In the Canadian Population, does Caesarean Delivery compared to Vaginal Birth Increase the Risk of Early Neonatal Mortality? An Instrumental Variable Method Approach

by

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A Thesis submitted to the

School of Graduate Studies

in partial fulfillment of the requirements for the degree of

Master of Science in Medicine

Clinical Epidemiology

Memorial University of Newfoundland

October 2015

St. John's Newfoundland and Labrador

Abstract

BACKGROUND: The lack of adjustment for unmeasured factors which may be associated with both delivery decisions and pregnancy outcomes has likely resulted in an overestimation of the risk associated with caesarean delivery on neonatal mortality. An instrumental variable method (IVM) originating from the field of econometrics has been utilized in modern epidemiological research to reduce the influence of unmeasured selection bias. By accounting for measured, unmeasured, and unknown confounding variables, utilizing the IVM can serve as a more valid approach in determining intervention effects amongst patients in observational studies.

OBJECTIVE: The purpose of this study is to compare the results from traditional multivariate methods and instrumental variable-adjusted analyses to determine if caesarean delivery increases the risk of early neonatal death in comparison to vaginal birth.

MATERIALS AND METHODS: This is a retrospective cohort study which compares the outcome of early neonatal mortality between 20 completed weeks of gestation and 7 days post-partum among women who delivered through a caesarean section and women who delivered vaginally. The cohort includes all in-hospital births during the fiscal years of April 1, 2006 - March 31, 2009 across Canada identified in the Discharge Abstract Database (DAD) from the Canadian Institute of Health Information (CIHI), excluding deliveries in Quebec. The effect of mode of delivery, being either caesarean or vaginal delivery, on early neonatal mortality was measured using a bivariate logistic regression, followed by a multivariate logistic regression and instrumental variable-adjusted analysis which controlled for 24 covariates.

RESULTS: Multivariate logistic regression indicated that caesarean delivery significantly reduced the risk of early neonatal death in comparison to vaginal birth by 21% (Adjusted OR =

0.79, 95%CI = 0.66-0.93, p = 0.006). Instrumental variable-adjusted regression indicated a lack of association between mode of delivery and early neonatal mortality (ARD = -0.0053, 95%CI = $-4.3x10^{-3}$-$3.0x10^{-3}$, p = 0.781).

CONCLUSION: In conclusion, the findings from the IVM analysis suggest that the risk of early neonatal mortality is not influenced by the mode of delivery. However, given the large discrepancy in risk estimates between analytic methods, health-system level recommendations towards altering local caesarean rates should be avoided until its impact on maternal and neonatal morbidities, hospital costs, and resulting factors are better understood. Future researchers should aim to answer these questions using similar analytic methods to help inform health-care policy makers and providers of the safety of caesarean deliveries.

Acknowledgements

I would especially like to thank Dr. Kris Aubrey-Bassler and Dr. Marshall Godwin for their invested support and guidance throughout this process. They have truly gone above and beyond to ensure all of my questions and concerns were addressed. I would also like to thank the other members of my supervisory committee, including Dr. Shabnam Asghari and Dr. Peter Wang, for reviewing my work and providing suggestions along the way. The feedback obtained from my supervisory committee was crucial in the development of this document and I am extremely grateful for their volunteered efforts.

I would also like to acknowledge Richard Cullen and Tao Chen, employees of the Primary Healthcare Research Unit (PHRU), for their assistance with coding and data preparation in the statistical software package STATA-13. Without them, this analysis would not have been possible.

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List of Symbols, Nomenclature or Abbreviations

Abbreviation	Full Description
AIC	Akaike Information Criterion
ARD	Absolute Risk Difference
BMI	Body Mass Index
CI	Confidence Interval
CCI	Canadian Classification of Health Interventions
CDA	Census Dissemination Area
CIHI	Canadian Institute for Health Information
DAD	Discharge Abstract Database
HHCA	Home Hospital Catchment Area
HIV	Human Immunodeficiency Virus
HMDB	Hospital Morbidity Database
HREB	Health Research Ethics Board
ICD-10 CA	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada
IV	Instrumental Variable
IVM	Instrumental Variable Method
NICU	Neonatal Intensive Care Unit
OR	Odds Ratio
P-P Plots	Probability-Probability Plots
PPV	Positive Predictive Value
RCT	Randomized Controlled Trial
SLS	Stage Least Squares
VBAC	Vaginal Birth After Caesarean
WHO	World Health Organization

Chapter One - Introduction

1.1 Background

As defined by Statistics Canada, early neonatal death is known as the death of a child under one week of age, excluding stillbirths.[1] In contrast to most developing nations, the incidence of early neonatal mortality in industrialized countries is typically low.[2,3] In Canada, early neonatal death comprised 0.31% of all live births in 2009 and has remained fairly constant over the last several decades.[2,3] The leading causes of early neonatal death in the developed nations include congenital and chromosomal abnormalities as well as complications related to low birth weight.[4] Other factors, such as intrauterine hypoxia, birth asphyxia, and complications of labor and delivery, have also been cited as significant contributors to early neonatal mortality rates.[4] While the majority of early neonatal deaths are due to genetic predispositions, identifying the preventable causes which can be modified through policy and practice change has become a primary focus in recent years.[4,5] Of these, the safety of caesarean delivery has been identified as an area in need of further evaluation in response to increasing caesarean delivery rates and its unclear relationship with neonatal survival.[6-21]

As shown in Figure 1, Canada has witnessed a rise in the proportion of caesarean deliveries which extends far beyond the recommended range of 10-15% established by the World Health Organization (WHO).[9,22] Driven primarily by a rise in the primary caesarean section rate, caesarean deliveries comprised 27.2% of all deliveries in 2012, an 8.5% increase since 1997.[9,23] Several studies have suggested that increases in caesarean delivery rates can be

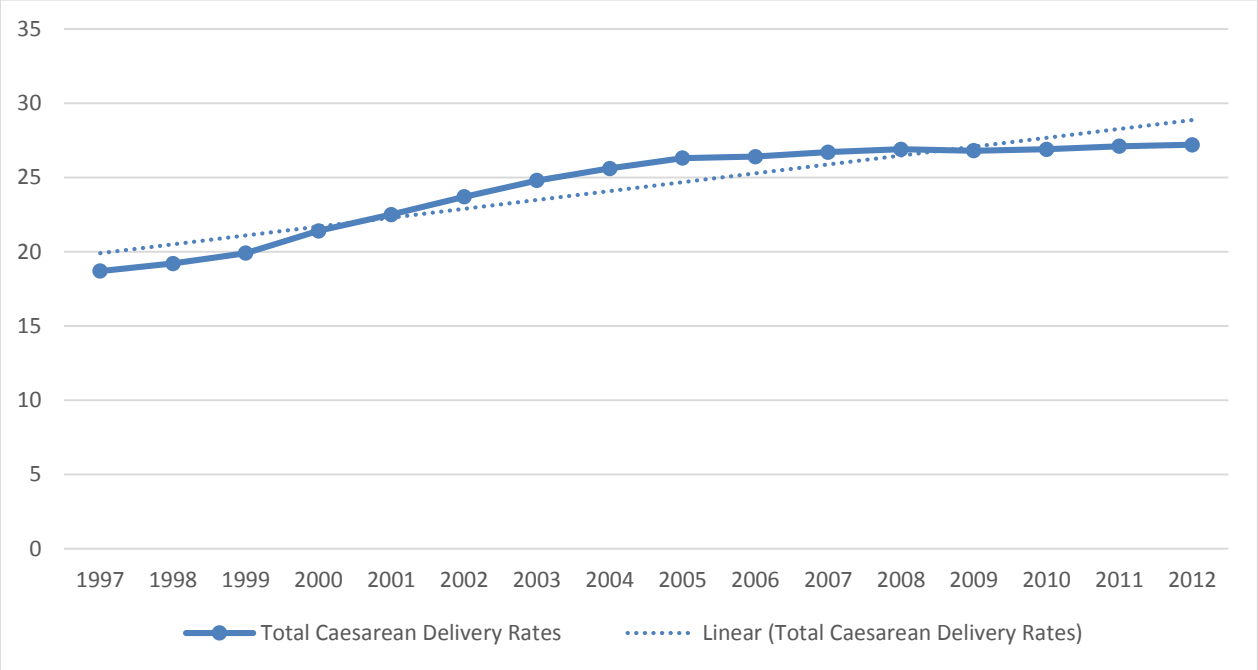
attributed to a higher incidence of risk factors during pregnancy, including multiple gestation, macrosomia, and older maternal age.[23,24] It has also been proposed that temporal changes in obstetrical management, which include routine caesarean deliveries for breech presentations and women with a history of caesarean delivery, may partly explain the observed trend.[25] Yet, despite uniform increases in risk factors for caesarean delivery across the country, distinct regional trends in caesarean delivery rates persist.[26] Among the provinces, the rate of caesarean sections in 2012 ranged from 21.4% in Manitoba to 32.0% in British Columbia, while the territories ranged from 11.3% in Nunavut to 25.0% in the Yukon.[26] This suggests that differences in obstetrical management, whether it be regional, practice, or individually-based, are influencing an individual's likelihood of receiving a caesarean delivery irrespective of their current health status.[26] This theory has been supported by several studies which have demonstrated that significant increases in caesarean delivery rates remained after controlling for factors, such as a history of previous caesarean section, which may have explained the increasing trend.[27]

It is apparent that the decision to provide a caesarean section is far from black and white; a complex interaction of medical indications, litigation deterrents, and personal preferences are likely influencing a provider's obstetrical management decisions and, in many cases, leading them to favor caesarean delivery over vaginal birth. Medico-legal factors have repeatedly shown to be predictive of an obstetrician's clinical behavior.[28-30] Fear of litigation for complications that arise during a vaginal delivery has partially contributed to an increase in caesarean delivery rates.[28-30] It has been suggested that personal preference, which is largely dependent on experience and training, can also have a significant influence on decisions regarding mode of

delivery.[31] One study found that a large portion of fourth year residents throughout the United States felt incompetent to perform obstetric forceps or vacuum deliveries and did not routinely incorporate them into their practice.[31] Consequently, alternative procedures such as caesarean delivery may be chosen by obstetric residents and staff when faced with complicated labors. Other motivators, such as scheduling benefits, may bias providers to perform a caesarean delivery as it can take substantially less time to complete than a women in prolonged labor managed vaginally. A combination of these factors may help explain why providers have been found to perform a caesarean section for subjective indications in comparison to past years, highlighting the influence of non-medical factors in the decision making process.[24]

Irrespective of the conflicting evidence surrounding their safety, caesarean deliveries continue to become increasingly more common in the developed nations.[32-41] To ensure that the incidence of early neonatal death is not affected by these increasing rates, it is important to determine whether the intervention itself poses any additional risk on neonatal survival when compared to vaginal birth. A better understanding of the association between caesarean delivery and early neonatal mortality is therefore warranted and crucial for health-care policy makers, providers, and expecting families.

Figure 1: Temporal Trend in Total Caesarean Delivery Rates within Canada



1.2 Literature Review

1.21 Details of Search Strategy

Pubmed was initially used to identify articles which studied the association between caesarean delivery and early neonatal/neonatal/perinatal mortality. Articles were limited to those in English, associated with an abstract, and pertaining to humans. The initial search incorporated a MeSH term search of caesarean delivery in conjunction with vaginal delivery and early neonatal/neonatal/perinatal death or early neonatal/neonatal/perinatal mortality. Combining searches resulted in 1817 articles. Although Embase and Cochrane Library were also used to identify articles, they did not identify unique papers from that of Pubmed.

