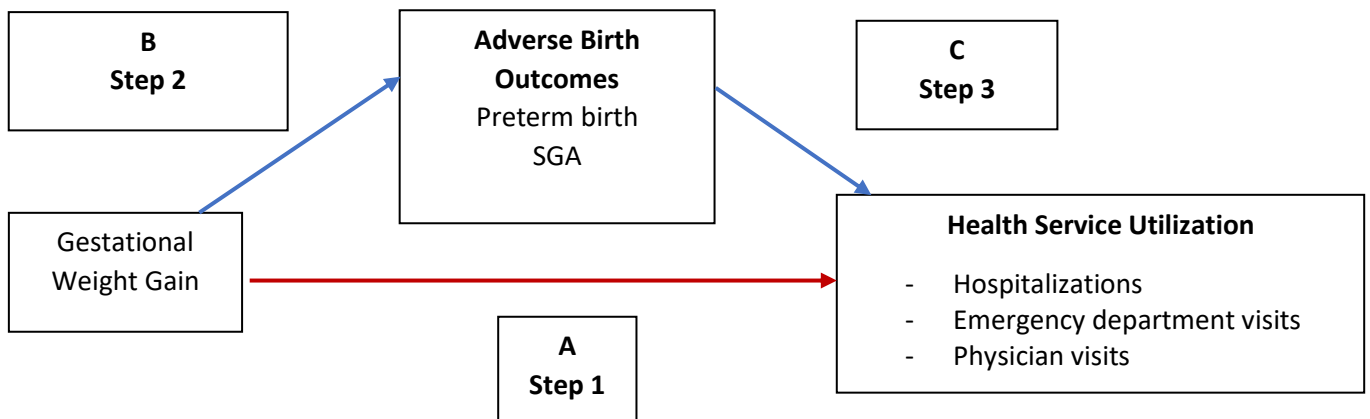


Figure 2: Study Flow Diagram

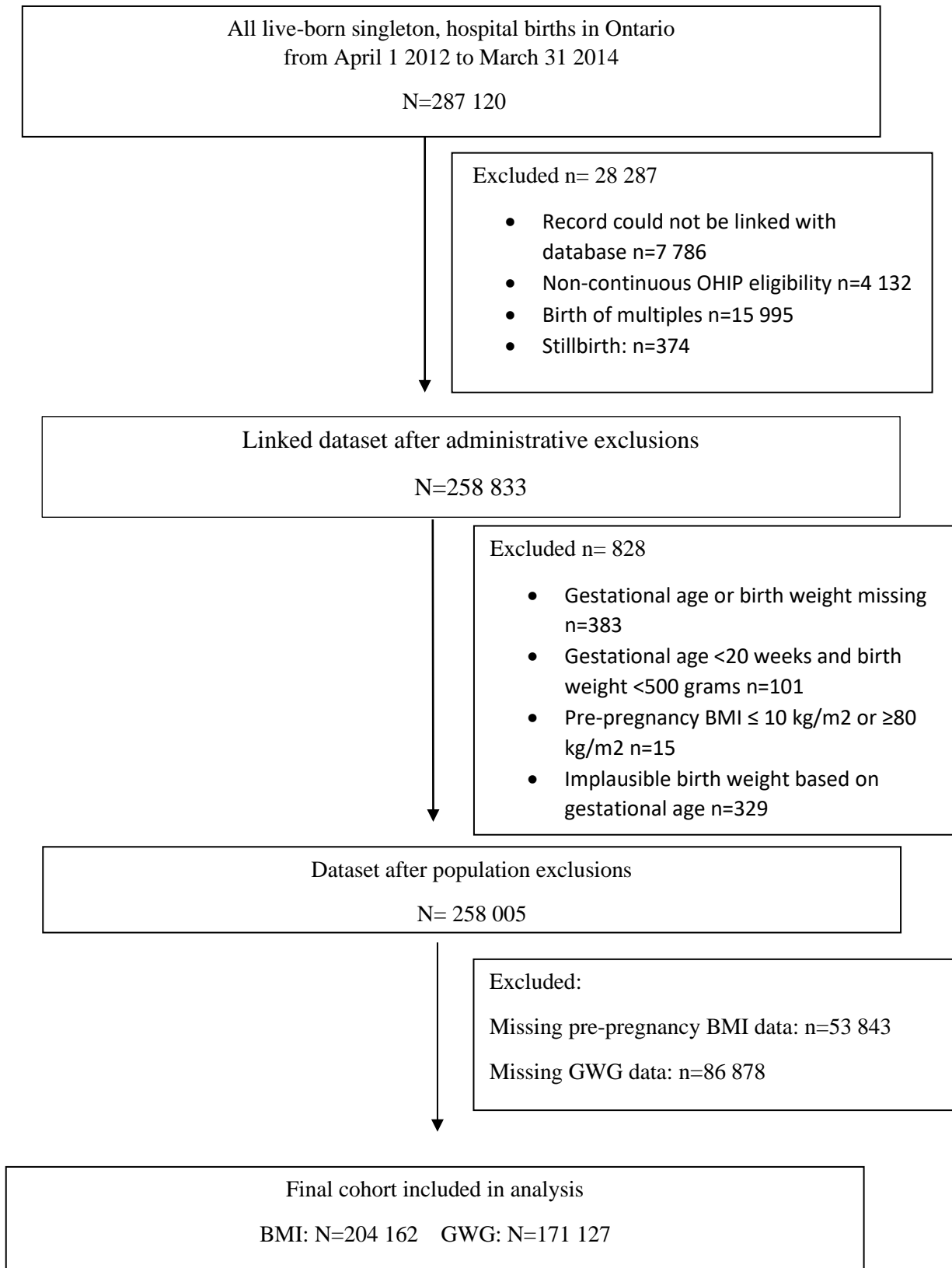


Figure 3: Schematic of model construction for each stage of the Baron-Kenny method and causal mediation for maternal pre-pregnancy BMI (removed =X, significant = *)

Exposure	Mediator	Outcome	Step 1	Step 2	Step 3	Step 4	Causal mediation
Underweight	PTB	Hospitalizations	X				
		ED visits	X				
		Physician visits	X				
	SGA	Hospitalizations	X				
		ED visits	X				
		Physician visits	X				
Overweight	PTB	Hospitalizations	*	X			
		ED visits	*	X			
		Physician visits	X				
	SGA	Hospitalizations	*	*	*	*	X
		ED visits	*	*	X		
		Physician visits	X				
Obese	PTB	Hospitalizations	*	X			
		ED visits	*	X			
		Physician visits	X				
	SGA	Hospitalizations	*	*	*	*	X
		ED visits	*	*	X		
		Physician visits	X				

Figure 4: Schematic of model construction for each stage of the Baron-Kenny method and causal mediation for GWG (removed =X, significant = *)

Exposure	Mediator	Outcome	Step 1	Step 2	Step 3	Step 4	Causal mediation
Below recommended GWG	PTB	Hospitalizations	*	*	*	*	*
		ED visits	X				
		Physician visits	X				
	SGA	Hospitalizations	*	*	*	*	*
		ED visits	X				
		Physician visits	X				
Above recommended GWG	PTB	Hospitalizations	X	X			
		ED visits	*	X			
		Physician visits	X	X			
	SGA	Hospitalizations	X	X			
		ED visits	*	X			
		Physician visits	X	X			

Table 1: Maternal and infant characteristics of the study population

Characteristics	N	%
All births	258005	100
Maternal age (years)		
<20	7012	2.7
20-24	29983	11.6
25-29	71571	27.7
30-34	92040	35.7
35-40	50852	19.7
≥41	6528	2.5
Missing	19	0
Smoking during pregnancy		
No	229007	88.7
Yes	21326	8.3
Missing	7672	3.0
Neighbourhood income quintile		
1 (lowest)	55701	21.6
2	51333	19.9
3	51866	20.1
4	54961	21.3
5 (highest)	41856	16.2
Missing	2288	0.9
Pre-pregnancy BMI (kg/m²)		
<18.5 (underweight)	10901	4.2
18.5-24.9 (normal)	108170	41.9
25-29.9 (overweight)	48141	18.7
≥30 (obese)	36950	14.3
Missing	53843	20.9
Maternal weight gain during pregnancy		
Below recommended	42826	16.6
Recommended	54302	21
Above recommended	73999	28.7
Missing	86878	33.7
Infant sex		
Male	132231	51.3
Female	125629	48.7
Missing	145	0.0
Gestational age at birth (weeks)		

<37	15211	5.9
≥37	242794	94.1
Birth weight (grams)		
<2500	11762	4.6
≥2500	246243	95.4
SGA		
No	234120	90.7
Yes	23653	9.2
Missing	232	0.09

Table 2: Relationship between maternal pre-pregnancy BMI and infant health service utilization in the first 24 months of life mediated by SGA.

	SGA [Beta Estimate (95% CI)]						% Mediated	
	Total Effect		Direct Effect		Indirect Effect		Unadjusted	Adjusted*
	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*		
<i>Hospitalizations</i>								
Overweight	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)	0.02 (0.02, 0.03)	0.02 (0.01, 0.03)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	**	**
Obese	0.05 (0.04, 0.06)	0.05 (0.04, 0.05)	0.05 (0.04, 0.06)	0.05 (0.04, 0.06)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	**	**

* Adjusted for maternal age, maternal smoking status, infant sex, maternal pre-existing medical conditions (diabetes, hypertension) and neighbourhood income quintile.

**The resulting percent mediated is not theoretically possible and has been omitted from the results

Referent group is children born to mothers with normal pre-pregnancy BMI

Table 3: Relationship between maternal gestational weight gain and infant hospitalizations in the first 24 months of life- mediated by PTB or SGA.

	PTB [Beta Estimate (95% CI)]						% Mediated	
	Total Effect		Direct Effect		Indirect Effect		Unadjusted	Adjusted*
	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*		
<i>Hospitalizations, mediated by PTB</i>								
Below recommended	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)	0.01 (0.00, 0.02)	0.01 (0.00, 0.02)	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	54.60	56.74
<i>Hospitalizations, mediated by SGA</i>								
Below recommended	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	7.25	6.83

* Adjusted for maternal age, maternal smoking status, infant sex, maternal pre-existing medical conditions (diabetes, hypertension), and neighbourhood income quintile.

**The resulting percent mediated is not theoretically possible and has been omitted from the results

Referent group is children born to mothers with recommended GWG

4.9 Declarations

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Disclosure of Interests

None of the authors in this study have any competing interests to disclose.