1.22 Inclusion Criteria for Selection of Articles

Articles were first selected based on the relevance of their title (n=85). These eighty-five articles were screened for applicability based on their abstract and a total of fourteen articles were reviewed.

1.23 Review of the Literature

In an era where caesarean sections have become one of the most common inpatient surgeries, a visible rise in studies examining the relationship between caesarean delivery and maternal and neonatal health outcomes has been observed in the literature.[42] While the effect of caesarean delivery in comparison to vaginal birth has been researched extensively with regard to maternal and neonatal morbidity, there are relatively few studies which have assessed its impact on neonatal mortality.[7,8,10-21] Of those examining high-risk populations, a clear protective effect of caesarean delivery has been shown in the context of neonates delivered at the threshold of viability.[13] Breech presentations managed by caesarean section have generally been shown to be protective across all birthweights, however some studies suggest that the protective effect is only present for specific birthweight categories.[11,12,16] Only one study found that caesarean delivery imposed a significant risk on neonatal survival for breech presentations between twenty-four and thirty-four weeks.[14] With respect to multiple gestations, Haest and his colleagues found no difference in perinatal mortality between twins born by caesarean section in comparison to vaginal birth.[18] When stratified by fetal weight, one author found that those twins weighing less than 1000 grams together had an improved survival rate when delivered by caesarean section.[17] Lastly, while most studies assessing vaginal birth after caesarean (VBAC) versus repeat caesarean deliveries have focused on neonatal morbidity as their primary outcome, one study found that neonatal mortality was significantly increased for women undergoing a repeat

caesarean delivery as opposed to a VBAC.[19] Many of these studies are limited by a small sample size and inadequate adjustment for important prognostic factors, likely impacting the validity of their results.

In studies which have not restricted their analyses to a specific sub-population, such as breech or preterm deliveries, caesarean section has consistently shown to increase the risk of neonatal mortality in comparison to vaginal birth.[7,8,20,21] The World Health Organization 2005 Global Survey on Maternal and Perinatal Health Research Group conducted a multi-center prospective study whereby one hundred and twenty three institutions were randomly assigned to take part in the study.[21] Nurses and midwives working in the labor and postpartum wards from the enrolled institutions and trained staff reviewed medical records and collected information on the deliveries.[21] Independent of measured confounding factors, the study found that elective caesarean delivery significantly increased the risk of neonatal death up to hospital discharge for fetuses in a cephalic presentation (Adjusted OR=1.66, 95%CI=1.26-2.20).[21] Major limitations of the study revolve around its inability to standardize the diagnoses and indications for a caesarean delivery across the institutions involved.[21] The authors also stress that a number of indications for a caesarean delivery which may have inflated risk estimates were not collected or adjusted for.[21] Likewise, subjective diagnoses which may have been managed differently between institutions were also not captured during data collection.[21]

In 2009, De Luca and his colleagues conducted a prospective cohort study of obstetric and neonatal outcomes between women delivering by caesarean section and women delivering vaginally from a tertiary care hospital in Switzerland.[20] They found that elective caesarean delivery significantly increased the risk of neonatal (intrapartum and predischarge) mortality by

109% relative to planned vaginal delivery, however the risk estimate was associated with a wide confidence interval (Adjusted OR= 2.09 , 95%CI= 1.07-4.09).[20]

In attempting to limit the study population to a low-risk group, MacDorman and her colleagues retroactively analyzed a United States linked birth/infant death dataset and found that in term births with no known risk factors, caesarean delivery significantly increased the risk of neonatal death by roughly three times that of vaginal birth (Adjusted OR = 2.71, 95%CI = 2.43-3.02).[7] It has been argued that the study itself is methodologically flawed by including high-risk pregnancies and labors in the low-risk caesarean delivery group, potentially over-estimating the risk associated with caesarean delivery.[43] In response, MacDorman and her colleagues examined a similar cohort using an intention-to-treat framework in hopes of accurately assigning deliveries to each study arm.[8] An emergency caesarean section performed after a woman was in labor was combined with vaginal births to create a "planned vaginal delivery" group, as this would indicate the intention to deliver vaginally.[8] Conversely, the "planned caesarean delivery" group included only deliveries where a caesarean section was performed in the absence of labor.[8] Caesarean delivery remained a significant predictor of neonatal death in comparison to vaginal birth in using the intention-to-treat framework, however the adjusted odds ratio was attenuated by almost half (Adjusted OR = 1.69, 95% CI = 1.35-2.11).[8] Although the intention-to-treat model was able to reduce the inflation of risk observed in the previous MacDorman study, it is likely that the risk associated with planned caesarean deliveries continues to be exaggerated due to a lack of adjustment for important unmeasured confounders.

Studies have shown that women receiving caesarean sections are more likely to have been affected by risk factors which are detrimental to their neonate's survival, including older

maternal age, comorbities, preterm delivery, HIV positive status, multiple gestation, pre-eclampsia, eclampsia, and previous caesarean section.[44-48] Women receiving caesarean sections are also more likely to have experienced complications during labor and delivery, such as cord prolapse, placenta previa, abruption placenta, hemorrhage, premature rupture of membranes, and oligohydramnios.[49-52] Likewise, the probability of neonates with low birth weights, macrosomia, and congenital anomalies in women delivered by caesarean section are much higher than those delivered vaginally, all of which have been shown to increase the odds of neonatal death.[53-57] In addition to an array of medical indications for a caesarean delivery which predispose newborns to adverse outcomes, socioeconomic factors such as aboriginal identify and lower levels of both education and income are primarily seen in women delivering by caesarean section and independently reduce newborn survival.[58,59] Hospital factors, such as high delivery volumes and levels of service, have also been associated with higher rates of both caesarean delivery and neonatal death due to the high-risk patients typically cared for at hospitals providing tertiary level care.[60,61]

Observational studies comparing neonatal death between caesarean and vaginal births have traditionally relied on standard statistical models to account for a large majority of the aforementioned confounding factors in their calculation of risk estimates. While standard statistical models are able to account for risk factors of early neonatal death which are captured in a hospital database, they are incapable of adjusting for hidden bias which may distort a researchers findings. Factors such as severity of comorbidities and patient frailty are rarely measured, yet would be inherently tied to a women's likelihood of receiving a caesarean section and to the neonate's survival. As a result, standard statistical methods used in observational

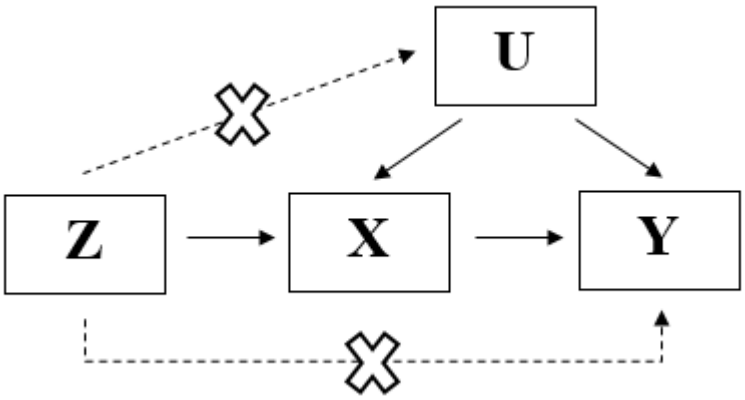
studies are more likely to produce biased findings since they are unable to account for unmeasured selection bias. Evidence for this can be seen in randomized controlled trials (RCTs) which have refuted the results of observational studies, presumably due to inadequate adjustment for unmeasured confounding factors in their multivariate analyses.[62] It is possible that the lack of adjustment for unmeasured selection bias has resulted in an overestimation of the risk associated with caesarean delivery on neonatal mortality and should be re-evaluated using more sophisticated analytic tools.

1.3 Instrumental Variable Method (IVM) Approach

As a way to overcome the shortcomings inherent in observational studies, many researchers have begun to apply analytic methodologies which mimic some of the advantageous features of an RCT to observational datasets.[62-65] One of these approaches, called the Propensity Score method, acts to evenly distribute measured baselines covariates between intervention and control groups by assigning a value to individuals who are likely to receive the intervention of interest based on a set of prognostic factors.[66] By matching or stratifying these scores between the intervention and control groups, overt bias can be reduced between individuals with the same propensity score.[62,66] However, analogous to multivariate models, the Propensity Score method does not account for unmeasured selection bias which may be associated with the intervention group.[62] In response, an instrumental variable method (IVM) originating from the field of econometrics has been utilized to not only remove the effects of overt bias, but to also adjust for hidden bias in observational studies.[62-65] When applied to observational datasets, this approach has yielded instrumental variable-adjusted estimates closely approximating those obtained from RCTs.[62]

Unlike multivariate and Propensity Score methods, the IVM is able to equally distribute unmeasured confounding factors between intervention and control groups through the use of an instrumental variable (IV). Chosen by the investigative team, an IV must be identified which satisfies several conditions (Figure 2): First, it must strongly predict an individual's likelihood of receiving the intervention.[67] Secondly, it must not directly predict the outcome of interest, except through its association with the receipt of the intervention.[67] Lastly, it must be an exogenous variable, so that it is not related to the outcome through measured or unmeasured paths.[67] The IV, a proxy for randomization, functions to naturally randomize patients into groups which differ based on their likelihoods of receiving an intervention of interest.[67] Individuals are then compared based on their likelihoods of receiving an intervention rather than on the actual intervention they received, effectively balancing measured, unmeasured, and unknown confounding variables.[67] This approach can be especially useful for observational studies assessing a surgical procedure, since patients who are candidates for a surgical intervention likely exhibit many unmeasured risk factors in comparison to their healthy counterparts which would inflate risk estimates. By accounting for unmeasured sources of bias, utilizing the IVM can serve as a more valid approach in determining intervention effects amongst patients in observational studies.

Figure 2: The Assumptions of the Instrumental Variable (IV)



1. The IV (Z) must strongly predict receipt of the intervention (X).[67]
2. The IV (Z) must only be associated with the outcome (Y) through its direct association with the intervention (X).[67]
3. The IV (Z) must not be associated with the outcome through measured or unmeasured (U) paths.[67]

1.4 Purpose of Study

The research surrounding the influence of caesarean delivery on neonatal mortality in comparison to vaginal birth is limited and is likely influenced by unmeasured selection bias. The purpose of this study is to compare the results from traditional multivariate methods and IV-adjusted analyses to determine if caesarean delivery increases the risk of early neonatal death in comparison to vaginal birth. Specifically, we will aim to address the following questions:

Objective 1: *In comparison to vaginal delivery, is caesarean delivery associated with an increased risk of early neonatal mortality in the Canadian obstetric population?*

Objective 2: *Is the association between mode of delivery, including caesarean or vaginal delivery, and early neonatal mortality dependent on the statistical method used?*

1.5 Significance of Study

To our knowledge, this will be the first study to utilize the IVM approach when assessing the relationship between caesarean delivery and early neonatal mortality in comparison to vaginal birth. The conclusions drawn from IVM analyses apply only to the marginal population, i.e. those who would receive a caesarean delivery in one region but not in another.[62] Due to the subjective nature of this definition, identifying a marginal individual in practice can be difficult. As a result, the conclusions drawn from instrumental variable analyses tend to be better suited for policy related questions related to health-system level factors as opposed to the clinical effectiveness for an individual patient.[62] The conclusions generated from this study can thus guide health policy initiatives to target factors at the hospital level which are responsible for decisions regarding mode of delivery for the Canadian obstetric population.