4.10 Supplemental Information

Supplemental Table 1A: Characteristics stratified by pre-pregnancy BMI

Characteristics	Total	Under-weight (N)	Normal weight (N)	Over-weight (N)	Obese (N)	Missing (N)
All births	258005	10901	108170	48141	36950	53843
Maternal age (years)						
<20	7012	767	3233	946	682	1384
20-24	29983	2023	12445	5292	4428	5795
25-29	71571	3317	30150	13358	10686	14060
30-34	92040	3186	39428	17384	12670	19372
35-40	50852	1475	20509	9871	7478	11519
≥41	6528	132	2403	1289	1004	1700
Missing	19	**	**	**	**	13
Smoking during pregnancy						
No	229007	9226	98264	43561	32529	45427
Yes	21326	1466	8195	3889	3901	3875
Missing	7672	209	1711	691	520	4541
Neighbourhood income quintile						
1 (lowest)	55701	2672	21064	10695	9189	12081
2	51333	2371	20797	9679	7780	10706
3	51866	2072	21846	9857	7550	10541
4	54961	2095	23982	10136	7274	11474
5 (highest)	41856	1596	19607	7345	4758	8550
Missing	2288	95	874	429	399	491
Infant sex						
Male	132231	5623	55459	24631	18939	27579
Female	125629	5274	52644	23477	17990	2624
Missing	145	**	67	33	21	20
Gestational age at birth (weeks)						
<37	15211	715	5670	2697	2244	3885
≥37	242794	10186	102500	45444	34706	49958
Birth weight (grams)						
<2500	11762	807	4648	1823	1416	3068
≥2500	246243	10094	103522	46318	35534	50775

** Compressed due to small cell size

Supplemental Table 1B: Characteristics stratified by GWG

Characteristics	Total	Below recommend. (N)	Recommend. (N)	Above recommend. (N)	Missing (N)
All births	258005	75861	54302	73999	53843
Maternal age (years)					
<20	7012	1900	1276	2452	1384
20-24	29983	8312	6034	9842	5795
25-29	71571	20017	15661	21833	14060
30-34	92040	27328	19956	25384	19372
35-40	50852	16079	10186	13068	11519
≥41	6528	2221	1189	1418	1700
Missing	19	**	**	**	13
Smoking during pregnancy					
No	229007	67911	49420	66249	45427
Yes	21326	6206	4262	6983	3875
Missing	7672	1744	620	767	4541
Neighbourhood income quintile					
1 (lowest)	55701	16647	10981	15992	12081
2	51333	15192	10689	14746	10706
3	51866	15021	11000	15304	10541
4	54961	15468	12078	15941	11474
5 (highest)	41856	12875	9110	11321	8550
Missing	2288	658	444	695	491
Infant sex					
Male	132231	38127	27758	38767	27579
Female	125629	37689	26516	35180	26244
Missing	145	45	28	52	20
Gestational age at birth (weeks)					
<37	15211	5641	2720	2965	3885
≥37	242794	70220	51582	71034	49958
Birth weight (grams)					
<2500	11762	4914	1995	1785	3068
≥2500	246243	70947	52307	72214	50775

** Compressed due to small cell size

Supplemental Table 2: Sensitivity Analyses of Factors by Missing BMI and GWG Data

Variable		BMI Standardized Difference*	GWG Standardized Difference*
Maternal smoking	Non-Smoker	-0.17	-0.09
	Smoker	-0.05	-0.10
	Missing	0.54	0.48
Gender	Male	0.00	-0.01
	Female	0.00	0.01
	missing	0.03	0.00
LGA ($\geq 90^{\text{th}}$ percentile)	No	0.04	0.04
	Yes	-0.04	-0.04
	missing	-0.01	0.00
SGA $\leq 10^{\text{th}}$ percentile)	No	-0.28	-0.04
	Yes	0.02	0.04
	missing	0.45	0.04
Presentation	Breech	-0.02	0.01
	Cephalic	-0.57	-0.45
	Transverse	0.00	0.01
	missing	0.65	0.65
Maternal Age (years)	<20	-0.01	-0.05
	20-24	-0.03	-0.09
	25-29	-0.05	-0.08
	30-34	0.01	0.04
	35-40	0.05	0.10
	≥ 41	0.05	0.07
	missing	0.09	0.08
Birth weight (grams)	<2500	0.07	0.08
	≥ 2500	-0.07	-0.08
Gestational Age (weeks)	<37	0.07	0.08
	≥ 37	-0.07	-0.08
Time to Death	≤ 42	0.00	0.03

	42-365	0.00	0.01
	365-730	0.00	0.01
	missing	0.00	-0.02
Birth Year	2012	0.14	0.10
	2013	-0.09	-0.05
	2014	-0.07	-0.08

*Standardized differences were calculated to compare the absolute differences between those with complete maternal weight (pre-pregnancy BMI or GWG) compared to those with missing maternal weight data to ascertain if there were differences in population characteristics among those with and those without weight data. An absolute difference of >10% was considered indicative of a different distribution between the two groups.

Pre-Pregnancy BMI: Baron-Kenny Results

Supplemental Table 3: Relationship between maternal pre-pregnancy BMI and rate of infant hospitalizations, physician visits and ED visits in the first 24 months of life (Step 1 of Baron-Kenny, Relationship A in Figure 1)

	Hospitalizations: IRR (95% CI)		Physician Visits: IRR (95% CI)		ED Visits: IRR (95% CI)	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Underweight	1.00 (0.94,1.05)	0.96 (0.91,1.02)	1.01 (1.00, 1.02)	1.02 (1.01,1.03)	1.06 (1.03,1.09)	0.96 (0.93,0.98)
Normal weight (ref)	1.0	1.0	1.0	1.0	1.0	1.0
Overweight	1.10 (1.07,1.14)	1.10 (1.07,1.13)	1.03 (1.05, 1.06)	1.03 (1.02,1.04)	1.12 (1.10,1.14)	1.13 (1.11,1.15)
Obese	1.25 (1.21,1.29)	1.23 (1.19,1.27)	1.06 (1.05, 1.06)	1.05 (1.04,1.06)	1.31 (1.29,1.33)	1.30 (1.28,1.32)

* Adjusted for maternal age, maternal smoking status, infant sex, maternal pre-existing medical conditions (diabetes, hypertension), and neighbourhood income quintile.

Supplemental Table 4: Relationship between maternal pre-pregnancy BMI and adverse event in the first 24 months of life (Step 2 of Baron-Kenny, Relationship B in Figure 1)

	PTB: IRR (95% CI)		SGA: IRR (95% CI)	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Normal weight (ref)	1.0	1.0	1.0	1.0
Overweight	1.07 (1.02, 1.12)	1.04 (0.99,1.09)	**	0.73 (0.70,0.76)
Obese	1.16 (1.10, 1.22)	1.07 (1.02,1.13)	**	0.63 (0.60 0.66)

* Adjusted for maternal age, maternal smoking status, infant sex, maternal pre-existing medical conditions (diabetes, hypertension), and neighbourhood income quintile.

** Hessian error message, attributed to the low cell sizes and lack of variation within the matrix.

Supplemental Table 5: Relationship between SGA and rate of infant hospitalizations and ED visits in the first 24 months of life (Step 3 of Baron-Kenny, Relationship C in Figure 1)

	Hospitalizations: IRR (95% CI)		ED Visits: IRR (95% CI)	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*
SGA	1.28 (1.24,1.33)	1.26 (1.21, 1.31)	1.01 (0.99, 1.03)	0.97 (0.95, 0.99)

* Adjusted for maternal age, maternal smoking status, infant sex, maternal pre-existing medical conditions (diabetes, hypertension), and neighbourhood income quintile.

Supplemental Table 6: Relationship between maternal pre-pregnancy BMI and and rate of infant hospitalizations and ED visits in the first 24 months of life after controlling for SGA (step 4 of Baron-Kenny mediation)

Hospitalizations: IRR (95% CI)		
	Unadjusted	Adjusted*
Normal weight (ref)	1.0	1.0
Overweight	1.11 (1.08, 1.15)	1.11 (1.08, 1.14)
Obese	1.26 (1.22,1.30)	1.24 (1.20, 1.28)

* Adjusted for maternal age, maternal smoking status, infant sex, maternal pre-existing medical conditions (diabetes, hypertension) and neighbourhood income quintile.

Gestational Weight Gain: Baron-Kenny Results

Supplemental Table 7: Relationship between maternal gestational weight gain and rate of infant hospitalizations, physician visits and ED visits in the first 24 months of life (Step 1 of Baron Kenny, Relationship A in Figure 1)

	Hospitalizations: IRR (95% CI)		Physician Visits: IRR (95% CI)		ED Visits: IRR (95% CI)	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Below recommended	1.11 (1.07,1.14)	1.10 (1.06,1.14)	1.05 (1.04,1.06)	1.05 (1.04,1.06)	1.02 (1.00,1.04)	1.00 (0.98,1.01)
Recommended (ref)	1.0	1.0	1.0	1.0	1.0	1.0
Above recommended	1.06 (1.03,1.09)	1.04 (1.01,1.08)	1.01 (1.01,1.02)	1.01 (1.01,1.02)	1.13 (1.12,1.15)	1.10 (1.09,1.12)

* Adjusted for maternal age, maternal smoking status, infant sex, maternal pre-existing medical conditions (diabetes, hypertension), and neighbourhood income quintile.

Supplemental Table 8: Relationship between maternal gestational weight gain and adverse event in the first 24 months of life (Step 2 of Baron Kenny, Relationship B in Figure 1)

	PTB: IRR (95% CI)		SGA: IRR (95% CI)	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Below recommended	1.78 (1.71,1.86)	1.77 (1.69,1.84)	1.84 (1.78,1.91)	1.82 (1.76,1.88)
Recommended (ref)	1.0	1.0	1.0	1.0
Above recommended	**	**	**	**

* Adjusted for maternal age, maternal smoking status, infant sex, maternal pre-existing medical conditions (diabetes, hypertension), and neighbourhood income quintile.

** Hessian error message, attributed to the low cell sizes and lack of variation within the matrix.

Supplemental Table 9: Relationship between adverse event and rate of infant hospitalizations in the first 24 months of life (Step 3 of Baron Kenny, Relationship C in Figure 1)

Hospitalizations: IRR (95% CI)		
	Unadjusted	Adjusted*
PTB	3.10 (2.99,3.21)	3.01 (2.90,3.12)
SGA	1.28 (1.24, 1.33)	1.26 (1.22, 1.31)

* Adjusted for maternal age, maternal smoking status, infant sex, maternal pre-existing medical conditions (diabetes, hypertension), and neighbourhood income quintile.

Supplemental Table 10: Relationship between GWG and rate of infant hospitalizations in the first 24 months of life after controlling for PTB and SGA (step 4 of Baron Kenny mediation)

	PTB: IRR (95% CI)		SGA: IRR (95% CI)	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Below recommended	1.00 (0.97,1.03)	1.01 (0.98,1.04)	1.05 (1.02, 1.09)	1.06 (1.02, 1.09)
Recommended (ref)	1.0	1.0	1.0	1.0

* Adjusted for maternal age, maternal smoking status, infant sex, maternal pre-existing medical conditions (diabetes, hypertension), and neighbourhood income quintile.

Supplemental Table 11: Sensitivity analysis of GWG of those with PTB or SGA versus those without PTB or SGA.

Variable		PTB Standardized Difference*	SGA Standardized Difference*
Pre-pregnancy BMI	Normal	0.06	-0.12
	Underweight	-0.04	-0.19
	Overweight	-0.01	0.14
	Obese	-0.05	0.15
GWG	Recommended	0.04	-0.01
	Below recommended	-0.28	-0.31
	Above Recommended	0.23	0.30

*Standardized differences were calculated to compare the absolute differences between those with PTB or SGA compared to those without PTB or SGA. An absolute difference of >10% was considered indicative of a different distribution between the two groups.

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Chapter 5

Framework for Assessing the Cost Effectiveness of Prenatal Intervention Programs Targeting Gestational Weight Gain to Limit Macrosomia

Authors: Lisa M. Currie, MSc ¹, Doug Coyle PhD ^{1,2}, Mark Walker MD ^{1,2} and Laura Gaudet MD ^{1,3}

Affiliations:

1. School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada
2. Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
3. Kingston Health Sciences Centre, Kingston, Ontario, Canada

5.1 Preface

This manuscript describes a cost effectiveness framework for the pediatric population that would permit the evaluation of prenatal intervention programs targeting GWG. To date, there are no intervention programs that target pre-pregnancy BMI, but there are programs that target GWG. Both below and above recommended GWG have been associated with increased pediatric health service utilization. Within this thesis below recommended GWG demonstrated the highest rates of pediatric health service utilization, but there were also elevated rates for above recommended GWG particularly in the normal weight population, which accounts for the highest proportion of study participants (41.9%). Macrosomia is known to be associated with elevated GWG and has the potential to have lifelong consequences. Thus, above recommended GWG with macrosomia as a potential consequence is used as an illustrative example in the cost-effectiveness framework presented. There are also severe outcomes associated with SGA and this framework could serve in future as a model for targeting below recommended GWG/SGA, by substituting the identified interventions and outcomes within this domain.