Chapter Two - Methodology

2.1 Study Design

This is a retrospective cohort study which compares the outcome of early neonatal mortality between women who delivered through a caesarean section with women who delivered vaginally. The cohort includes all in-hospital births during the fiscal years of April 1, 2006 - March 31, 2009 across Canada, excluding deliveries in Quebec. The exposed group (women who delivered by caesarean section) and the non-exposed group (women who delivered vaginally) were identified in the Discharge Abstract Database (DAD) from the Canadian Institute of Health Information (CIHI) using Canadian Classification of Health Interventions (CCI) codes. Linkage of the maternal data file and neonatal data file from CIHI allowed mother's to be associated with their respective neonates. Newborns were followed between 20 completed weeks of gestation and 7 days post-partum in order for the incidence of early neonatal mortality to be compared between groups.

2.2 Study Population

Exclusion Criteria

To be consistent with other studies, newborns with a weight at delivery of less than 500 grams were excluded because at the limit of viability, decisions regarding the mode of delivery would be highly variable.[68,69] All stillbirths were removed from the study since they are likely unrelated to mode of delivery and largely dependent on non-intrapartum factors, such as genetic predispositions and pre-existing maternal comorbidities. Removing stillbirths, which comprise a

large proportion of early neonatal deaths, can thus help determine the effect of caesarean delivery on neonatal survival. Lastly, all deliveries in which additional instrumentation was used, in the form of obstetric forceps or vacuum, were excluded from the study population. Obstetric forceps and vacuum deliveries, in addition to deliveries in which both instruments were used, have been shown to increase the risk of neonatal morbidity in comparison to unassisted vaginal birth.[70] Similarly, deliveries where either intervention was followed by a caesarean section have also been shown to increase the risk of adverse neonatal outcomes.[71] Caesarean or vaginal deliveries simultaneously coded with obstetric forceps or vacuum extraction were therefore excluded from the study population to remove any potential adverse effect the instrumentation, as opposed to the caesarean section itself, had on the neonatal outcome.

2.3 Data Sources

The primary data source used in this study was the Discharge Abstract Database (DAD), which includes hospital discharge records collected by the Canadian Institute of Health Information (CIHI).[72] The DAD encompasses administrative, medical and demographic information from hospital in-patient discharges and day surgery interventions.[72] With exception to Quebec, records are received directly from either acute care facilities, health/regional authorities, or ministries/departments of health across Canada.[72] Unlike other regions of Canada, data from Quebec is collected in the Hospital Morbidity Database (HMDB), which we did not have access to.[72] Comorbidities and complications are coded according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada - [ICD-10 CA], while procedures are coded according to the Canadian Classification of Health Interventions, Volume Three – [CCI]. In a data quality study using 2007-2008 DAD data

conducted by CIHI, it was found that the sensitivity for significant diagnoses relative to the gold standard of expert chart re-abstractions was 80.1% (95% CI 78.4% – 81.9%), showing a high degree of consistency for the completeness of reporting across all regions.[73]

Socioeconomic factors were obtained using 2006 Canadian Census Data aggregated at the Census Dissemination Area (CDA) level and mapped to patient postal codes. This study was approved by the Health Research Ethics Board (HREB) of Newfoundland and Labrador.

2.4 Exposure Variable

Exposed Group – Caesarean Delivery

Includes exclusive caesarean deliveries, excluding those in which additional instrumentation was used. The CCI codes used to identify exclusive caesarean deliveries can be seen in Appendix A.

Non-exposed Group – Vaginal Delivery

Includes exclusive vaginal deliveries, excluding those in which additional instrumentation was used. The CCI codes used to identify exclusive vaginal deliveries can be seen in Appendix A.

2.5 Dependent Variable

Early Neonatal Mortality

Given that three quarters of all neonatal deaths occur during the first week of life, of which 25%-45% occur within the first day, the primary neonatal outcome of early neonatal mortality was defined as death between 20 completed weeks of gestation and 7 days post-partum.[74] This includes deaths that occurred in newborns who were discharged and then re-

admitted to hospital within 7 days of birth. We also decided to include deaths that occurred after 7 days of age for newborns that were continuously hospitalized to help protect against bias due to hospitals that have the technological capabilities to keep infants alive on life support for greater than 7 days but who end up dying early in life. Stillbirths were excluded from the analysis. CIHI variables and ICD-10 codes were used to identify early neonatal deaths. The ICD-10 codes used to identify early neonatal mortality can be found in Appendix B.

2.6 Instrumental Variable (IV)

Local Caesarean Delivery Rate

The local caesarean delivery rate was defined as the percentage of caesarean deliveries out of the total number of deliveries in the home hospital catchment area (HHCA). In this study, the local caesarean delivery rate (measured as the caesarean delivery rate at an individual's home hospital based on their place of residence) will serve as the instrumental variable for several reasons. Local caesarean delivery rates are highly variable across Canada and would therefore strongly predict an individual's likelihood of receiving a caesarean section. To ensure that our instrumental variable is exogenous, i.e. not related to the outcome of early neonatal mortality through measured or unmeasured paths, we will use home hospital caesarean delivery rates as opposed to delivery hospital caesarean delivery rates. This is because most high risk pregnancies, which have an increased likelihood of caesarean section associated with them, are typically identified prenatally and referred to higher level hospitals for delivery. Consequently, delivery hospitals would likely show a strong association between caesarean section rates, risk factors, and the outcome of neonatal mortality and reduce the validity of the IV. A patient's home hospital was determined using the hospital service area method.[75] Using this method, a

postal code was attributed to a given hospital's catchment area when a plurality of patients from the same postal code chose to obtain their care there. All (not just obstetrical) acute care hospital admissions during the study period were used to determine catchment areas.

2.7 Statistical Analysis

Descriptive statistics, in the form of frequency (proportion) and mean $\pm$ standard deviation, were conducted on categorical and continuous variables, respectively. The effect of mode of delivery, being either caesarean or vaginal delivery, on early neonatal mortality was measured using a bivariate logistic regression, followed by a multivariate logistic regression.

Upon completing these traditional analyses, an instrumental variable-adjusted analysis was conducted. Several models which support IV-adjusted analyses were considered, including a probit model, a model incorporating both ordinary least squares and logistic regressions, and a 2-stage least squares (2SLS) model.[76] IV-probit models are typically used in the setting of a dichotomous outcomes variable; however, when endogenous regressors are continuous, the use of IV-probit models are inappropriate.[77] One author explains that another challenge with using IV-probit models is that their beta coefficients are difficult to interpret and often require varying scaling factors to produce a meaningful estimate.[78] While theoretically ideal, risk estimates produced from models incorporating both an ordinary least squares regression and a secondary logistic regression for binary outcome variables are biased even when the IV is strong.[79] Instead, we chose to perform the IV-adjusted analysis using a 2SLS model based on a linear distribution.[76] In this model, the likelihood of receiving an intervention of interest is first assessed in a regression model as a function of measured covariates and the IV.[76] Next, the intervention effect is estimated in a regression of the outcome on the predicted receipt of

intervention (as assessed in the first stage) while simultaneously adjusting for measured covariates.[76] This step allows for groups to be compared based on their likelihood of receiving the intervention rather than actual intervention received.[76] Although this study has a dichotomous outcome variable, the 2SLS model does not appear to affect risk estimates and may only marginally influence their standard errors.[76] Similarly, little difference between point estimates and their precision has been shown between 2SLS models and models incorporating a logistic regression with an ordinary least squares regression for binary outcome variables.[78,79] Stukel and her colleagues used a similar approach when comparing catheterization with mortality at one and four years, implementing a 2SLS IV-adjusted analysis for exposure and outcome variables which were dichotomous in nature.[62]

To assess the effect of different levels of local caesarean delivery rates on early neonatal mortality, the IV was dummy coded into quintiles. These quintiles were entered into a multivariate logistic regression as the independent variable, using the lowest quintile as the reference category, to determine the impact of varying rates of local caesarean delivery on early neonatal mortality. While this constitutes an "implicit" use of the IVM and has been previously used in the literature, the majority of estimates drawn from this method can be hard to interpret individually.[62] However, by specifically comparing the highest and lowest quintiles, we can better understand how regions experiencing high rates of caesarean sections compare to those experiencing low rates of caesarean sections with respect to the incidence of early neonatal death.

Both multivariate and instrumental variable-adjusted analyses adjusted for the following 24 covariates: Gestational age at delivery, maternal age, HIV positive status, diabetes,

hypertension, multiple gestation, pre-eclampsia, eclampsia, previous caesarean section, neonatal sex, birth weight, congenital anomalies, cord prolapse, placenta previa, abruption placenta, hemorrhage, premature rupture of membranes, oligohydramnios, education level, income, aboriginal identity, level of hospital service, hospital delivery volume, and specialty of provider. The ICD-10 codes used to identify maternal risk factors, labor/delivery complications, and neonatal congenital anomalies can be found in Appendices C and D.

Hospital level of service was classified according to criteria published by the American Academy of Pediatrics and Canadian Pediatric Society with modifications for use with administrative data.[80,81] Within this classification system, there are four levels of hospital service including Level 0, 1, 2, and 3 (Appendix E). Sub-classification of hospital service into Level 3b and Level 3c was dependent on a minimum of 5 records from a given hospital containing both the prerequisite procedure code and a compatible diagnosis code found in Appendix F. Socioeconomic (SES) factors were not directly available through the DAD, however we obtained this information through the 2006 Canadian Census Data aggregated at the Census Dissemination Area (CDA) level mapped to maternal postal codes. Income was defined by the Canadian Census as the mean "total household income in Canadian dollars from all sources minus federal, provincial and territorial income taxes paid for 2005 for individuals aged 15 years and older, excluding institutionalized residents".[82] Aboriginal identity was defined by the Canadian Census as the "percentage of individuals who reported identifying with at least one Aboriginal group, that is, North American, Indian, Métis or Inuit, and/or those who reported being a Treaty Indian or a Registered Indian, as defined by the Indian Act of Canada, and/or those who reported they were members of an Indian band or First Nation".[82] Lastly, education

level was defined by the Canadian Census as the "percentage of individuals aged 15 years or older excluding institutional residents and employees who obtained at least a high school education, including both diplomas and degrees".[82]

We used categorical variables to control for maternal age, delivery gestational age, and neonatal weight since they were shown to produce a better fit in the statistical models (i.e. multivariate logistic model of early neonatal death which adjusted for 398 delivery hospitals clusters) than transforming the variables and incorporating them as continuous variables. This was determined by referring to the Akaike information criterion (AIC) value, a measure of the quality of a statistical model. Subsequently, the interval division of a categorical variable resulting in the lowest Akaike information criterion (AIC) value, indicating a higher quality statistical model, was incorporated in the statistical analyses. Maternal age, measured in years, was categorized into 8 categories as follows: <= 14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-59, >=60 using the age range 25-29 as the reference group in the predictive model. Delivery gestational age, measured in weeks, was categorized into 9 categories as follows: <28, 28-29, 30-31, 32-33, 34-35, 36-37, 38-39, 40-41, >41 using the delivery gestational age of 40-41 as the reference group in the predictive model. Lastly, neonatal weight, measured in grams, was categorized into 13 categories as follows: 500-749, 750-999, 1000-1249, 1250-1499, 1500-1999, 2000-2499, 2500-2999, 3000-3499, 3500-3999, 4000-4499, 4500-4999, 5000-9000 using 3500-4000 grams as the reference group in the predictive model. Conversely, the socioeconomic factors and delivery hospital volume were found to produce a better fit upon transformation as continuous variables than as categorical variables. Normality was assessed by graphing probability-probability (P-P) plots, which illustrate whether the observed data follows a linear or

non-linear distribution. Based on the results of the P-P plots for each of the variables analyzed, the following three transformations were performed and incorporated into the predictive models: $(\text{Education})^3$, $\sqrt{}$(Aboriginal identity), and $\sqrt{}$(Delivery hospital delivery volume).