The presented framework has the flexibility to assess prenatal intervention programs targeting either pre-pregnancy BMI (when they are developed) or GWG. The short- (neonatal), medium- (childhood) and long-term (adult outcomes) are ascertained within this framework. Three adverse birth outcomes commonly associated with macrosomia (an adverse birth event associated with above recommended GWG) were identified for demonstrative purposes within this framework. However, additional outcomes could be added to the model if/when required.

This model provides insight into the public health policy implications of an intervention program targeting this dissertation's exposure of interest. Its application would allow assessment of the total cost effectiveness of the intervention to be evaluated. This study addressed the third objective of the dissertation, *to develop a cost effectiveness framework targeting early*

intervention in pregnancy for women with above recommended maternal weight to mitigate the lifetime health service use and costs of the child. All authors were involved in the conception and planning of the project. LC was responsible for project completion with guidance from DC and assistance from LG. LC and DC were involved in the analysis and interpretation of the findings. All authors contributed to the writing of the document and reviewed and approved the final manuscript prior to submission.

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5.2 Background

The impact of maternal obesity on pregnancy and neonatal outcomes is well known (1). Women of child bearing age are encouraged to achieve a health body mass index (BMI) to offset negative consequences, such as gestational diabetes, pre-eclampsia, caesarean delivery, macrosomic offspring and children requiring NICU admission (2). Further, the risk to the mother and the child increases as maternal weight increases (3–6). Pre-pregnancy weight loss is associated with a decrease in adverse pregnancy outcomes. Schummers et al (2015) indicated that a 10% decrease in pre-pregnancy BMI is associated with a decrease in pre-eclampsia, gestational diabetes, preterm delivery, macrosomia, and stillbirth (7). Further, 20-30% decreases in pre-pregnancy BMI resulted in reductions in caesarean section delivery, shoulder dystocia, NICU admissions, and newborn mortality (7). Unfortunately, there have been no randomized trials completed to date to identify effective preconception health programs addressing BMI with an aim to improve pregnancy outcomes (8). However, there has been investigation of interventions targeting achievement of optimal gestational weight gain (GWG) (9). A study of Ontario data suggests that children born to women with excessive GWG had an increased incidence of ED visits (Currie et al., in press) in the first twenty-four months following birth (underweight aIRR: 1.14, 95% CI: 1.07, 1.21; normal weight: aIRR: 1.07, 95% CI: 1.05, 1.09; overweight: aIRR: 1.04, 95% CI: 1.01, 1.07) (10). GWG elevated beyond recommended ranges is associated with an increased risk of macrosomia in the infant (OR: 1.95, 95% CI: 1.79-2.11) (11). Macrosomia is associated with neonatal risks, such as brachial plexus injury, fractures of the humerus or clavicle, facial nerve injury, birth asphyxia or mortality (12). In addition to these immediate neonatal outcomes, macrosomia has been independently associated with life-long adverse health outcomes including brain injury (13), nerve palsy (14), obesity and metabolic syndrome (15).

Weight management during pregnancy is a well explored topic, and several studies have identified key aspects of weight management programs in pregnancy including exercise, dietary management (9) and information/counselling (16). While there are no standardized recommendations for elements of intervention programs, appropriate nutritional intake (17), an exercise regime (either in class or individual exercises) and supportive counselling in combination have shown evidence of success (9). For example, research demonstrated that both low and moderate intensity exercise programs with a nutritional element decreased the risk of excessive GWG and weight retention compared to those in the control arm (18).

To assess the long-term benefit of an intervention targeting gestational weight gain to decrease the risk of macrosomia, an appropriate intervention with supportive results that lead to a decrease in macrosomia should first be evaluated. While there have been few such interventions identified (9,16–19), research suggests that a combination of physical activity, dietary restriction and counselling is likely effective at reducing the risk of excessive gestational weight gain. The Nutrition and Exercise Lifestyle Intervention Program (NELIP) is a multidimensional intervention program and will be utilized as the intervention for this cost effectiveness analysis. Of note, this is an example of a program that could be evaluated within this framework, and investigation of other comparable interventions should be completed prior to a program implementation.

The NELIP is effective at reducing excessive gestational weight gain as well as weight retention postpartum in overweight women and those living with obesity (20). A clinical trial was recently completed by the Lawson Health Research Institute and University of Western Ontario to assess improvements in maternal and pediatric outcomes in women living with obesity following the

use of the NELIP compared to nutrition or exercise interventions alone (21) and results are pending. This research group provides an opportunity for collaboration for this analysis.

Elements to be measured when administering an intervention should include sociodemographic factors independent of the intervention, such as race, education, income, and gravida. Other important variables to be considered include the percentage of program participants with program adherence, nutritional intake, and physical activity level compared to pre-pregnancy activity to assess the probability of the disease states based on the intervention.

If optimal GWG can be achieved using intervention programs prior to birth, a benefit to the child is the potential for decreased risk of macrosomia and its long term sequelae. Current studies of cost effectiveness suggest that elective caesarean delivery is more cost-effective than vaginal delivery for a fetus with macrosomia (22,23). However, caesarean section delivery is associated with its own risks. The proactive implementation of an intervention program prior to birth that targets GWG may decrease the associated risk of macrosomia; but ideally these benefits need to be considered alongside the costs of such interventions in a robust cost-effectiveness analysis.

The purpose of this paper is to develop a framework for assessing the cost effectiveness of interventions. The framework highlights the complexity of such evaluations given the impact of interventions on both short- and long-term outcomes on the infant. This framework will focus on macrosomia and the impact on the infant. There are multiple maternal factors that can influence GWG and/or macrosomia, such as social determinants of health (e.g., nutritional status, access to health care) and pregnancy complications (e.g., gestational diabetes, gestational hypertension). It is acknowledged that these factors could also impact access to an intervention program. These factors would be important considerations for the implementation of any intervention program and the complexity of their interconnectedness would require an in-depth investigation that is

beyond the scope of the present framework. The framework details the following features of an appropriate economic evaluation in this context: ensuring the correct definition of the decision problem; determining the optimal model design by, first, identifying the disease/patient pathway and subsequently identifying all pertinent health states; identifying how interventions can impact the pathway; identifying the appropriate costs and utility weights necessary for populating the chosen model; and describing the appropriate analytical plan for an analysis. It is anticipated that this framework could be implemented when an intervention is identified, by incorporating intervention-specific characteristics into an application of the framework to estimate the cost effectiveness of the intervention. This can better inform policy for implementation of a program targeting gestational weight gain in pregnant women to limit macrosomia.

5.3 Defining the Decision Problem

Economic evaluations are specifically designed to address a specific reimbursement related to a decision problem facing a health care decision maker (24). Thus, it is necessary to define the decision problem prior to developing any framework for the evaluation. In this context, the overall aim of the evaluation is to facilitate a decision relating to the funding of potential intervention programs designed to maintain optimal GWG in all pregnant women with excessive GWG to reduce the risk of macrosomia. A framework must include the appropriate elements necessary to complete a cost effectiveness analysis of such programs. As long-term health outcomes must be measured in a form which allows comparison across disease areas, health benefits will be measured by quality adjusted life years (QALYs). Given that in most jurisdictions, health care is funded by governmental agencies, costs should be measured from a health care system perspective. Both costs and QALYs should be measured over a lifetime horizon given the long-term impact of interventions (24).

5.4 Determining the Appropriate Model Type and Design

Health economic models continue to grow in complexity (25). Markov models are often used to provide an analytical framework for health economic decision analyses that describe cost effectiveness (26). These models are useful for risks that run over time (27), time periods that are referred to as *Markov cycles*. Models assume that each individual in a defined population is in one specific state at any time but can transition between states. For each cycle, a Markov model allows identification of the proportion of a population cohort who will be in each of the finite states. Weights relating to the costs and quality of life (utility) for individuals in each state are required. From here the estimated costs and QALYs for interventions can be obtained by summing over the duration of the model and the probability weighted sum of the costs and utility values associated with each state.

The Markovian assumption indicates that the occupancy of a state is not dependent on the previous state (e.g. all subjects in an illness state have an equal probability to one another of transitioning to death, that is not dependent on how long they were previously within a healthy state) (27). Further, the probability of transitioning between states changes over time and may be caused by a variety of factors.

A decision tree is a model format that relates to the probability of a set of finite outcomes over a distinct period of time (27). Thus, decision trees are only relevant for acute events with no long-term consequences. In this example framework a hybrid model is required which includes a decision tree that relates to the set of outcomes over an initial period – from the initial pregnancy to the post natal period – followed by Markov models relating to each individual outcome over the longer term.

The full economic model is presented in Figure 1. The two phases of the model are presented.

The first is the immediate pathway (*pathway 1*), represented by a decision tree, which represents the impact of the intervention program on GWG. Pregnant women enrol in the intervention program to decrease the risk of above recommended GWG. Following the intervention, women may or may not have above recommended GWG, which may be impacted by program effectiveness, adherence, or other individual factors. A pregnant woman may or may not deliver a child with macrosomia. The decision tree also covers the neonatal period, which models the immediate impacts of macrosomia. Infants with and without macrosomia can then develop the following critical sequelae: brachial plexus injury, facial nerve palsy, and birth asphyxia. These conditions are initially temporary states that subjects will pass through, some with only short-term effects. However, each of these can also lead to long term disease states, nerve palsy and brain injury, with lifetime consequences. Thus, the decision tree models the probability with or without intervention that an infant will be in one of three states: with nerve palsy, with brain injury and with no sequelae.

The second pathway (*pathway 2*) considers the long-term impact of macrosomia following live birth. This pathway relates to three separate Markov models for infants – one model representing an infant with nerve palsy, another model representing an infant with brain injury, and a final model for an infant with no long-term sequelae. The long-term disease states cover from the initial neonatal phase leading to childhood and then adulthood. The Markov model thus covers the life course from childhood to adulthood. The two pathways are combined to inform the economic evaluation of the impact of the intervention on preventing above recommended GWG and macrosomia, and in turn preventing long-term sequelae and associated long term health care utilization.

5.5 States within the health economic model

There are three key stages within this economic model: 1. Intervention and its impact on GWG, 2. Incidence of a macrosomic birth event and short-term complications, 3. Long term states over the life course, as presented in Figure 1. Each stage impacts the probability of being present in a healthy or illness status in the subsequent stage.

5.5.1 Stage 1: Intervention and Its Impact on GWG

As above recommended GWG is a risk for all women, the study population of interest are singleton, cephalic infants born to any pregnant woman, regardless of pre-pregnancy BMI. The impact of an intervention program, in this case to maintain optimal GWG, will be compared to standard of care. Thus, this stage of the model relates to the impact of intervention on maternal outcomes in terms of the proportion of mothers who have below recommended GWG, recommended GWG and above recommended GWG, outcomes that are estimated for “without the intervention” and “with the intervention”. This should be derived from appropriate clinical trial evidence.

5.5.2 Stage 2: Incidence of a Macrosomic Birth Event and Short-Term Complications

GWG is associated with an increased risk of macrosomia (11), defined as a birth weight ≥ 4000 grams (28,29). In one Canadian study, it was estimated that 16.7% of infants children in the community based sample were macrosomic (29). Macrosomic infants have a six times greater risk of significant birth injury compared to non-macrosomic infants (30). The impact of reduction of macrosomia on the child on various health outcomes that can result from macrosomia will need to be assessed, and associated costs will be estimated over the life course.

Based on the proportion of women in the specific GWG categories, the model allows assessment of the impact of the intervention program to decrease the risk of macrosomia, on the neonatal period, childhood, and adulthood. This requires data which facilitates estimation of the percentage of infants born to mothers in each of the GWG categories who will develop macrosomia. The model will then allow estimation of the probability that an infant will have one of the outcomes linked to macrosomia. This will be derived by obtaining estimates from the literature of the incidence of the outcomes for infants with or without macrosomia.

Three disease states have been identified for inclusion within this framework: brachial plexus injury, facial nerve injury, and birth asphyxia. These three states are not strictly associated with a macrosomic birth. However, the risk of these three states increases with the presence of macrosomia. It is acknowledged that this is not an exhaustive list of all disease states and that there are other potential disease states resulting from macrosomia (e.g., caesarean section delivery, shoulder dystocia, etc.), however, these three states were determined through a process of considering impact on health care use, quality of life, mortality, and incidence and through clinical consultation as part of the example used in framework development. The hybrid nature of the model allows the addition of further disease states if judged appropriate.

The intervention will have an impact on the proportion of children with macrosomia, and subsequently on the proportion of infants with the identified disease states and the complementary proportion of children without the identified disease states.

5.5.3 Stage 3: Long term States over the Life Course

From the second stage, the model will determine the proportion of the cohort of infants who will have nerve palsy, birth asphyxia or neither of these complications. The Markov models for each

condition are similar with health states representing *Alive* (with no complications, with brain injury or with nerve palsy dependent on the model) and *Dead*, the absorbing state (27). Patients with sequelae are assumed to remain with sequelae until death. For each model, the probabilities of mortality, and costs and utility values relating to the *Alive* state will differ. The cycle length for each model will be assumed to be one year.

5.5.3.1 Brachial Plexus Injury

Brachial plexus injury is the result of damage to the brachial plexus region of the upper extremity during the perinatal period (31), resulting in flaccid paralysis of the arm (32). There are four classifications of brachial plexus injury (upper, intermediate, lower, and total palsy) (31), depending on which nerve roots from the spinal cord are damaged. Macrosomia is associated with brachial plexus injury due to complications during the birth resulting from the infant's larger size (28) and occurs in less than 1/1000 births (33). It is estimated that approximately 12% of birth brachial plexus injuries continue to have adverse outcomes one-year following injury (34). Early treatment of brachial plexus injury includes operative repair, including nerve grafting and nerve repair, followed by rehabilitative care (33). Long term impacts include permanent nerve palsy, which can have a significant impact on health utilization (e.g. surgical interventions, rehabilitative services) (34), as well as quality of life (Figure 2).

5.5.3.2 Facial Nerve Palsy

Paralysis of the facial nerve can result from trauma during the perinatal period (32) and occurs in approximately 0.74/1000 births (35). Infants typically present with motor, sensory or visceral deficits on one side of the face (36). The impact is typically short term, with the majority of cases

resolving in two months (32). However, in unresolved cases, surgical exploration may be warranted (37), and can impact long term quality of life (Figure 3).

5.5.3.3 Birth Asphyxia

Birth asphyxia occurs in approximately 2.8% of all births (38), and has been found to be significantly associated with macrosomia (39). It is defined as a lack of exchange of respiratory gases during the perinatal period, resulting in a lack of oxygen to the vital organs, including the brain (40). In infants with minor asphyxia, there are minimal long term impacts (41). However, with moderate to severe asphyxia, short term outcomes could result in hypoxic ischemic encephalopathy, seizures, or mortality. In the long term, these children may face impairments in motor function (e.g. cerebral palsy), sensory function (e.g. hearing and or vision impairment) cognitive deficits (e.g. memory and attention issues), educational issues with the need for additional supports, behavioral concerns, neuropsychiatric issues (e.g. psychotic symptoms) and neurodevelopmental delays (e.g. autism spectrum disorder) (41). Therefore, depending on the severity of the asphyxia, this birth event can have a considerable impact on both health-related costs and quality of life in the short- and long-term (Figure 4).

5.6 Temporality of Assessment

The models allow for the estimation of both short- and long-term impact. That is, a disease state may only impact the neonatal period, then may resolve, and not have long term consequences into child or adulthood. However, it is also possible that the disease state may be severe enough to impact the entire lifespan. Each of the transition states within the figures are evaluated, and the proportions of individuals in a given state may change depending on the intervention and severity of disease. A model is also presented (Figure 5) where there are no neonatal

complications. The individual is either alive, ill, or dead at each stage over the life course and condition-specific age specific mortality rates and utility scores would be used in the modelling calculations.

Costs and utility measures will need to be obtained for each of these states as elements for consideration within a health economic model. Table 1 presents possible data sources that could be used to inform each of these measures through the life course in a study taking place in an Ontario/Canada context. In regard to utility, a literature review should be used to ascertain estimates, and only supplemented via additional data collection if required. In regard to cost measures, various population level data sources should be consulted, including Statistics Canada and the Canadian Institute for Health Information databases, as well as provincial information (e.g., physician billing codes), and literature review, if required. It should be noted that delivery of a macrosomic infant may also impact maternal morbidity by increasing complications such as perinatal trauma and postpartum hemorrhage (42). While this is an important consideration in the full economic analysis, the present framework will focus on the sequelae of macrosomia for the infant.

5.6.1 Neonatal Period

The neonatal state is defined by events that happen at or around the time of birth. Infants born with macrosomia have increased risks of adverse birth outcomes, as previously described. Health service delivery (inclusive of interventions), physician encounters, length of hospital stay and associated ambulatory services would be included to determine the impact on health care resource use.

5.6.2 Childhood

When assessing childhood health complications, all events that occur in childhood are considered independent of those that occurred in the prenatal period in this framework. The age range of childhood should be predetermined, and independent of the aforementioned category. To ensure that each state is independent of the preceding state, billing codes associated with the prenatal complications state should be omitted from the analyses of childhood health. Similar principles apply when capturing elements associated with this state, in that health care encounters, such as physician billing records (stratified as specialist and non specialist), hospitalizations, emergency department visits, and ambulatory care services should be captured. If possible, additional information such as drug costs and medical devices should also be captured.

5.6.3 Adulthood

Long term complications captured within this state should also be independent of those within the previous states. An in-depth analysis of long-term consequences resulting from macrosomia would be required. For example, infants that experienced a severe brain injury as a result of asphyxiation at birth may transition to care facilities or have increased ambulatory care services as their primary caregivers age. Again, health care service costs including costs associated with hospitalizations, ambulatory and emergency care services, and physician encounters, should be captured, as well as drug, device and indirect costs associated with travel and time away from work for treatment. The complications/disease states considered in childhood are also relevant to adult illness, but with a consideration for the impact on the ability to live independently based on the consequence of the illness.

5.6.4 Death

Finally, as outlined in the Markov model, the final state is death. Each of the above states can lead to death, and exposure to macrosomia as an infant is not the only cause of death in these individuals. A state of death contributes zero to the cost and effect measurements. The simulation is complete when all individuals within the model have transitioned to this state.

5.7 Identification, Measurement and Valuation of Resource Use

To calculate cost effectiveness within Markov Models, there are two overarching data elements which are applied to health states within the model: cost data and quality of life (utility) data.

Cost data elements are associated with health costs associated with each disease state, within each temporal state on an annual basis. They include the costs of intervention but also the costs of management of complications and diseases. The complications to be considered within this model include brachial plexus injury, facial nerve injury, birth asphyxia (12), as well as long term consequences such as brain injury (13) and nerve palsy (14). Within this analysis, administration of treatment will include hospitalizations, physician visits and emergency department (ED) visits. In an Ontario/Canada context, various data sources can be explored to obtain this specific data, including Statistics Canada, the Discharge Abstract Database (hospitalization data) and the National Ambulatory Care Reporting System (emergency department and ambulatory care data), both available from the Canadian Institute for Health Information (CIHI), and Ontario Health Insurance Program billing codes. Total cost is calculated by first estimating the cost per cycle as the probability weighted sum of the proportions in each state and the cost per state. From this we can estimate the total cost:

$$\sum Cost = Cost_{cycle1} + Cost_{cycle2} + \dots Cost_{cyclex}$$

The cost of complications stemming from macrosomia, specifically brachial plexus injury, facial nerve injury and birth asphyxia (12) will be considered within the model, while other complications, such as brain injury (13), or obesity and metabolic syndrome (15) could be considered in future frameworks.

5.8 Determining the Value/Quality of Life Throughout the Pathway

Natural history data and intervention effectiveness data elements are used to determine the disease pathway of individuals over their lifespan. All data elements for this framework are outlined in Table 1. Given the impact of different pathways on the quality of life of individuals, difference in outcomes with the introduction of the intervention need to consider both the impact on the quantity and the quality of life. Quality Adjusted Life Years (QALY) can be used to measure effectiveness, and is calculated by summing probability weighted sums of utility values across all cycles within a model (26):

$$\sum QALY = Utility_{cycle 1} + Utility_{cycle 2} + \dots + Utility_{cycle x}$$

Utility data for macrosomia related complications over time will be determined by literature review. If condition specific utility data is not available in the literature, primary data collection via survey methods of a sample population would be explored. Within the neonatal period, the impact of utility to the infant and the family will be calculated for brachial plexus injury, facial nerve injury and birth asphyxia (12). For the childhood period, the impact of utility of brachial plexus injury (12), brain injury (13) and nerve palsy (14) on both the child and the family will be considered. The same elements will be considered on the adult, acknowledging that the Monte Carlo simulations may need to consider the impact on the adult as well as the family depending on the severity of the complication (e.g., brain injury).

5.9 Developing an Appropriate Analytical Plan

The incremental cost effectiveness ratio (ICER) demonstrates the cost effectiveness of the intervention (Figure 6).

$$ICER = \frac{\sum Cost_{intervention} - \sum Cost_{nointervention}}{\sum QALY_{intervention} - \sum QALY_{nointervention}}$$

Monte Carlo simulations are conducted to obtain less biased estimates of the expected values for costs QALYs for the different interventions being compared. Markov chain Monte Carlo allows for simulations based on random sampling (43). Due to the inherent complexity and multiple components utilized to estimate QALYs, repeated simulations using the Monte Carlo method allow for determination of a more accurate estimate (43). Ranges of probabilities for the various elements used to determine the QALY will be considered within the simulations, including the range of impact on the child as well as the family in the adult period, depending on the severity of disease. To fully assess the cost effectiveness of the program, the comparison between an intervention to standard of care or another intervention is required to ascertain the impact of implementing the program on harm reduction of associated sequelae of macrosomia as previously discussed.

If an intervention is both less costly and produces more QALYs than on other intervention it is said to be dominant, and this intervention is cost effective. However, if an intervention is more costly and produces more QALYs, its cost effectiveness requires judgement based on a consideration of the ICER in the context of what is the decision-makers maximum willingness to pay for a QALY.

5.10 Strengths and Limitations

This novel framework has several strengths to validate its utilization to assess the cost effectiveness of the specified intervention on limiting the health impacts of macrosomia. First, it is comprehensive, as it extends beyond the neonatal period and is inclusive of the potential impacts of the condition throughout the lifespan. Second, it has been designed to capture access to several health services. Third, it can assess the impact of an intervention administered prior to birth on the child's full lifespan, thereby maximizing the data capture of potential benefits.