The strength and validity of the instrumental variable were assessed through an F-statistic test and an analysis of the distribution of measured covariates across different levels of the IV. If the IV is strongly associated with the receipt of a caesarean delivery, the F statistic should be equal to or greater than 10 and the partial correlation coefficient between the IV and the receipt of a caesarean delivery will be large.[76] Next, the IV, local caesarean delivery rates, was divided into quintiles to visualize the distribution of measured covariates across different levels of the IV. While it cannot be proven, it is assumed that if measured risk factors are evenly distributed across different levels of the IV, that unmeasured risk factors are similarly distributed. This would provide evidence that the IV we have chosen is exogenous.

The statistical software program STATA-13 was used for all analyses and a p-value less than 0.05 was considered to be statistically significant. Given that patients admitted to the same hospital may exhibit similar outcomes (thus violating the independence assumption), all analyses were adjusted for clustering at the delivery hospital using the "cluster" option in the IVREG2 syntax.

Chapter Three – Results

3.1 Descriptive Statistics

The study cohort consisted of 844,410 mothers who delivered a total of 859,180 infants. Ninety-nine point four percent of the neonates were linked to a maternal record, representing 842,278 deliveries. Of those deliveries, 0.05% were excluded due to inability to link to a single maternal record, 0.7% were excluded due to newborn weight <500 grams, 0.4% were excluded due to stillbirths, and 12.4% were excluded due to the use of forceps or vacuum during the delivery. After these exclusions, the study population included 728,235 unique deliveries. Covariate data was missing for 1.7% of deliveries. After removal of missing data, 715,615 deliveries remained for the final analyses. All analyses adjusted for clustering in 398 hospitals.

Out of the 728,235 births included in this study, 29% (n = 211,226) were delivered by caesarean section, 71% (n = 517,009) were delivered vaginally, and early neonatal mortality occurred in 0.26% of cases (n = 1,907). All characteristics of the study population by mode of delivery can be seen in Table 1.

Table 1 - Characteristics of the Study Population based on Mode of Delivery

	Caesarean Delivery (n=211,226)	**Vaginal Delivery (n=517,009)**
Maternal Risk Factors		
GA at Delivery *mean weeks ± SD*	38.3 ± 2.6	39.0 ± 2.3
Age *mean years ± SD*	30.5 ± 5.6	28.8 ± 5.6
HIV positive status *n (%)*	211 (0.10)	231 (0.04)
Type 1 Diabetes Mellitus *n (%)*	1,117 (0.53)	613 (0.12)
Type 2 Diabetes Mellitus *n (%)*	1,139 (0.54)	960 (0.19)
Gestational Diabetes Mellitus *n (%)*	13,572 (6.43)	19,402 (3.75)
Unspecified Diabetes Mellitus *n (%)*	1,771 (0.84)	1,424 (0.28)
Hypertension *n (%)*	19,417 (9.19)	24,014 (4.64)
Twin *n (%)*	13,145 (6.22)	6,352 (1.23)
Triplet *n (%)*	624 (0.30)	63 (0.01)
Pre-Eclampsia *n (%)*	5,050 (2.39)	3,357 (0.65)
Eclampsia *n (%)*	298 (0.14)	142 (0.03)
Previous Caesarean Section *n (%)*	74,732 (35.38)	15,521 (3.00)
Neonatal Risk Factors		
Birth Weight *mean grams ± SD*	3,313 ± 691	3,396 ± 544
Male *n (%)*	110,436 (52.28)	257,874 (49.88)
Female *n (%)*	100,786 (47.71)	259,114 (50.12)
Congenital Anomalies *n (%)*	8,876 (4.20)	13,647 (2.64)
Labour/Delivery Complications		
Cord Prolapse *n (%)*	182 (0.09)	26 (0.01)
Placenta Praevia *n (%)*	3,879 (1.84)	332 (0.06)
Abruption Placenta *n (%)*	4,192 (1.98)	3,963 (0.77)
Hemorrhage *n (%)*	1,743 (0.83)	2,024 (0.39)
Premature Rupture *n (%)*	22,455 (10.63)	66,475 (12.86)
Oligohydramnios *n (%)*	361 (0.17)	299 (0.06)
CDA Socioeconomic Factors*		
High School Education† *mean percentage ± SD*	84.3 ± 12.4	83.1 ± 13.8
Income‡ *mean Canadian dollars ± SD*	27,950 ± 9,108	27,335 ± 9,168
Aboriginal Identity$^{\Phi}$ *mean percentage ± SD*	56.0 ± 17.4	8.14 ± 21.1
Delivery Hospital Factors		
Annual		
Delivery Volume *mean ± SD*	2,546 ± 1,601	2,426 ± 1,590
Obstetrician Delivery Volume *mean ± SD*	224 ± 157	192 ± 171

Hospital Level of Service		
Level 0 *n (%)*	49 (0.02)	665 (0.13)
Level 1 *n (%)*	48,072 (22.76)	134,882 (26.09)
Level 2 *n (%)*	102,410 (48.48)	246,446 (47.67)
Level 3 *n (%)*	60,695 (28.73)	134,997 (26.11)
Provider Type		
General Practitioner *n (%)*	9,861 (4.67)	168,886 (32.67)
Obstetrician *n (%)*	198,323 (93.89)	320,313 (61.96)
Midwife *n (%)*	47 (0.02)	25,159 (4.87)
Other *n (%)*	2,995 (1.42)	2,651 (0.51)

Abbreviations: GA= Gestational Age; CDA= Census Dissemination Area

* All variables measured by CDA using 2006 Canadian Census Data

† Data represents the average percentage of individuals aged 15 years or older excluding institutional residents and employees who obtained at least a high school education, including both diplomas and degrees

‡ Data represents the average household income in Canadian dollars from all sources minus federal, provincial and territorial income taxes paid for 2005 for individuals aged 15 years and older, excluding institutionalized residents

Φ Data represents the average percentage of individuals who reported identifying with at least one Aboriginal group, that is, North American, Indian, Métis or Inuit, and/or those who reported being a Treaty Indian or a Registered Indian, as defined by the Indian Act of Canada, and/or those who reported they were members of an Indian band or First Nation

3.2 Testing the Validity of the Instrumental Variable

The IV, local caesarean delivery rates, was highly variable across regions, ranging from 0%-100%. In a multivariate logistic regression of the IV on the receipt of a caesarean delivery after adjusting for all 24 covariates, the adjusted r^2 was 33.35%, the F statistic was 6552.53, and the p-value was <0.05. This indicates that the IV is strongly predictive of whether or not an individual received a caesarean section. Further analysis of the validity of the IV shows that using local caesarean delivery rates as a proxy for randomization resulted in the majority of measured covariates to be equally distributed across different quintiles of the IV, with exception to previous caesarean section and education level (Table 2). Although we cannot prove that unmeasured covariates are equally distributed as well, it is fair to conclude that unmeasured covariates likely exhibit the same equal distribution across different levels of the IV.

Furthermore, the fact that early neonatal mortality did not show an increasing trend across quintiles of the IV gives evidence that the IV is not directly associated with the outcome, further strengthening the use of local caesarean delivery rates as our IV.

Table 2 - The Distribution of Measured Covariates by Quintile of Local Caesarean Delivery Rates

	Local Caesarean Section Rates by Quintile				
	Q1 (0^-)	**Q2 (24.8^-)**	**Q3 (28.3^-)**	**Q4 (31.2^-)**	**Q5 (32.8^-)**
Maternal Risk Factors					
GA at Delivery *mean weeks*	38.9	38.9	38.8	38.7	38.8
Age *mean years*	27.8	29.0	29.4	30.1	30.1
HIV positive status *%*	0.06	0.05	0.07	0.07	0.05
Type 1 Diabetes Mellitus *%*	0.25	0.23	0.24	0.25	0.23
Type 2 Diabetes Mellitus *%*	0.42	0.29	0.24	0.24	0.25
Gestational Diabetes Mellitus *%*	3.49	3.59	4.66	5.48	5.37
Unspecified Diabetes Mellitus *%*	0.48	0.44	0.43	0.49	0.35
Hypertension *%*	5.62	5.64	6.31	5.79	6.47
Twin *%*	2.28	2.50	2.80	2.86	2.94
Triplet *%*	0.07	0.09	0.09	0.13	0.09
Pre-Eclampsia *%*	1.12	1.07	1.22	1.03	1.34
Eclampsia *%*	0.08	0.06	0.05	0.05	0.06
Previous Caesarean *%*	10.1	11.8	12.6	13.3	14.1
Neonatal Risk Factors					
Birth Weight *mean grams*	3,422	3,393	3,356	3,312	3,379
Male *%*	50.5	50.6	50.4	50.8	50.6
Female *%*	49.5	49.4	49.6	49.2	49.4
Congenital Anomalies *%*	2.98	3.06	3.20	3.17	3.06
Labour/Delivery Complications					
Cord Prolapse *%*	0.02	0.03	0.03	0.04	0.03
Placenta Praevia *%*	0.41	0.55	0.55	0.70	0.68
Abruption Placenta *%*	1.15	1.22	1.14	1.02	1.08
Hemorrhage *%*	0.50	0.47	0.57	0.50	0.55
Premature Rupture *%*	12.08	11.55	12.13	11.10	14.19
Oligohydramnios *%*	0.07	0.14	0.13	0.07	0.04

CDA Socioeconomic Factors*					
High School Education† *mean percentage*	77.4	83.6	84.4	85.3	86.4
Income‡ *mean Canadian dollars*	25,231	27,959	27,953	27,862	28,509
Aboriginal IdentityΦ *mean percentage*	18.7	6.05	5.05	3.12	4.74
Delivery Hospital Factors					
Hospital Level of Service					
Level 0 *%*	0.28	0.05	0.10	0.03	0.04
Level 1 *%*	35.8	27.5	21.6	14.6	26.4
Level 2 *%*	29.7	52.0	55.5	60.3	42.0
Level 3 *%*	34.2	20.5	22.9	25.1	31.6
Annual					
Delivery Volume *mean*	2,164	2,147	2,590	2,959	2,437
Obstetrician Delivery *mean*	221	200	193	240	151
Volume *mean*	28.1	24.6	26.0	13.4	30.9
Provider Type					
General Practitioner *%*					
Obstetrician *%*	65.7	71.2	71.0	83.4	64.7
Midwife *%*	3.83	4.03	2.72	2.85	3.88
Other *%*	2.39	0.25	0.28	0.40	0.56
Neonatal Outcome					
Early Mortality *%*	0.31	0.24	0.25	0.27	0.24

Abbreviations: Q1-5= Quintile 1-5; GA= Gestational Age; CDA= Census Dissemination Area
Note: Local caesarean delivery rates ranged from 0%-100%

* All variables measured by CDA using 2006 Canadian Census Data

† Data represents the average percentage of individuals aged 15 years or older excluding institutional residents and employees who obtained at least a high school education, including both diplomas and degrees by quintile

‡ Data represents the average household income in Canadian dollars from all sources minus federal, provincial and territorial income taxes paid for 2005 for individuals aged 15 years and older, excluding institutionalized residents by quintile

Φ Data represents the average percentage of individuals who reported identifying with at least one Aboriginal group, that is, North American, Indian, Métis or Inuit, and/or those who reported being a Treaty Indian or a Registered Indian, as defined by the Indian Act of Canada, and/or those who reported they were members of an Indian band or First Nation by quintile

3.3 Significance Testing

Caesarean delivery was not associated with an increased risk of early neonatal mortality compared with vaginal delivery in the bivariate logistic regression analysis. Multivariate logistic

regression indicated that after adjusting for all 24 covariates, caesarean delivery significantly reduced the odds of early neonatal death in comparison to vaginal birth by 21%. Instrumental variable-adjusted regression indicated a lack of association between mode of delivery and early neonatal mortality after adjusting for all 24 covariates. In comparison to the multivariate logistic regression, the instrumental variable-adjusted regression showed a lower goodness-of-fit (r^2 = 0.602 vs r^2 = 0.345). All analyses were adjusted for 398 delivery hospitals clusters. These results can be seen in Table 3.