However, there are also several limitations to the framework. First, it has the inherent assumption that all health events and potential impacts on cost or effectiveness are linked to macrosomia when it may be caused by other health conditions (44). Second, there are numerous indirect or unmeasured costs that are not captured in this model. Treatment of a childhood illness impacts the family. Third, the model assumes that gestational weight gain alone is responsible for macrosomia. Other health conditions, such as gestational diabetes (45), or maternal weight or events prior to the intervention may lead to macrosomia or other adverse neonatal events.

5.11 Conclusion

In conclusion, the proposed framework serves as a basis for assessing the impact of an intervention to decrease macrosomia, through a public health lens. This novel approach will provide insight on whether macrosomia can be offset by a maternal intervention that is cost-effective over the long-term. The model has the flexibility to allow other interventions to be substituted and run through the simulation models to assess their impact on the outcome. It has the potential to guide future studies that assess the cost effectiveness of maternal intervention programs on neonatal outcomes and its long-term implications.

5.12 Declarations

Funding

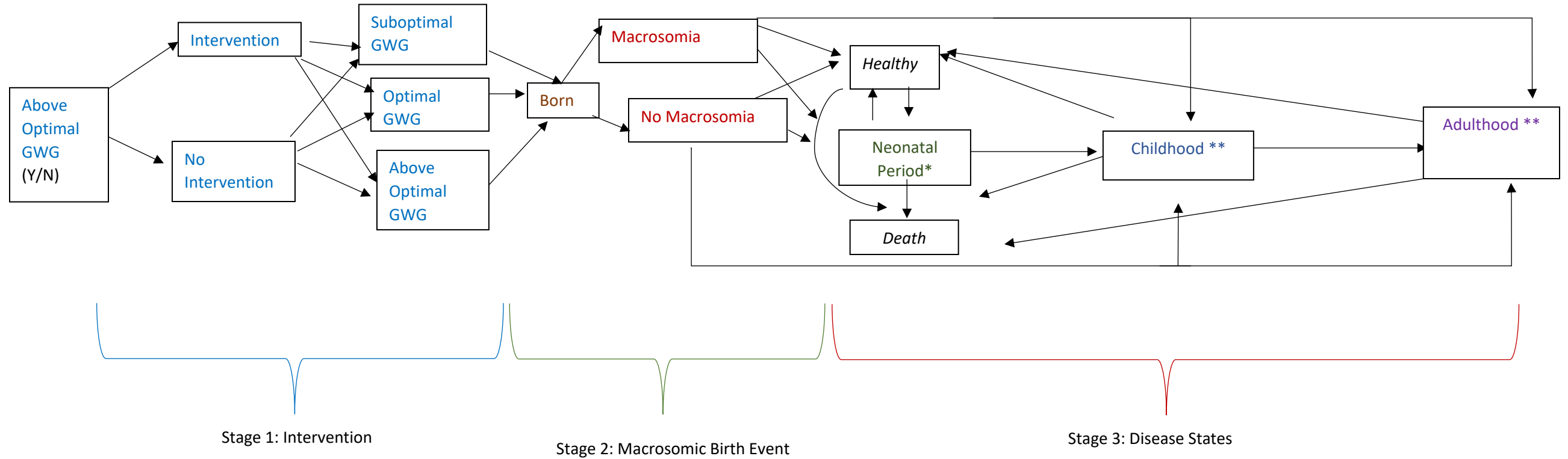
This study was supported by a CIHR research grant awarded to Laura Gaudet (MFM 146444).

Disclosure of Interests

None of the authors in this study have any competing interests to disclose.

5.13 Figures and Tables

Figure 1: Economic model to inform cost effectiveness assessment of a prenatal intervention on macrosomia and the long-term health service implications.



Costs attributable to associated disease states should be estimated at each period:

* brachial plexus injury, facial nerve injury, birth asphyxia

** brain injury, nerve palsy

Figure 2: Markov Model for Brachial Plexus Injury

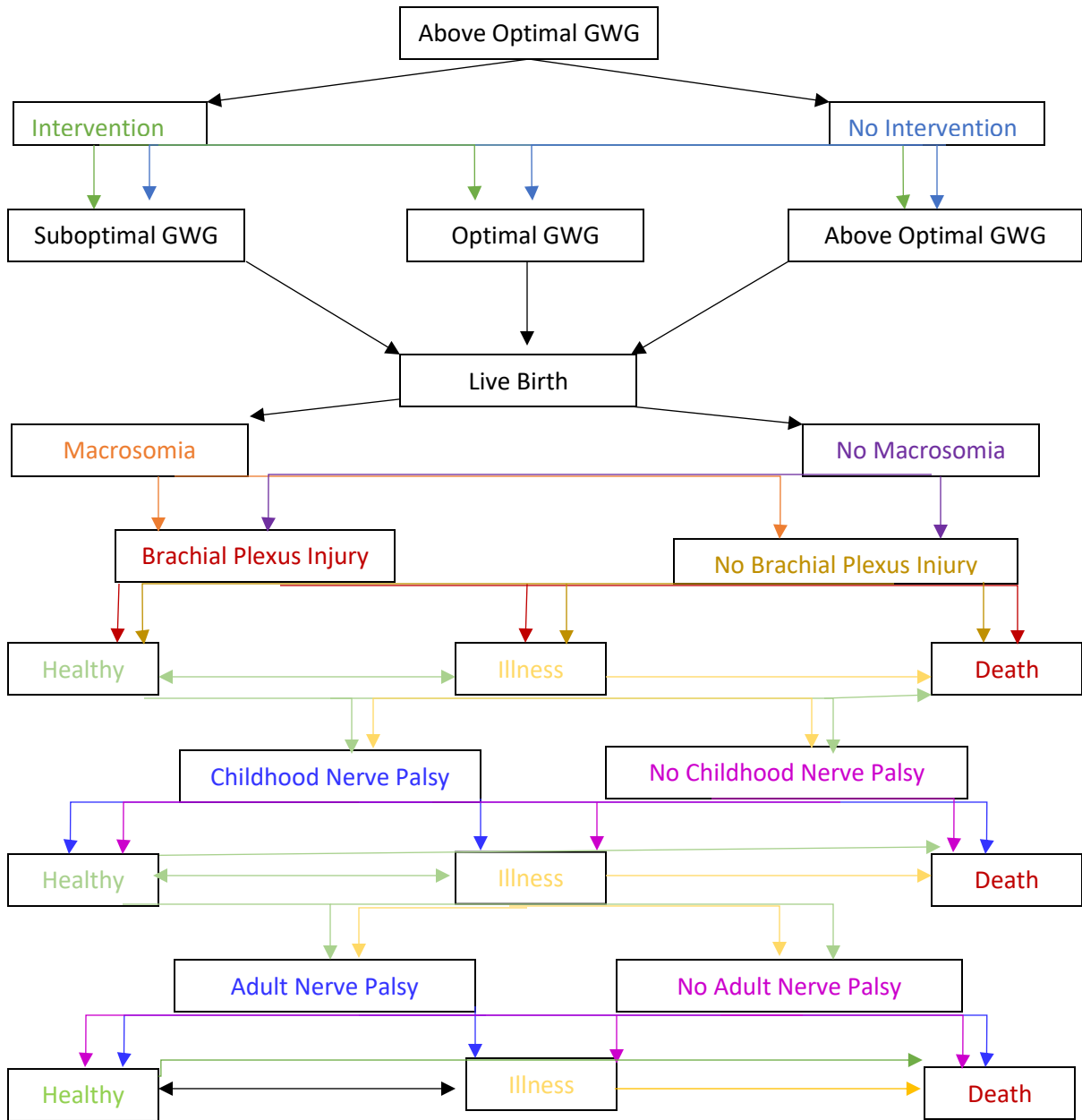


Figure 3: Markov Model for Facial Nerve Injury

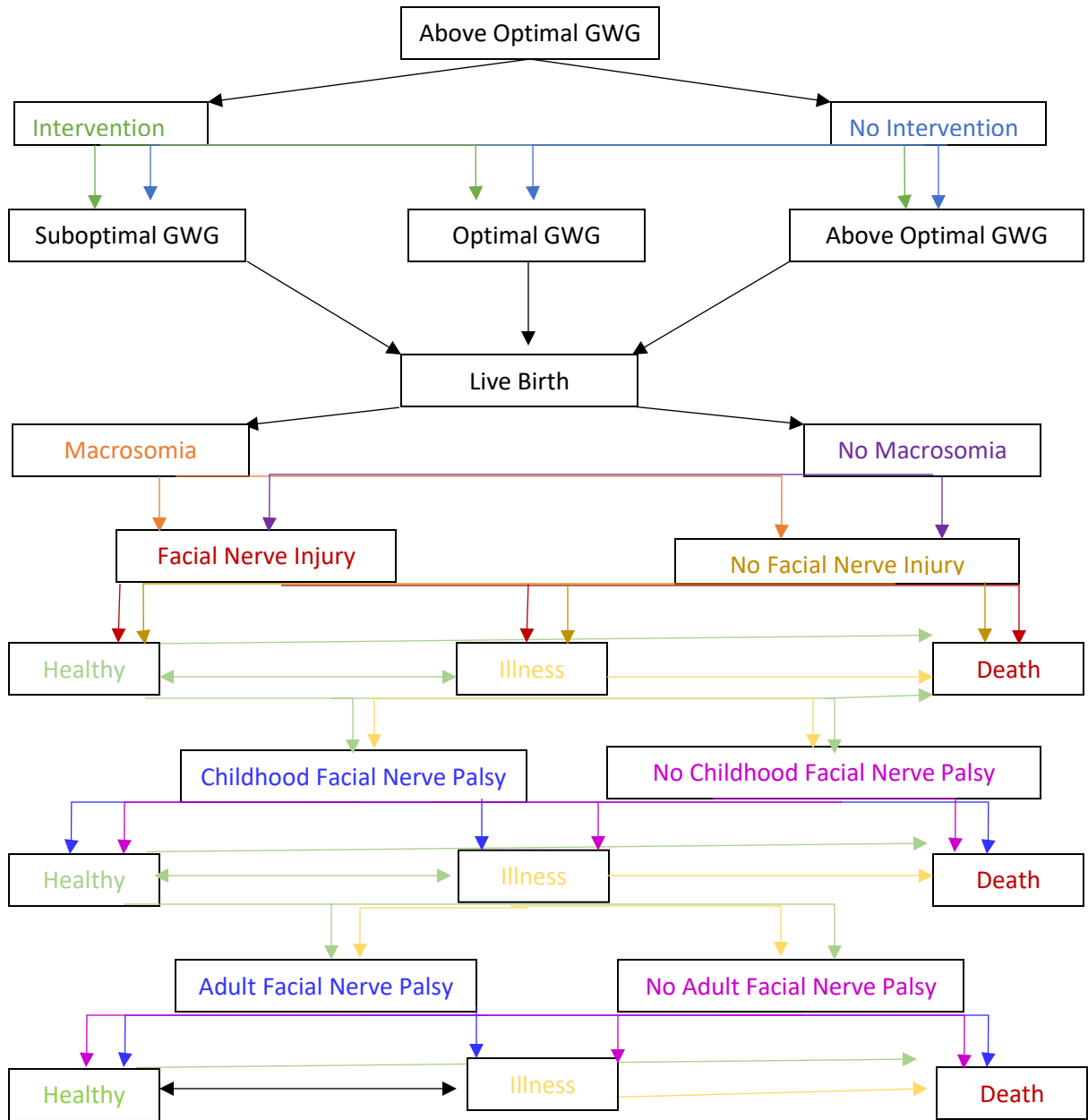


Figure 4: Markov Model for Birth Asphyxia

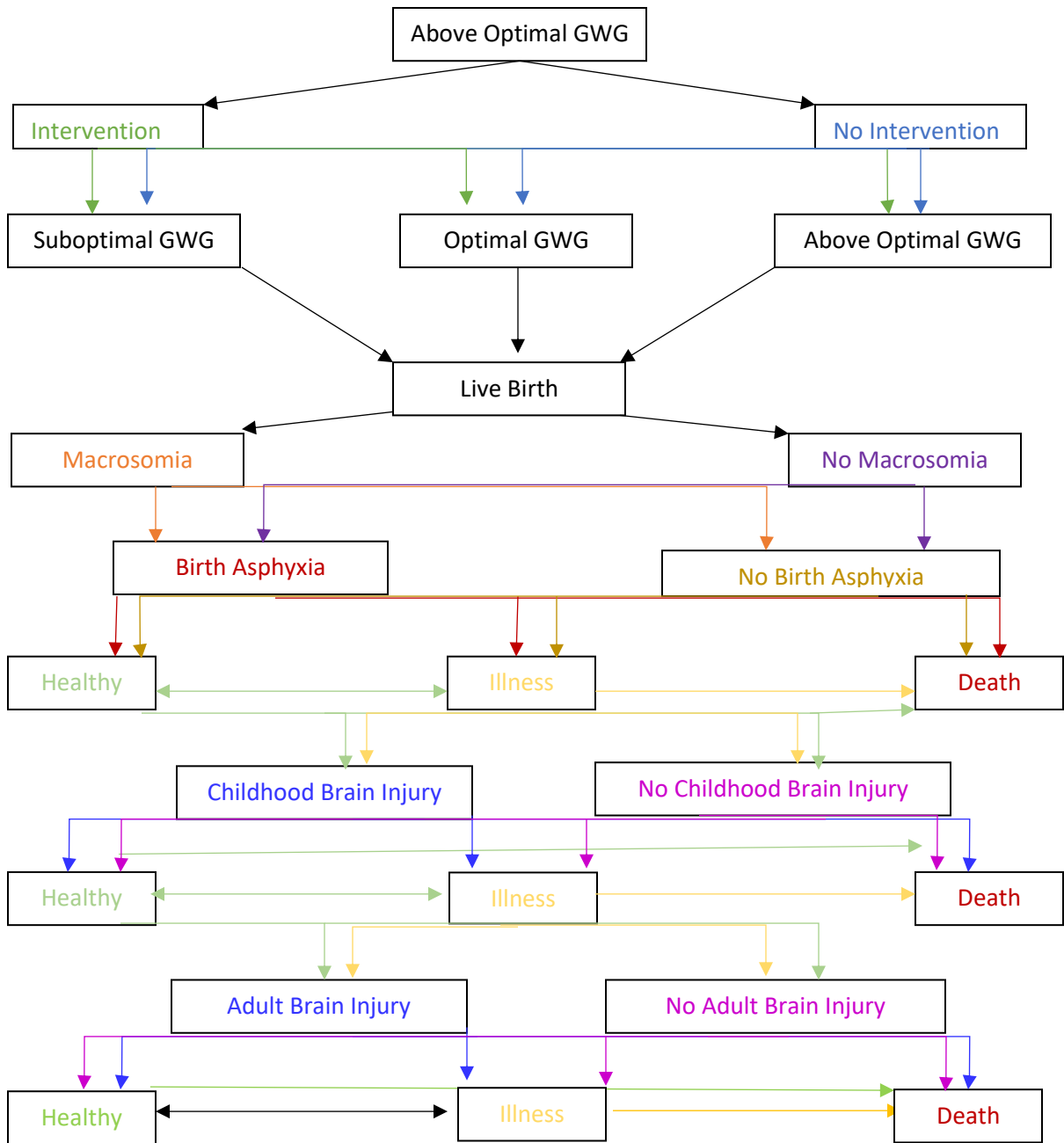


Figure 5: Markov Model for No Childhood Event

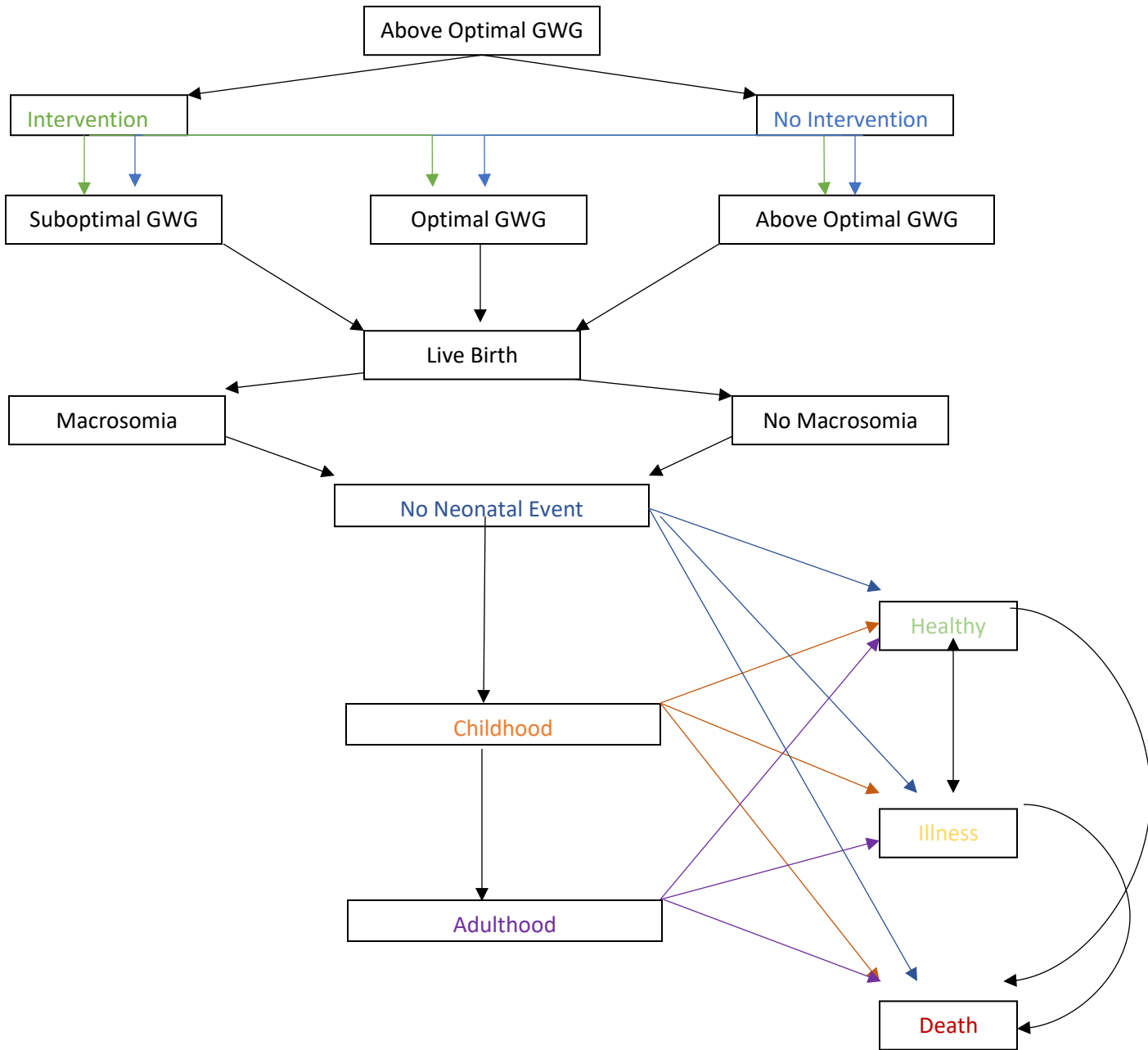


Figure 6: ICER matrix illustrating the relationship of cost effectiveness assessed within the proposed model

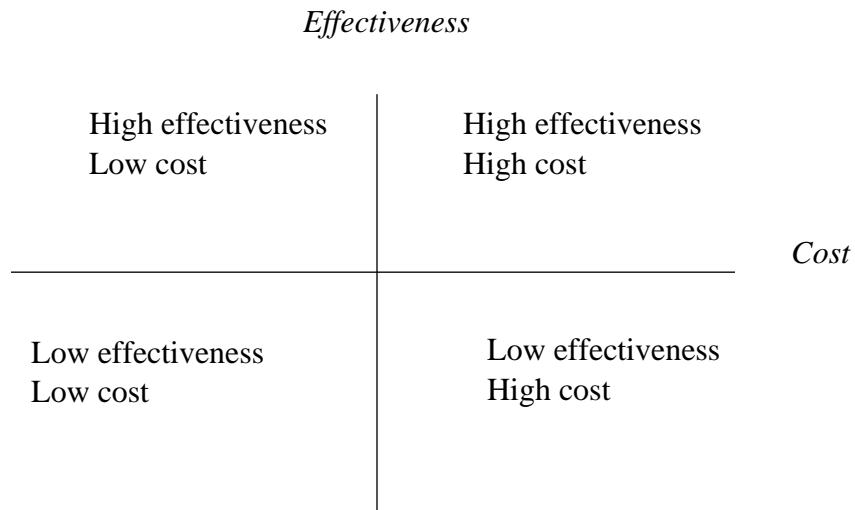


Table 1: Data Elements Table

Time States	Data Type	Data Element	Data Source
Maternal	Probability	Probability of inadequate GWG with intervention	Literature review, intervention data
Maternal	Probability	Probability of inadequate GWG without intervention	Literature review, intervention data
Maternal	Probability	Probability of adequate GWG with intervention	Literature review, intervention data
Maternal	Probability	Probability of adequate GWG without intervention	Literature review, intervention data
Maternal	Probability	Probability of excessive GWG with intervention	Literature review, intervention data
Maternal	Probability	Probability of excessive GWG without intervention	Literature review, intervention data
Maternal	Probability	Probability of macrosomia with inadequate GWG with intervention	Literature review, intervention data
Maternal	Probability	Probability of macrosomia with inadequate GWG without intervention	Literature review, intervention data
Maternal	Probability	Probability of macrosomia with adequate GWG with intervention	Literature review, intervention data
Maternal	Probability	Probability of macrosomia with adequate GWG without intervention	Literature review, intervention data
Maternal	Probability	Probability of macrosomia with excessive GWG with intervention	Literature review, intervention data
Maternal	Probability	Probability of macrosomia with excessive GWG without intervention	Literature review, intervention data
Neonatal period	Probability	Probability of brachial plexus injury with macrosomia	Literature Review, BORN Registry
Neonatal period	Probability	Probability of brachial plexus injury without macrosomic event	Literature Review, BORN Registry
Neonatal period	Probability	Probability of facial nerve injury with macrosomia	Literature Review, BORN Registry
Neonatal period	Probability	Probability of facial nerve injury without macrosomic event	Literature Review, BORN Registry
Neonatal period	Probability	Probability of birth asphyxia with macrosomia	Literature Review, BORN Registry
Neonatal period	Probability	Probability of of birth asphyxia without macrosomic event	Literature Review, BORN Registry
Neonatal period	Probability	Probability of brachial plexus injury with maternal inadequate GWG	Literature Review, BORN Registry