Table 3 - The Effect of Caesarean Delivery on Early Neonatal Mortality in Comparison to Vaginal Birth

	Risk Estimate	**95% CI**	**p-value**	**Measure of Risk**
Bivariate Logistic Regression	1.10	(0.93-1.31)	0.283	OR
Multivariate Logistic Regression	0.79	(0.66-0.93)	0.006*	OR
Instrumental Variable Adjusted 2 Stage Least Squares	-0.00053	($-4.3x10^{-3}$-$3.0x10^{-3}$)	0.781	ARD

Abbreviations: OR= Odds Ratio; ARD= Absolute Risk Difference
*p<0.05
Adjusted for 398 delivery hospital clusters
"Other" provider type was omitted in the multivariate and IV-adjusted analyses due to collinearity

In a multivariate logistic regression of the quintiles of the IV (local caesarean delivery rates) on early neonatal mortality which adjusted for all 24 covariates, the results indicated that the highest local caesarean delivery rates did not significantly increase the risk of early neonatal mortality in comparison with the lowest local caesarean delivery rates (Adjusted OR= 0.95, p= 0.664, 95% CI= 0.76-1.19).

Chapter Four - Discussion

4.1 Main Findings

The protective effect of caesarean delivery has been demonstrated in the context of postpartum stress, urinary incontinence, symptomatic pelvic organ prolapse, and major and minor birth trauma in comparison with spontaneous vaginal births.[32,33] Similarly, elective caesarean delivery has been shown to pose no additional risk on neonatal Apgar scores at 1 and 5 minutes, neonatal infection and overall neonatal complications.[34,35] To our knowledge, this is the first study to demonstrate a protective effect of caesarean delivery on early neonatal mortality when utilizing standard statistical methods. In contrast to the existing literature, this study indicates that caesarean delivery significantly decreases the risk of early neonatal death by 21% compared to vaginal delivery in the average obstetric population. There are several possible explanations for these findings. Earlier studies which have investigated the relationship between caesarean delivery and neonatal mortality analyzed obstetrical data between the mid 1990's and early 2000's, a time during which caesarean deliveries may have been performed in higher-risk individuals. To illustrate this point, one study found that increases in caesarean deliveries in Canada between 1994 and 2001 were largely attributed to an increase in the diagnosis of dystocia which is a somewhat subjective assessment of delayed progression of labor.[24] The shift towards a more subjective approach in delivery management decisions may have led to a greater proportion of low-risk pregnancies being delivered by caesarean section. In addition, previous studies have typically defined neonatal mortality as death within 28 days of life and have

included stillbirths in this mortality count, likely resulting in a greater number of neonatal deaths being observed. Together, these factors may be responsible for the apparent discrepancy between risk estimates.

Variability between risk estimates from standard and IV-adjusted models have been previously observed in the invasive management of acute myocardial infarction and its impact on survival.[62] In comparison to the multivariate analysis, this study found that the protective effect of caesarean delivery on early neonatal mortality was lost when applying the IVM, demonstrating that the observed association between caesarean delivery and early neonatal death is dependent on the statistical method used. These findings suggest that the risk estimates obtained from the multivariate model are biased by unmeasured factors which are responsible for the perceived safety of caesarean sections. In a report awaiting publication, primary author Dr. Aubrey-Bassler proposes that the apparent protective effect of caesarean delivery on neonatal outcomes may be a result of a disproportionate number of obese women delivering vaginally, given the risk of surgical complications in this population is high.[83,84] Similarly, it is possible that women who do not avail of prenatal services are less likely of being offered a caesarean section and thus at an increased odds of delivering vaginally. Both an increased maternal body mass index (BMI) and lack of prenatal care have consistently shown to increase the risk of adverse neonatal outcomes and may explain some of the variability observed between analytic models.[83,85,86]

Discrepancies between the risk estimates obtained from the multivariate and IV-adjusted models may also be partially explained by differences in the interpretation of the coefficients from each model and the population to which they generalize. For instance, in a multivariate

regression, the beta coefficient associated with the exposure variable is representative of the adjusted odds ratio, a relative measure of risk which generalizes to the entire population from which the sample was drawn.[87] Conversely, the beta coefficient associated with the exposure variable in a 2SLS IV-adjusted regression depicts the adjusted absolute risk difference, an absolute measure of risk which generalizes to the "marginal population".[87] The marginal population is defined as the sub-population of individuals whose intervention status depend on the value of the IV.[87] Using the IVM, the calculated intervention effect would therefore not apply to patients who either always or never undergo a caesarean delivery; it only applies to the marginal population of patients for which the mode of delivery might vary between hospitals.[87,88] The findings from the IV-adjusted model would not apply to women who would virtually always receive a caesarean section despite local caesarean delivery rates, and may include women with serious heart conditions who cannot labor well or women with complete placenta previa - similarly, the findings would not apply to first time mothers with no risk factors prenatally or in labor since they would virtually never receive a caesarean section despite local caesarean delivery rates. Instead, our findings would only extend to women with uncertain and highly subjective indication(s) for a caesarean section, such as women with comorbidities of varying severity or women experiencing dystocia.

Given the subjective definition of the "marginal population", identifying a marginal patient in practice would be challenging and likely differ between maternity care providers. As a result, it has been suggested that conclusions drawn from the IVM are better suited for health-system level recommendations rather than the clinical effectiveness for an individual patient.[62]

However, given the large discrepancy in risk estimates we observed between analytic methods, recommendations towards the provision of caesarean sections at a local level should be avoided until a higher powered IV-controlled study is conducted to determine the impact on maternal and neonatal outcomes, and other relevant factors such as length of stay and hospital costs. Compared with spontaneous vaginal deliveries, previous studies have found an increased risk of anesthetic complications, venous thromboembolism, hemorrhage, wound hematoma, endometriosis, peripartum blood transfusion, hysterectomy, major puerperal infection, and re-hospitalization within 30 days postpartum in the context of planned caesarean sections.[36-38] Neonatal complications, such as persistent pulmonary hypertension, respiratory problems, low Apgar scores, transient tachypnea, and $\geq$ 24 hour neonatal intensive care unit (NICU) admission have also been observed in neonates delivered by elective caesarean section compared with those delivered spontaneously.[39-41] Furthermore, CIHI has estimated that in comparison to vaginal birth, caesarean delivery is associated with nearly twice the cost ($4,600 versus $2,700) and hospital length of stay (4 versus 2 days) in the Canadian population.[89] Assuming that the existing evidence is also affected by unadjusted selection bias, future research should utilize the IVM to help health-care policy makers and providers establish well-evidenced recommendations towards the provision of caesarean sections.

4.2 Limitations

The tests used to assess the strength and validity of the IV show that our use of local caesarean delivery rates satisfies the conditions of an IV fairly well. However, among increasing quintiles of the IV, there was a clear trend noted between local caesarean delivery rates and previous caesarean sections. Similarly, education level was associated with increasing levels of

the IV and was found to significantly predict early neonatal mortality in both multivariate and instrumental variable-adjusted models (Table 2). Considering the variability noted among these measured covariates, it is plausible that unmeasured covariates lack an equal distribution across levels of the IV as well. The presence of unmeasured covariates which significantly predict early neonatal mortality could have potentially decreased the validity of our IV and biased the results obtained from the IV-adjusted analysis.

In this study, both caesarean and vaginal deliveries simultaneously coded with forceps or vacuum-use were excluded. This was done to remove the negative impact that a forceps or vacuum intervention, rather than the caesarean or vaginal delivery itself, may have had on the delivery outcome. Thus, "failed" vaginal deliveries that went on to be delivered by a caesarean section were not captured in the analyses and may explain some of the discrepancy between the findings of this study and the previous literature. We also failed to adjust for women who have contributed more than one birth to the database over the three year period. Neonates born from the same mother are more likely to exhibit similar outcomes than those born from different mothers, a factor which may have led to a violation of the independence assumption and impacted the validity of our results.

The analyses conducted in this study have relied on the accuracy of in-hospital records in order to identify caesarean deliveries, which may be prone to coding errors, however in-hospital interventions were shown to have a high degree of accuracy when compared with a patient's medical chart in a 2007-2008 Data Quality study by CIHI using the DAD (PPV = 94, 95%CI = 91-98).[73] Mortality may also be prone to similar coding errors. To decrease this possibility, we used both ICD-10 coding as well as CIHI variables to capture mortality. Although the DAD data

may technically be incomplete for early neonatal mortality (death before 7 days of age) because of deaths occurring after hospital discharge, it is highly likely that early neonatal deaths following hospital discharge and before 7 days of age would be extremely small in number and would be attributable to factors other than the quality of obstetrical care provided. Given privacy concerns, we were unable to obtain individual-level socioeconomic data. Instead, socioeconomic variables were aggregated by CDAs from the 2006 Canadian Census and it is uncertain whether generalizations of socioeconomic factors at the aggregated level extend to each individual. Despite these limitations, this study has yielded estimates which are less likely to be affected by unmeasured selection bias since the IV was highly predictive of the receipt of a caesarean delivery and was not directly associated with early neonatal mortality.

4.3 Conclusion

In conclusion, the findings from the IVM analysis suggest that the risk of early neonatal mortality is not influenced by the mode of delivery. Given that the natural randomization of patients was based on local hospital-level factors and generalize only to the marginal population, the conclusions drawn from IVM analyses tend to be better suited for policy related questions directed at health-system level changes as opposed to the clinical effectiveness for an individual patient. Until a more in-depth understanding of local caesarean rates on maternal and neonatal morbidities, hospital costs, and resulting factors are established, health-system level recommendations towards altering local caesarean rates should be avoided. Consequently, future researchers should aim to answer these questions using similar analytic methods to help inform health-care policy makers and providers.

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Appendix A – CCI Codes used to Identify Exclusive Caesarean and Vaginal Deliveries

CCI Code	Description
Exclusive Caesarean Section Delivery	
5MD60KE	Caesarean hysterectomy
5MD60JY	Classical section (vertical incision in upper segment)
5MD60KB	Extraperitoneal section
5MD60KG	Inverted T incision
5MD60KF	Laparotomy (for abdominal pregnancy)
5MD60AA	Lower segment transverse incision
5MD60KT	Other type of Caesarean section NEC (e.g. vaginal, J incision)
Exclusive Vaginal Delivery	
5MD50^^	Manually assisted vaginal delivery (vertex) Includes: - Crede maneuver - that with easy cord disentanglement (e.g. slipping cord over head of the fetus) - that with or without perineal massage - those classed as normal spontaneous vertex delivery, requiring minimal assistance from obstetrical personnel (e.g. Ritgen maneuver)
5MD51^^	Unassisted spontaneous vaginal delivery Includes: - autonomous delivery where health professionals do not intervene or assist during the delivery (e.g. unattended delivery)

Appendix B – ICD-10 Codes used to Identify Early Neonatal Mortality

ICD-10 Codes	Description
R96.0	Instantaneous death
R96.1	Death occurring less than 24 hours from onset of symptoms, not otherwise explained
R98	Unattended death
R99	Other ill-defined and unspecified causes of mortality
I461	Sudden cardiac death, so described

Appendix C – ICD-10 Codes used to Identify Maternal and Labor or Delivery Complications

Condition	ICD-10 Code	Description
Type 1 Diabetes Mellitus		
	E10.0	Type 1 diabetes mellitus with coma
	E10.2	Type 1 diabetes mellitus with renal complications
	E10.3	Type 1 diabetes mellitus with ophthalmic complications
	E10.4	Type 1 diabetes mellitus with neurological complications
	E10.5	Type 1 diabetes mellitus with circulatory complications
	E10.6	Type 1 diabetes mellitus with other specified complications
	E10.7	Type 1 diabetes mellitus with multiple complications
	E10.8	Type 1 diabetes mellitus with unspecified complications
	E10.9	Type 1 diabetes mellitus without (mention of) complication
	O24.0	Pre-existing type 1 diabetes mellitus in pregnancy
Type 2 Diabetes Mellitus		
	E11.0	Type 2 diabetes mellitus with coma
	E11.2	Type 2 diabetes mellitus with kidney complications
	E11.3	Type 2 diabetes mellitus with ophthalmic complications
	E11.4	Type 2 diabetes mellitus with neurological complications
	E11.5	Type 2 diabetes mellitus with circulatory complications
	E11.6	Type 2 diabetes mellitus with other specified complications
	E11.7	Type 2 diabetes mellitus with multiple complications

	E11.8	Type 2 diabetes mellitus with unspecified complications
	E11.9	Type 2 diabetes mellitus without (mention of) complications
	O24.1	Pre-existing type 2 diabetes mellitus in pregnancy
Gestational Diabetes Mellitus		
	O24.4	Diabetes mellitus arising in pregnancy, gestational
	P70.0	Syndrome of infant of mother with gestational diabetes
Unspecified Diabetes Mellitus		
	E13.0	Other specified diabetes mellitus with coma
	E13.2	Other specified diabetes mellitus with kidney
	E13.3	Other specified diabetes mellitus with ophthalmic complications
	E13.3	Other specified diabetes mellitus with ophthalmic complications
	E13.4	Other specified diabetes mellitus with neurological complications
	E13.5	Other specified diabetes mellitus with circulatory complications
	E13.6	Other specified diabetes mellitus with other specified complications
	E13.7	Other specified diabetes mellitus with multiple complications
	E13.8	Other specified diabetes mellitus with unspecified complications
	E13.9	Other specified diabetes mellitus without (mention of) complication
	E14.0	Unspecified diabetes mellitus with coma
	E14.2	Unspecified diabetes mellitus with kidney complications
	E14.3	Unspecified diabetes mellitus with ophthalmic complications
	E14.4	Unspecified diabetes mellitus with neurological complications
	E14.5	Unspecified diabetes mellitus with circulatory complications

	E14.6	Unspecified diabetes mellitus with other specified complications
	E14.7	Unspecified diabetes mellitus with multiple complications
	E14.8	Unspecified diabetes mellitus with unspecified complications
	E14.9	Unspecified diabetes mellitus without (mention of) complication
	N08.3	Glomerular disorders in diabetes mellitus (E10-E14† with common fourth character .2)
	O24.3	Glomerular disorders in diabetes mellitus (E10-E14† with common fourth character .2)
	G63.2	Diabetic polyneuropathy (E10-E14† with common fourth character .4)
	H36.0	Diabetic retinopathy (E10-E14† with common fourth character .3)
	P70.1	Syndrome of infant of a diabetic mother
Hypertension		
	I10	Essential (primary) hypertension
	I11.0	Hypertensive heart disease with (congestive) heart failure
	I11.9	Hypertensive heart disease without (congestive) heart failure
	I12.0	Hypertensive renal disease with renal failure
	I12.9	Hypertensive renal disease without renal failure
	I13.0	Hypertensive heart and renal disease with (congestive) heart failure
	I13.1	Hypertensive heart and renal disease with renal failure
	I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
	I13.9	Hypertensive heart and renal disease, unspecified
	I15.0	Renovascular hypertension
	I15.1	Hypertension secondary to other renal disorders
	I15.2	Hypertension secondary to endocrine disorders
	I15.8	Other secondary hypertension

	I15.9	Secondary hypertension, unspecified
	O10.0	Pre-existing essential hypertension complicating pregnancy, childbirth and the puerperium
	O10.1	Pre-existing hypertensive heart disease complicating pregnancy, childbirth and the puerperium
	O10.2	Pre-existing hypertensive renal disease complicating pregnancy, childbirth and the puerperium
	O10.3	Pre-existing hypertensive heart and renal disease complicating pregnancy, childbirth and the puerperium
	O10.4	Pre-existing secondary hypertension complicating pregnancy, childbirth and the puerperium
	O10.9	Unspecified pre-existing hypertension complicating pregnancy, childbirth and the puerperium
	O13	Gestational (pregnancy-induced) hypertension without significant proteinuria
	O16	Unspecified maternal hypertension
	P00.0	Fetus and newborn affected by maternal hypertensive disorders
Pre-Eclampsia	O14.0	Moderate pre-eclampsia
	O14.1	Severe pre-eclampsia
	O14.2	HELLP syndrome
	O14.9	Pre-eclampsia, unspecified
Twin or Unspecified Multiple		
	O30.0	Twin pregnancy
	O30.8	Other multiple gestation
	O31.1	Continuing pregnancy after spontaneous abortion of one fetus or more or selective fetal reduction
	O31.2	Continuing pregnancy after intrauterine death of one fetus or more
	O30.9	Multiple gestation, unspecified
	O32.5	Maternal care for multiple gestation with malpresentation of one fetus or more
	O66.1	Obstructed labour due to locked twins
Triplet or Higher		
	O30.1	Triplet pregnancy

	O30.2	Quadruplet pregnancy
Previous Caesarean Section		
	O34.2	Uterine scar due to previous Caesarean section
	O75.7	Vaginal delivery following previous Caesarean section
Eclampsia		
	O15.0	Eclampsia in pregnancy
	O15.1	Eclampsia in labour
	O15.2	Eclampsia in the puerperium
	O15.9	Eclampsia, unspecified as to time period
HIV Positive Status		
	B20.0	HIV disease resulting in mycobacterial infection
	B20.1	HIV disease resulting in other bacterial infections
	B20.2	HIV disease resulting in cytomegaloviral disease
	B20.3	HIV disease resulting in other viral infections
	B20.4	HIV disease resulting in candidiasis
	B20.5	HIV disease resulting in other mycoses
	B20.6	HIV disease resulting in Pneumocystis jirovecii pneumonia
	B20.7	HIV disease resulting in multiple infections
	B20.8	HIV disease resulting in other infectious and parasitic diseases
	B20.9	HIV disease resulting in unspecified infectious or parasitic disease
	B21.0	HIV disease resulting in Kaposi sarcoma
	B21.1	HIV disease resulting in Burkitt lymphoma
	B21.2	HIV disease resulting in other types of non-Hodgkin lymphoma
	B21.3	HIV disease resulting in other malignant neoplasms of lymphoid, haematopoietic and related tissue
	B21.7	HIV disease resulting in multiple malignant neoplasms
	B21.8	HIV disease resulting in other malignant neoplasms
	B21.9	HIV disease resulting in unspecified malignant neoplasm

	B22.0	HIV disease resulting in encephalopathy
	B22.1	HIV disease resulting in lymphoid interstitial pneumonitis
	B22.2	HIV disease resulting in wasting syndrome
	B22.7	HIV disease resulting in multiple diseases classified elsewhere
	B23.0	Acute HIV infection syndrome
	B23.1	HIV disease resulting in (persistent) generalized lymphadenopathy
	B23.2	HIV disease resulting in haematological and immunological abnormalities, not elsewhere classified
	B23.8	HIV disease resulting in other specified conditions
	B24	Unspecified human immunodeficiency virus [HIV] disease
	F024	Dementia in human immunodeficiency virus [HIV] disease (B22.0+)
	O98.7	Human immunodeficiency [HIV] disease complicating pregnancy, childbirth and the puerperium
	R75	Laboratory evidence of human immunodeficiency virus [HIV]
	Z21	Asymptomatic human immunodeficiency virus [HIV] infection status
Premature Rupture of Membranes		
	O42.0	Premature rupture of membranes, onset of labour within 24 hours
	O42.1	Premature rupture of membranes, onset of labour after 24 hours
	O42.2	Premature rupture of membranes, labour delayed by therapy
	O42.9	Premature rupture of membranes, unspecified
	P01.1	Fetus and newborn affected by premature rupture of membranes
Hemorrhage		
	O20.0	Threatened abortion
	O20.8	Other haemorrhage in early pregnancy
	O20.0	Haemorrhage in early pregnancy, unspecified

	O46.0	Antepartum haemorrhage with coagulation defect
	O46.8	Other antepartum haemorrhage
	O46.9	Antepartum haemorrhage, unspecified
	O67.0	Intrapartum haemorrhage with coagulation defect
	O67.8	Other intrapartum haemorrhage
	O67.9	Intrapartum haemorrhage, unspecified
Cord Prolapse		
	O69.0	Labour and delivery complicated by prolapse of cord
	P02.4	
Placenta Praevia		
	O44	Fetus and newborn affected by prolapsed cord
	P02.0	Fetus and newborn affected by placenta praevia
Abruption Placenta		
	O45.0	Premature separation of placenta with coagulation defect
	O45.8	Other premature separation of placenta
	O45.9	Premature separation of placenta, unspecified
	P02.1	Fetus and newborn affected by other forms of placental separation and haemorrhage