Neonatal period	Probability	Probability of brachial plexus injury with maternal adequate GWG	Literature Review, BORN Registry
Neonatal period	Probability	Probability of brachial plexus injury with maternal excessive GWG	Literature Review, BORN Registry
Neonatal period	Probability	Probability of facial nerve palsy with maternal inadequate GWG	Literature Review, BORN Registry
Neonatal period	Probability	Probability of facial nerve palsy with maternal adequate GWG	Literature Review, BORN Registry
Neonatal period	Probability	Probability of facial nerve palsy with maternal excessive GWG	Literature Review, BORN Registry
Neonatal period	Probability	Probability of birth asphyxia with maternal inadequate GWG	Literature Review, BORN Registry
Neonatal period	Probability	Probability of birth asphyxia with maternal adequate GWG	Literature Review, BORN Registry
Neonatal period	Probability	Probability of birth asphyxia with maternal excessive GWG	Literature Review, BORN Registry
Neonatal period	Probability	Annual probability of mortality in a health infant born to a mother with inadequate GWG	Literature Review, BORN Registry, Registered Persons Database (RPDB), Discharge Abstract Database (DAD)
Neonatal period	Probability	Annual probability of mortality in a health infant born to a mother with adequate GWG	Literature Review, BORN Registry, RPDB, DAD
Neonatal period	Probability	Annual probability of mortality in a health infant born to a mother with excessive GWG	Literature Review, BORN Registry, RPDB, DAD
Neonatal period	Probability	Annual probability of mortality of an infant born with brachial plexus injury to a mother with inadequate GWG	Literature Review, BORN Registry, RPDB, DAD
Neonatal period	Probability	Annual probability of mortality of an infant born with brachial plexus injury to a mother with adequate GWG	Literature Review, BORN Registry, RPDB, DAD
Neonatal period	Probability	Annual probability of mortality of an infant born with brachial plexus injury to a mother with excessive GWG	Literature Review, BORN Registry, RPDB, DAD
Neonatal period	Probability	Annual probability of mortality of an infant born with facial nerve injury to a mother with inadequate GWG	Literature Review, BORN Registry, RPDB, DAD
Neonatal period	Probability	Annual probability of mortality of an infant born with facial nerve injury to a mother with adequate GWG	Literature Review, BORN Registry, RPDB, DAD

Neonatal period	Probability	Annual probability of mortality of an infant born with facial nerve injury to a mother with excessive GWG	Literature Review, BORN Registry, RPDB, DAD
Neonatal period	Probability	Annual probability of mortality of an infant born with birth asphyxia to a mother with inadequate GWG	Literature Review, BORN Registry, RPDB, DAD
Neonatal period	Probability	Annual probability of mortality of an infant born with birth asphyxia to a mother with adequate GWG	Literature Review, BORN Registry, RPDB, DAD
Neonatal period	Probability	Annual probability of mortality of an infant born with birth asphyxia to a mother with excessive GWG	Literature Review, BORN Registry, RPDB, DAD
Neonatal period	Cost	Annual health care cost for healthy infant	StatsCan, Literature Review, DAD, OHIP billing codes, National Ambulatory Care Reporting System (NACRS)
Neonatal period	Cost	Annual health care cost for infant with facial nerve injury	StatsCan, Literature Review, DAD, NACRS, OHIP billing codes
Neonatal period	Cost	Annual health care cost for infant with brachial plexus injury	StatsCan, Literature Review, DAD, NACRS, OHIP billing codes
Neonatal period	Cost	Annual health care cost for infant with birth asphyxia injury	StatsCan, Literature Review, DAD, NACRS, OHIP billing codes
Neonatal period	Utility	Utility value of a healthy infant	Literature review
Neonatal period	Utility	Utility value of a healthy infant for the family	Literature review
Neonatal period	Utility	Utility value of an infant with brachial plexus injury	Literature review
Neonatal period	Utility	Utility value of an infant with brachial plexus injury for the family	Literature review
Neonatal period	Utility	Utility value of an infant with facial nerve injury	Literature review
Neonatal period	Utility	Utility value of an infant with facial nerve injury for the family	Literature review
Neonatal period	Utility	Utility value of an infant with birth asphyxia	Literature review
Neonatal period	Utility	Utility value of an infant with birth asphyxia for the family	Literature review
Childhood	Probability	Annual probability of mortality in childhood if a healthy infant	Literature Review, BORN Registry, RPDB

Childhood	Probability	Annual probability of mortality in childhood following brachial plexus injury at birth	Literature Review, BORN Registry, RPDB
Childhood	Probability	Annual probability of mortality in childhood following facial nerve injury at birth	Literature Review, BORN Registry, RPDB
Childhood	Probability	Annual probability of mortality in childhood following birth asphyxia at birth	Literature Review, BORN Registry, RPDB
Childhood	Probability	Probability of facial nerve palsy following macrosomia at birth	Literature Review, BORN Registry, DAD, OHIP billing records
Childhood	Probability	Probability of facial nerve palsy without macrosomic event at birth	Literature Review, BORN Registry, DAD, OHIP billing records
Childhood	Probability	Probability of nerve palsy following macrosomia at birth	Literature Review, BORN Registry, DAD, OHIP billing records
Childhood	Probability	Probability of nerve palsy without macrosomic event at birth	Literature Review, BORN Registry, DAD, OHIP billing records
Childhood	Probability	Probability of brain injury (mild) following birth asphyxia and macrosomia at birth	Literature Review, BORN Registry, DAD, OHIP billing records
Childhood	Probability	Probability of brain injury (moderate) following birth asphyxia and macrosomia at birth	Literature Review, BORN Registry, DAD, OHIP billing records
Childhood	Probability	Probability of brain injury (severe) following birth asphyxia and macrosomia at birth	Literature Review, BORN Registry, DAD, OHIP billing records
Childhood	Probability	Probability of brain injury (mild) without birth asphyxia and a macrosomic event at birth	Literature Review, BORN Registry, DAD, OHIP billing records
Childhood	Probability	Probability of brain injury (moderate) without birth asphyxia or macrosomic event at birth	Literature Review, BORN Registry, DAD, OHIP billing records
Childhood	Probability	Probability of brain injury (severe) without birth asphyxia and a macrosomic event at birth	Literature Review, BORN Registry, DAD, OHIP billing records
Childhood	Cost	Annual health care cost for healthy child	StatsCan, Literature Review, DAD, OHIP billing codes, National Ambulatory Care Reporting System (NACRS)
Childhood	Cost	Annual health care cost for child with nerve palsy	StatsCan, Literature Review, DAD, NACRS, OHIP

Childhood	Cost	Annual health care cost for child with facial nerve palsy	StatsCan, Literature Review, DAD, NACRS, OHIP
Childhood	Cost	Annual health care cost for child with brain injury (mild to severe)	StatsCan, Literature Review, DAD, NACRS, OHIP
Childhood	Utility	Utility value of a healthy child	Literature review
Childhood	Utility	Utility value of a healthy child for family	Literature review
Childhood	Utility	Utility value of a child with brachial plexus injury for the child and family	Literature review
Childhood	Utility	Utility value of a child with brachial plexus injury for the family	Literature review
Childhood	Utility	Utility value of a child with nerve palsy	Literature review
Childhood	Utility	Utility value of a child with nerve palsy for the family	Literature review
Childhood	Utility	Utility value of a child with brain injury (mild to severe)	Literature review
Childhood	Utility	Utility value of a child with brain injury (mild to severe) for the family	Literature review
Adulthood	Probability	Annual probability of mortality in adulthood if a healthy infant	Literature Review, RPDB
Adulthood	Probability	Annual probability of mortality in adulthood following brachial plexus injury at birth	Literature Review, RPDB
Adulthood	Probability	Annual probability of mortality in adulthood following facial nerve injury at birth	Literature Review, RPDB
Adulthood	Probability	Annual probability of mortality in adulthood following birth asphyxia at birth	Literature Review, RPDB
Adulthood	Probability	Probability of facial nerve palsy following macrosomia at birth	Literature Review, DAD, OHIP billing records
Adulthood	Probability	Probability of facial nerve palsy without macrosomic event at birth	Literature Review, DAD, OHIP billing records
Adulthood	Probability	Probability of nerve palsy following macrosomia at birth	Literature Review, DAD, OHIP billing records
Adulthood	Probability	Probability of nerve palsy without macrosomic event at birth	Literature Review, DAD, OHIP billing records
Adulthood	Probability	Probability of brain injury (mild) following macrosomia at birth	Literature Review, DAD, OHIP billing records
Adulthood	Probability	Probability of brain injury (moderate) following macrosomia at birth	Literature Review, DAD, OHIP billing records
Adulthood	Probability	Probability of brain injury (severe) following macrosomia at birth	Literature Review, DAD, OHIP billing records
Adulthood	Probability	Probability of brain injury (mild) without macrosomic event at birth	Literature Review, DAD, OHIP billing records

Adulthood	Probability	Probability of brain injury (moderate) without macrosomic event at birth	Literature Review, DAD, OHIP billing records
Adulthood	Probability	Probability of brain injury (severe) without macrosomic event at birth	Literature Review, DAD, OHIP billing records
Adulthood	Cost	Annual health care cost for healthy adult	StatsCan, Literature Review, DAD, NACRS, OHIP
Adulthood	Cost	Annual health care cost for adult with nerve palsy	StatsCan, Literature Review, DAD, NACRS, OHIP
Adulthood	Cost	Annual health care cost for adult with facial nerve palsy	StatsCan, Literature Review, DAD, NACRS, OHIP
Adulthood	Cost	Annual health care cost for adult with brain injury (mild to severe)	StatsCan, Literature Review, DAD, NACRS, OHIP
Adulthood	Utility	Utility value of a healthy adult	Literature review
Adulthood	Utility	Utility value of an adult with brachial plexus injury	Literature review
Adulthood	Utility	Utility value of an adult with nerve palsy	Literature review
Adulthood	Utility	Utility value of an adult with brain injury (mild to severe)	Literature review
Adulthood	Utility	Utility value of a family/caregiver of an adult with brain injury (mild to severe)	Literature review

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Chapter 6

Integrated Discussion

6.1 Overview

The world is facing an obesity epidemic (1), and reproductive aged persons are not exempt. The impacts of below recommended and above recommended maternal weight have been clearly documented (2). As demonstrated in this dissertation, maternal weight is associated with pediatric health service utilization. While the effect was small, the findings suggest the need to proactively address this modifiable risk factor of pediatric concern to offset potential lifelong health issues (3).

Health experiences in young children can have long term consequences. Dependent on the health condition, sequelae can extend into adulthood. For example, respiratory illness as a young child, as was predominant in this cohort (Chapter 2, supplemental), can result in long term pulmonary health issues (4). Also, gastrointestinal issues in early life, also a common indication for health care encounter in this study, has the potential to be linked to long term adverse health outcomes such as colic, regurgitation, and constipation (5). Experiences of pain, which can be associated with the condition or the treatment for care, can have long term physiological impacts on the central nervous system as well as in the neuroendocrine and immune systems (6). The impact of early childhood illness is not isolated to the child. Parents who care for a sick infant have demonstrated increased risk of mental health concerns (7), stress, and disruption to family relationships (8). Beyond the direct impacts on the child and family, increased health service utilization has a direct impact on the health system and resource allocation in it. A recent Canadian study indicated that children born to mothers with obesity have \$1415 greater hospital costs and \$356 greater physician visit costs in their childhood (9). Of note, this study was limited

to pre-pregnancy BMI and to those with normal or above recommended weight: based on the findings of this dissertation it is estimated that actual costs are greater when considering the increased pediatric health service utilization associated with GWG, as well as those with mothers who were underweight prior to pregnancy.