Appendix D – ICD-10 Codes used to Identify Neonatal Congenital Anomalies

ICD-10 Code	Congenital Anomaly
Q00.0	Anencephaly
Q00.1	Craniorachischisis
Q00.2	Iniencephaly
Q01.0	Frontal encephalocele
Q01.1	Nasofrontal encephalocele
Q01.2	Occipital encephalocele
Q01.8	Encephalocele of other sites
Q01.9	Encephalocele, unspecified
Q03.0	Malformations of aqueduct of Sylvius
Q03.1	Atresia of foramina of Magendie and Luschka
Q03.8	Other congenital hydrocephalus
Q03.9	Congenital hydrocephalus, unspecified
Q04.0	Congenital malformations of corpus callosum
Q04.1	Arhinencephaly
Q04.2	Holoprosencephaly
Q04.3	Other reduction deformities of brain
Q04.4	Septo-optic dysplasia
Q04.5	Megalencephaly
Q04.6	Congenital cerebral cysts
Q04.8	Other specified congenital malformations of brain
Q04.9	Congenital malformation of brain, unspecified
Q05.0	Cervical spina bifida with hydrocephalus
Q05.1	Thoracic spina bifida with hydrocephalus
Q05.2	Lumbar spina bifida with hydrocephalus
Q05.3	Sacral spina bifida with hydrocephalus
Q05.4	Unspecified spina bifida with hydrocephalus
Q05.5	Cervical spina bifida without hydrocephalus
Q05.6	Thoracic spina bifida without hydrocephalus
Q05.7	Lumbar spina bifida without hydrocephalus
Q05.8	Sacral spina bifida without hydrocephalus
Q05.9	Spina bifida, unspecified
Q06.0	Amyelia
Q06.1	Hypoplasia and dysplasia of spinal cord
Q06.2	Diastematomyelia
Q06.3	Other congenital cauda equina malformations
Q06.4	Hydromyelia
Q06.8	Other specified congenital malformations of spinal cord

Q06.9	Congenital malformation of spinal cord, unspecified
Q07.0	Arnold-Chiari syndrome
Q07.8	Other specified congenital malformations of nervous system
Q07.9	Congenital malformation of nervous system, unspecified
Q10.0	Congenital ptosis
Q10.6	Other congenital malformations of lacrimal apparatus
Q10.7	Congenital malformation of orbit
Q11.0	Cystic eyeball
Q11.1	Other anophthalmos
Q11.2	Microphthalmos
Q11.3	Macrophthalmos
Q12.0	Congenital cataract
Q12.1	Congenital displaced lens
Q12.2	Coloboma of lens
Q12.3	Congenital aphakia
Q12.4	Spherophakia
Q12.8	Other congenital lens malformations
Q12.9	Congenital lens malformation, unspecified
Q13.0	Coloboma of iris
Q13.1	Absence of iris
Q13.2	Other congenital malformations of iris
Q13.3	Congenital corneal opacity
Q13.4	Other congenital corneal malformations
Q13.8	Other congenital malformations of anterior segment of eye
Q13.9	Congenital malformation of anterior segment of eye, unspecified
Q14.0	Congenital malformation of vitreous humour
Q14.1	Congenital malformation of retina
Q14.2	Congenital malformation of optic disc
Q14.3	Congenital malformation of choroid
Q14.8	Other congenital malformations of posterior segment of eye
Q14.9	Congenital malformation of posterior segment of eye, unspecified
Q15.0	Congenital glaucoma
Q15.8	Other specified congenital malformations of eye
Q15.9	Congenital malformation of eye, unspecified
Q16.0	Congenital absence of (ear) auricle
Q16.1	Congenital absence, atresia and stricture of auditory canal (external)
Q16.2	Absence of eustachian tube
Q16.3	Congenital malformation of ear ossicles
Q16.4	Other congenital malformations of middle ear
Q16.5	Congenital malformation of inner ear

Q16.9	Congenital malformation of ear causing impairment of hearing, unspecified
Q17.8	Other specified congenital malformations of ear
Q18.3	Webbing of neck
Q20.0	Common arterial trunk
Q20.1	Double outlet right ventricle
Q20.2	Double outlet left ventricle
Q20.3	Discordant ventriculoarterial connection
Q20.4	Double inlet ventricle
Q20.5	Discordant atrioventricular connection
Q20.6	Isomerism of atrial appendages
Q20.8	Other congenital malformations of cardiac chambers and connections
Q20.9	Congenital malformation of cardiac chambers and connections, unspecified
Q21.0	Ventricular septal defect
Q21.2	Atrioventricular septal defect
Q21.3	Tetralogy of Fallot
Q21.4	Aortopulmonary septal defect
Q21.8	Other congenital malformations of cardiac septa
Q21.9	Congenital malformation of cardiac septum, unspecified
Q22.0	Pulmonary valve atresia
Q22.0	Congenital pulmonary valve stenosis
Q22.2	Congenital pulmonary valve insufficiency
Q22.3	Other congenital malformations of pulmonary valve
Q22.4	Congenital tricuspid stenosis
Q22.5	Ebstein anomaly
Q22.6	Hypoplastic right heart syndrome
Q22.8	Other congenital malformations of tricuspid valve
Q22.9	Congenital malformation of tricuspid valve, unspecified
Q23.0	Congenital stenosis of aortic valve
Q23.1	Congenital insufficiency of aortic valve
Q23.2	Congenital mitral stenosis
Q23.3	Congenital mitral insufficiency
Q23.4	Hypoplastic left heart syndrome
Q23.8	Other congenital malformations of aortic and mitral valves
Q23.9	Congenital malformation of aortic and mitral valves, unspecified
Q24.0	Dextrocardia
Q24.1	Laevocardia
Q24.2	Cor triatriatum
Q24.3	Pulmonary infundibular stenosis
Q24.4	Congenital subaortic stenosis
Q24.5	Malformation of coronary vessels

Q24.6	Congenital heart block
Q24.8	Other specified congenital malformations of heart
Q24.9	Congenital malformation of heart, unspecified
Q25.0	Patent ductus arteriosus
Q25.1	Coarctation of aorta
Q25.2	Atresia of aorta
Q25.3	Stenosis of aorta
Q25.4	Other congenital malformations of aorta
Q25.5	Atresia of pulmonary artery
Q25.6	Stenosis of pulmonary artery
Q25.7	Other congenital malformations of pulmonary artery
Q25.8	Other congenital malformations of great arteries
Q25.9	Congenital malformation of great arteries, unspecified
Q26.0	Congenital stenosis of vena cava
Q26.1	Persistent left superior vena cava
Q26.2	Total anomalous pulmonary venous connection
Q26.3	Partial anomalous pulmonary venous connection
Q26.4	Anomalous pulmonary venous connection, unspecified
Q26.5	Anomalous portal venous connection
Q26.6	Portal vein-hepatic artery fistula
Q26.8	Other congenital malformations of great veins
Q26.9	Congenital malformation of great vein, unspecified
Q27.1	Congenital renal artery stenosis
Q27.2	Other congenital malformations of renal artery
Q27.3	Peripheral arteriovenous malformation
Q27.4	Congenital phlebectasia
Q27.8	Other specified congenital malformations of peripheral vascular system
Q27.9	Congenital malformation of peripheral vascular system, unspecified
Q28.0	Arteriovenous malformation of precerebral vessels
Q28.1	Other malformations of precerebral vessels
Q28.2	Arteriovenous malformation of cerebral vessels
Q28.3	Other malformations of cerebral vessels
Q28.8	Other specified congenital malformations of circulatory system
Q28.9	Congenital malformation of circulatory system, unspecified
Q30.0	Choanal atresia
Q30.1	Agenesis and underdevelopment of nose
Q30.2	Fissured, notched and cleft nose
Q30.3	Congenital perforated nasal septum
Q30.8	Other congenital malformations of nose
Q30.9	Congenital malformation of nose, unspecified
Q31.0	Web of larynx
Q31.1	Congenital subglottic stenosis

Q31.2	Laryngeal hypoplasia
Q31.3	Laryngocele
Q31.8	Other congenital malformations of larynx
Q31.9	Congenital malformation of larynx, unspecified
Q32.1	Other congenital malformations of trachea
Q32.2	Congenital bronchomalacia
Q32.3	Congenital stenosis of bronchus
Q32.4	Other congenital malformations of bronchus
Q33.0	Congenital cystic lung
Q33.2	Sequestration of lung
Q33.3	Agenesis of lung
Q33.4	Congenital bronchiectasis
Q33.5	Ectopic tissue in lung
Q33.6	Hypoplasia and dysplasia of lung
Q33.8	Other congenital malformations of lung
Q33.9	Congenital malformation of lung, unspecified
Q34.0	Anomaly of pleura
Q34.1	Congenital cyst of mediastinum
Q34.8	Other specified congenital malformations of respiratory system
Q34.9	Congenital malformation of respiratory system, unspecified
Q35.1	Cleft hard palate
Q35.3	Cleft soft palate
Q35.5	Cleft hard palate with cleft soft palate
Q35.7	Cleft uvula
Q35.9	Cleft palate, unspecified
Q36.0	Cleft lip, bilateral
Q36.1	Cleft lip, median
Q36.9	Cleft lip, unilateral
Q37.0	Cleft hard palate with bilateral cleft lip
Q37.1	Cleft hard palate with unilateral cleft lip
Q37.2	Cleft soft palate with bilateral cleft lip
Q37.3	Cleft soft palate with unilateral cleft lip
Q37.4	Cleft hard and soft palate with bilateral cleft lip
Q37.5	Cleft hard and soft palate with unilateral cleft lip
Q37.8	Unspecified cleft palate with bilateral cleft lip
Q37.9	Unspecified cleft palate with unilateral cleft lip
Q38.0	Congenital malformations of lips, not elsewhere classified
Q38.3	Other congenital malformations of tongue
Q38.4	Congenital malformations of salivary glands and ducts
Q38.6	Other congenital malformations of mouth
Q38.7	Pharyngeal pouch
Q38.8	Other congenital malformations of pharynx
Q39.0	Atresia of oesophagus without fistula
Q39.1	Atresia of oesophagus with tracheo-oesophageal fistula

Q39.2	Congenital tracheo-oesophageal fistula without atresia
Q39.3	Congenital stenosis and stricture of oesophagus
Q39.4	Oesophageal web
39.5	Congenital dilatation of oesophagus
Q39.6	Diverticulum of oesophagus
Q39.8	Other congenital malformations of oesophagus
Q39.9	Congenital malformation of oesophagus, unspecified
Q40.2	Other specified congenital malformations of stomach
Q40.3	Congenital malformation of stomach, unspecified
Q40.8	Other specified congenital malformations of upper alimentary tract
Q40.9	Congenital malformation of upper alimentary tract, unspecified
Q41.0	Congenital absence, atresia and stenosis of duodenum
Q41.1	Congenital absence, atresia and stenosis of jejunum
Q41.2	Congenital absence, atresia and stenosis of ileum
Q41.8	Congenital absence, atresia and stenosis of other specified parts of small intestine
Q41.9	Congenital absence, atresia and stenosis of small intestine, part unspecified
Q42.0	Congenital absence, atresia and stenosis of rectum with fistula
Q42.1	Congenital absence, atresia and stenosis of rectum without fistula
Q42.2	Congenital absence, atresia and stenosis of anus with fistula
Q42.3	Congenital absence, atresia and stenosis of anus without fistula
Q42.8	Congenital absence, atresia and stenosis of other parts of large intestine
Q42.9	Congenital absence, atresia and stenosis of large intestine, part unspecified
Q43.1	Hirschsprung disease
Q43.2	Other congenital functional disorders of colon
Q43.3	Congenital malformations of intestinal fixation
Q43.4	Duplication of intestine
Q43.5	Ectopic anus
Q43.6	Congenital fistula of rectum and anus
Q43.7	Persistent cloaca
Q43.8	Other specified congenital malformations of intestine
Q43.9	Congenital malformation of intestine, unspecified
Q44.0	Agenesis, aplasia and hypoplasia of gallbladder
Q44.1	Other congenital malformations of gallbladder
Q44.2	Atresia of bile ducts
Q44.3	Congenital stenosis and stricture of bile ducts
Q44.4	Choledochal cyst
Q44.5	Other congenital malformations of bile ducts