Maternal weight is a potentially modifiable factor, and with increasing evidence of its association with maternal and child health outcomes and associated health care use and costs, preventative care and messaging should be undertaken to promote healthy body weight prior to pregnancy. Additionally, interventions should be developed, evaluated, and implemented to target GWG that is either below or above recommended values.

Social determinants of health play a key role in health research. As outlined in the health impact pyramid (10), adequate and equitable social and economic resources are foundational to improving public health and required to facilitate effective implementation of health interventions. While large administrative databases are useful to capture a breadth of topics, they often do not capture data in depth, particularly in relation to social determinants of health (11). For example, women with lower income may have difficulties accessing healthy foods that are cost- and potentially geographically prohibitive (12,13). Social and economic factors also present barriers for maintaining appropriate physical activity during pregnancy (14). The impact of social determinants of health impacts women even prior to pregnancy. For example, a woman may have an intention to attain a more appropriate weight prior to pregnancy, but lack of access to birth control may result in an unplanned pregnancy (15), thereby highlighting the importance of early intervention prior to pregnancy. As it relates to the child, even though the measures of health service utilization in this study are publicly funded, access may be limited depending on geographical location (16), as well as a parent's ability to access the service (17). It is difficult to ascertain from this data alone if visits to the ED are due to health seeking attributed to limitations in access to primary care (e.g. hours of operation, location) or true medical emergencies. Well baby visits were generally

unimpacted by maternal weight, which suggests that preventive health care was not impacted by this exposure. However, given the increase in health service visits that may be associated with more severe disease states (e.g., hospitalizations, specialist visits) in women who are overweight or obese, further research is warranted to determine if health service access is delayed until the medical condition is more severe in individuals facing barriers to accessing care.

6.2 Summary of research findings

An overarching summary of the research findings is presented in Table 6.1. The first study of this dissertation aimed to assess the association between maternal pre-pregnancy BMI and pediatric health service use. Following adjustment, children born to overweight mothers and mothers living with obesity had increased rates of hospitalization (overweight aIRR: 1.09, 95% confidence interval [CI]: 1.06, 1.12; obese aIRR: 1.20, 95% CI: 1.17,1.24), physician visits (overweight aIRR: 1.03, 95% CI: 1.03,1.04; obese aIRR: 1.05, 95% CI: 1.04,1.05) and emergency department (ED) visits (overweight aIRR: 1.12, 95% CI: 1.10,1.13; obese aIRR: 1.27, 95% CI: 1.25,1.29) compared to infants born to mothers with normal pre-pregnancy BMI. Children born to mothers who were underweight prior to pregnancy did not experience a higher frequency of health service use. Rather, they experienced slightly fewer ED visits (aIRR: 0.93, 95% CI: 0.91, 0.95) and hospitalizations (aIRR: 0.96, 95% CI: 0.92,1.00) and a very slight increase in physician visits (aIRR: 1.02, 95% CI: 1.02,1.03), primarily attributable to non-specialist physician visits (aIRR: 1.03, 95% CI: 1.02,1.04) compared to children born to mothers with normal pre-pregnancy BMI. The results of this study suggest that as maternal pre-pregnancy BMI increases, rates of pediatric health service use in the first two years of life also increase. Upon assessment of GWG, underweight women with below recommended GWG had the greatest increase in pediatric hospitalizations (aIRR: 1.31, 95% CI: 1.14, 1.51) and physician

visits (aIRR: 1.14, 95% CI: 1.10, 1.17) relative to underweight women with GWG in the recommended range. The increase in physician visits was attributable to both specialist (aIRR: 1.27, 95% CI: 1.16, 1.38) and non-specialist (aIRR: 1.11, 95% CI: 1.08, 1.14) visits. This finding suggests that even with below recommended weight prior to pregnancy, there remains an importance to maintain an optimal GWG throughout pregnancy to offset potential impact on the child.

It was important to ascertain if the relationships observed in Chapter 2 and Chapter 3 were directly related to maternal weight, or if adverse birth outcomes that are associated with both below or above recommended maternal weight and pediatric health service use mediated the relationship. Upon investigation utilizing mediation analysis in Chapter 4, PTB, and to a lesser extent SGA, appear to mediate the relationship between hospitalizations and below recommended GWG only. Otherwise, these adverse birth outcomes did not mediate the relationship between maternal weight and pediatric health service outcome.

These direct and indirect associations of maternal pre-pregnancy BMI and GWG with pediatric health service use highlight the importance of proactively addressing maternal weight both prior to pregnancy and throughout the prenatal period. From a health policy perspective, it is important to identify and implement effective intervention strategies to optimize health outcomes and reduce the risk of increased health service utilization. Chapter 5 outlines a cost effectiveness framework for the economic evaluation of such strategies throughout the life course.

This dissertation is a contribution to the scientific literature as it demonstrates the importance of both below recommended and above recommended pre-pregnancy BMI and GWG in the relationship with pediatric health service utilization. This work also provided new insights on the impact of maternal weight on subtypes of physician visits (well baby, specialist, and non-

specialist) across maternal weight categories. Additionally, this dissertation investigated potential mediators of these relationships and provided clarity in regard to the direct and indirect associations of maternal weight with pediatric health service use, an area not previously explored.

Previous work by Kuhle et al investigated the association between maternal obesity and pediatric health service utilization limited to hospitalizations and physician visits in Nova Scotia, with a focus on overweight and obesity, in a much smaller cohort (9). This dissertation aligns with the findings of Kuhle et al in mutual areas of investigation, in that children born to mothers living with obesity had higher rates of physician visits and hospitalizations, as illustrated in Chapter 2. Additionally, a study by Cameron et al investigated the association of pre-pregnancy BMI, inclusive of underweight women, with pediatric hospitalizations in their Australian cohort (18). However, they limited their analyses to one type of health service use and did not investigate GWG. The findings of this dissertation align with the findings of the Cameron study, in that children born to mothers living with obesity had an increase in all cause hospitalizations, a finding that they identified extended to five years of age. They also identified that children born to underweight mothers were more likely to sustain an injury or poisoning, a variable not within the scope of this dissertation.

A strength of this dissertation is the capture of both maternal weight and height at the population level and the ability to link maternal weight to pediatric health service utilization. The BORN registry provides an ability to analyze this information. Limitations in the use of BMI have previously been explored (19). However BMI remains the most commonly used measure of body size in the clinical community (20), augmenting the ability to translate the results of these studies to a clinical environment. In order to access the BORN data via ICES, the data is required to be

linked within the ICES data catalogue prior to availability. As this is an extensive task, there were significant delays in obtaining timely data for this cohort, with the above noted dataset becoming available in January 2018. It is not thought to impact the interpretation of the findings and applicability to the current environment. Despite the capture of this information within the registry, there was a high level of missing data for both pre-pregnancy BMI and GWG. Statistical analyses, including sensitivity analyses and multiple imputation, were utilized to investigate and minimize the impact of this missingness. Additionally, data pertaining to race/ethnicity was not available within these databases. This limitation can impact both the exposure, as race/ethnicity has been demonstrated to impact the classification of maternal weight (21), as well as the outcome, given potential differences in health service access and culturally appropriate care (22). Finally, it is acknowledged that health service utilization is not a direct proxy for pediatric health. Physician visit type was stratified by well baby visits to specialist/non-specialist visits to gain a better understanding of preventative health visits, but there are other factors that may be contributing to health service utilization beyond poor health, such as timely access to a family health care practitioner (thereby increasing ED visits) or allied health professionals (thereby increasing physician encounters) (23,24). Future research via observational studies should further investigate the indication for visit beyond what was presented in Chapter 2 (supplemental) to gain a better understanding of pediatric health specifically as it relates to maternal weight.

In summary, this dissertation demonstrates a small increase in pediatric health service utilization in the first twenty-four months following birth associated with pre-pregnancy BMI in the overweight and obese categories; and with GWG below recommendations, particularly among women with pre-pregnancy BMI in the underweight category. Despite small effect sizes, these

are important findings as even small increases in health service utilization can have large impacts at a population level. While health service utilization increases as maternal BMI increases, there is also an increase in health service use in children born to mothers with suboptimal weight gain below recommendations, suggesting that any weight that deviates from medical recommendations contributes to increased pediatric health service utilization. This relationship is only slightly mediated by the investigated adverse birth outcomes, suggesting a direct association of maternal weight with pediatric health service use or mediation through other pathways. A framework for assessing cost effectiveness of an intervention program to offset maternal weight gain is outlined.

Table 6.1: Summary of findings: Association between maternal weight and pediatric health service utilization relative to normal BMI or normal GWG reference group

Pre-Pregnancy BMI Category	Categorization	Health Service Utilization					
		Hospital-izations	Physician Visits	ED Visits	Well Baby Visits	Specialist visits	Non-Specialist visits
<i>Underweight</i>	BMI	↓	↑	↓	↑	ns	↑
	Below recommended GWG	↑ *	↑	ns	ns	↑	↑
	Above recommended GWG	ns	ns	↑	ns	ns	ns
<i>Normal weight</i>	BMI (ref)	-	-	-	-	-	-
	Below recommended GWG	↑	↑	↓	↓	↑	↑
	Above recommended GWG	ns	↑	↑	↑	↑	↑
<i>Overweight</i>	BMI	↑	↑	↑	↑	↑	↑
	Below recommended GWG	↑	↑	↑	↓	↑	↑
	Above recommended GWG	ns	ns	↑	↓	ns	↓
<i>Obese</i>	BMI	↑	↑	↑	↑	↑	↑
	Below recommended GWG	ns	↑	ns	↓	↑	↑
	Above recommended GWG	ns	↑	↓	↑	ns	↑

↑ increased rate of outcome when referencing the aIRR compared to normal BMI or GWG

↓ decreased rate of outcome when referencing the aIRR compared to normal BMI or GWG

* Mediated by PTB and SGA

ns=non-significant

6.3 Implications

Research has consistently shown that long-term weight loss in adults is very difficult to achieve (25). Thus, efforts to minimize the health impacts of excess maternal weight on pregnancy and childhood outcomes have focused on achieving optimal GWG – a more modifiable risk factor. Ultimately, achieving and maintaining healthy weight among youth may be the best strategy for promoting optimal maternal weight, given the difficulty in decreasing weight after it has been gained, or gaining weight after negative lifestyle habits are formed (26). This will require instilling positive lifestyle habits, supporting mental health among youth (27) and recognizing and addressing the social and socioeconomic conditions that contribute to these proximal influences (28). Healthy weight leads to decreased obesity-related health conditions such as heart disease, type II diabetes mellitus, and musculoskeletal conditions, and can ultimately decrease mortality risk (29).

However, to minimize the impact of maternal weight on the child once pregnancy has occurred, a focus on optimizing GWG may be beneficial. As illustrated in the proposed cost effectiveness framework in Chapter 5, the implementation of an intervention program during pregnancy specific to GWG has the potential to limit the short- and long-term health implications for the child. As outlined, a successful intervention has the potential to have widespread cost and quality of life implications. Until effective early intervention and promotion of healthy weight at the population level are possible, pre-pregnancy and pregnancy related weight interventions remain the only viable options.

6.4 Conclusion

Maternal weight is associated with an increase in pediatric health service utilization and appears to be minimally mediated by adverse birth outcomes. Promoting strategies in the population to achieve optimal weight has the potential to improve the overall health of the mother and child and decrease the need for health service utilization. This dissertation serves as a call to action to address the importance of maintaining a healthy weight within our population, not only for ourselves but for subsequent generations.

6.5 Citations

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