Q44.6	Cystic disease of liver
Q44.7	Other congenital malformations of liver
Q45.0	Agenesis, aplasia and hypoplasia of pancreas
Q45.1	Annular pancreas
Q45.2	Congenital pancreatic cyst
Q45.3	Other congenital malformations of pancreas and pancreatic duct
Q45.8	Other specified congenital malformations of digestive system
Q45.9	Congenital malformation of digestive system, unspecified
Q50.0	Congenital absence of ovary
Q50.1	Developmental ovarian cyst
Q50.2	Congenital torsion of ovary
Q50.3	Other congenital malformations of ovary
Q50.4	Embryonic cyst of fallopian tube
Q50.5	Embryonic cyst of broad ligament
Q50.6	Other congenital malformations of fallopian tube and broad ligament
Q51.0	Agenesis and aplasia of uterus
Q51.1	Doubling of uterus with doubling of cervix and vagina
Q51.2	Other doubling of uterus
Q51.3	Bicornate uterus
Q51.4	Unicornate uterus
Q51.5	Agenesis and aplasia of cervix
Q51.6	Embryonic cyst of cervix
Q51.7	Congenital fistulae between uterus and digestive and urinary tracts
Q51.8	Other congenital malformations of uterus and cervix
Q51.9	Congenital malformation of uterus and cervix, unspecified
Q52.0	Congenital absence of vagina
Q52.1	Doubling of vagina
Q52.2	Congenital rectovaginal fistula
Q52.4	Other congenital malformations of vagina
Q52.6	Congenital malformation of clitoris
Q52.7	Other congenital malformations of vulva
Q52.8	Other specified congenital malformations of female genitalia
Q52.9	Congenital malformation of female genitalia, unspecified
Q53.1	Undescended testicle, unilateral
Q53.2	Undescended testicle, bilateral
Q53.9	Undescended testicle, unspecified
Q54.0	Hypospadias, balanic
Q54.1	Hypospadias, penile
Q54.2	Hypospadias, penoscrotal
Q54.3	Hypospadias, perineal
Q54.4	Congenital chordee

Q54.8	Other hypospadias
Q54.9	Hypospadias, unspecified
Q55.0	Absence and aplasia of testis
Q55.1	Hypoplasia of testis and scrotum
Q55.3	Atresia of vas deferens
Q55.4	Other congenital malformations of vas deferens, epididymis, seminal vesicles and prostate
Q55.5	Congenital absence and aplasia of penis
Q55.6	Other congenital malformations of penis
Q55.8	Other specified congenital malformations of male genital organs
Q55.9	Congenital malformation of male genital organ, unspecified
Q56.0	Hermaphroditism, not elsewhere classified
Q56.1	Male pseudohermaphroditism, not elsewhere classified
Q56.2	Female pseudohermaphroditism, not elsewhere classified
Q56.3	Pseudohermaphroditism, unspecified
Q56.4	Indeterminate sex, unspecified
Q60.0	Renal agenesis, unilateral
Q60.1	Renal agenesis, bilateral
Q60.2	Renal agenesis, unspecified
Q60.3	Renal hypoplasia, unilateral
Q60.4	Renal hypoplasia, bilateral
Q60.5	Renal hypoplasia, unspecified
Q60.6	Potter syndrome
Q61.1	Polycystic kidney, autosomal recessive
Q61.2	Polycystic kidney, autosomal dominant
Q61.3	Polycystic kidney, unspecified
Q61.4	Renal dysplasia
Q61.5	Medullary cystic kidney
Q61.8	Other cystic kidney diseases
Q61.9	Cystic kidney disease, unspecified
Q62.0	Congenital hydronephrosis
Q62.1	Atresia and stenosis of ureter
Q62.2	Congenital megaloureter
Q62.3	Other obstructive defects of renal pelvis and ureter
Q62.4	Agenesis of ureter
Q62.5	Duplication of ureter
Q62.6	Malposition of ureter
Q62.8	Other congenital malformations of ureter
Q63.0	Accessory kidney
Q63.1	Lobulated, fused and horseshoe kidney
Q63.2	Ectopic kidney
Q63.8	Other specified congenital malformations of kidney
Q63.9	Congenital malformation of kidney, unspecified

Q64.0	Epispadias
Q64.1	Exstrophy of urinary bladder
Q64.2	Congenital posterior urethral valves
Q64.3	Other atresia and stenosis of urethra and bladder neck
Q64.4	Malformation of urachus
Q64.5	Congenital absence of bladder and urethra
Q64.6	Congenital diverticulum of bladder
Q64.7	Other congenital malformations of bladder and urethra
Q64.8	Other specified congenital malformations of urinary system
Q64.9	Congenital malformation of urinary system, unspecified
Q65.0	Congenital dislocation of hip, unilateral
Q65.1	Congenital dislocation of hip, bilateral
Q65.2	Congenital dislocation of hip, unspecified
Q65.8	Other congenital deformities of hip
Q65.9	Congenital deformity of hip, unspecified
Q66.0	Talipes equinovarus
Q66.1	Talipes calcaneovarus
Q68.1	Congenital deformity of hand
Q68.8	Other specified congenital musculoskeletal deformities
Q69.0	Accessory finger(s)
Q69.1	Accessory thumb(s)
Q69.2	Accessory toe(s)
Q69.9	Polydactyly, unspecified
Q70.0	Fused fingers
Q70.1	Webbed fingers
Q70.2	Fused toes
Q70.3	Webbed toes
Q70.4	Polysyndactyly
Q70.9	Syndactyly, unspecified
Q71.0	Congenital complete absence of upper limb(s)
Q71.1	Congenital absence of upper arm and forearm with hand present
Q71.2	Congenital absence of both forearm and hand
Q71.3	Congenital absence of hand and finger(s)
Q71.4	Longitudinal reduction defect of radius
Q71.5	Longitudinal reduction defect of ulna
Q71.6	Lobster-claw hand
Q71.8	Other reduction defects of upper limb(s)
Q71.9	Reduction defect of upper limb, unspecified
Q72.0	Congenital complete absence of lower limb(s)
Q72.1	Congenital absence of thigh and lower leg with foot present
Q72.2	Congenital absence of both lower leg and foot
Q72.3	Congenital absence of foot and toe(s)
Q72.4	Longitudinal reduction defect of femur

Q72.5	Longitudinal reduction defect of tibia
Q72.6	Longitudinal reduction defect of fibula
Q72.7	Split foot
Q72.8	Other reduction defects of lower limb(s)
Q72.9	Reduction defect of lower limb, unspecified
Q73.0	Congenital absence of unspecified limb(s)
Q73.1	Phocomelia, unspecified limb(s)
Q73.8	Other reduction defects of unspecified limb(s)
Q74.1	Congenital malformation of knee
Q74.2	Other congenital malformations of lower limb(s), including pelvic girdle
Q74.3	Arthrogryposis multiplex congenital
Q74.8	Other specified congenital malformations of limb(s)
Q74.9	Unspecified congenital malformation of limb(s)
Q75.0	Craniosynostosis
Q75.1	Craniofacial dysostosis
Q75.4	Mandibulofacial dysostosis
Q75.5	Oculomandibular dysostosis
Q75.8	Other specified congenital malformations of skull and face bones
Q75.9	Congenital malformation of skull and face bones, unspecified
Q76.1	Klippel-Feil syndrome
Q76.2	Congenital spondylolisthesis
Q76.3	Congenital scoliosis due to congenital bony malformation
Q76.8	Other congenital malformations of bony thorax
Q76.9	Congenital malformation of bony thorax, unspecified
Q77.0	Achondrogenesis
Q77.1	Thanatophoric short stature
Q77.2	Short rib syndrome
Q77.3	Chondrodysplasia punctata
Q77.4	Achondroplasia
Q77.5	Dystrophic dysplasia
Q77.6	Chondroectodermal dysplasia
Q77.7	Spondyloepiphyseal dysplasia
Q77.8	Other osteochondrodysplasia with defects of growth of tubular bones and spine
Q77.9	Osteochondrodysplasia with defects of growth of tubular bones and spine, unspecified
Q78.0	Osteogenesis imperfecta
Q78.1	Polyostotic fibrous dysplasia
Q78.2	Osteopetrosis
Q78.3	Progressive diaphyseal dysplasia
Q78.4	Enchondromatosis
Q78.5	Metaphyseal dysplasia

Q78.6	Multiple congenital exostoses
Q78.8	Other specified osteochondrodysplasias
Q78.9	Osteochondrodysplasia, unspecified
Q79.0	Congenital diaphragmatic hernia
Q79.1	Other congenital malformations of diaphragm
Q79.2	Exomphalos
Q79.3	Gastroschisis
Q79.4	Prune belly syndrome
Q79.5	Other congenital malformations of abdominal wall
Q79.6	Ehlers-Danlos syndrome
Q79.8	Other congenital malformations of musculoskeletal system
Q79.9	Congenital malformation of musculoskeletal system, unspecified
Q80.0	Ichthyosis vulgaris
Q80.1	X-linked ichthyosis
Q80.2	Lamellar ichthyosis
Q80.3	Congenital bullous ichthyosiform erythroderma
Q80.4	Harlequin fetus
Q80.8	Other congenital ichthyosis
Q80.9	Congenital ichthyosis, unspecified
Q81.0	Epidermolysis bullosa simplex
Q81.1	Epidermolysis bullosa letalis
Q81.2	Epidermolysis bullosa dystrophica
Q81.8	Other epidermolysis bullosa
Q81.9	Epidermolysis bullosa, unspecified
Q82.0	Hereditary lymphoedema
Q82.1	Xeroderma pigmentosum
Q82.2	Mastocytosis
Q82.3	Incontinentia pigmenti
Q82.4	Ectodermal dysplasia (anhidrotic)
Q82.8	Other specified congenital malformations of skin
Q82.9	Congenital malformation of skin, unspecified
Q83.0	Congenital absence of breast with absent nipple
Q83.1	Accessory breast
Q83.2	Absent nipple
Q83.8	Other congenital malformations of breast
Q83.9	Congenital malformation of breast, unspecified
Q84.0	Congenital alopecia
Q84.1	Congenital morphological disturbances of hair, not elsewhere classified
Q84.2	Other congenital malformations of hair
Q84.3	Anonychia
Q84.4	Congenital leukonychia
Q84.6	Other congenital malformations of nails

Q84.8	Other specified congenital malformations of integument
Q84.9	Congenital malformation of integument, unspecified
Q85.0	Neurofibromatosis (nonmalignant)
Q85.1	Tuberous sclerosis
Q85.8	Other phakomatoses, not elsewhere classified
Q85.9	Phakomatosis, unspecified
Q86.0	Fetal alcohol syndrome (dysmorphic)
Q86.1	Fetal hydantoin syndrome
Q86.2	Dysmorphism due to warfarin
Q86.8	Other congenital malformation syndromes due to known exogenous causes
Q87.0	Congenital malformation syndromes predominantly affecting facial appearance
Q87.1	Congenital malformation syndromes predominantly associated with short stature
Q87.2	Congenital malformation syndromes predominantly involving limbs
Q87.3	Congenital malformation syndromes involving early overgrowth
Q87.4	Marfan syndrome
Q87.5	Other congenital malformation syndromes with other skeletal changes
Q87.8	Other specified congenital malformation syndromes, not elsewhere classified
Q89.0	Congenital malformations of spleen
Q89.1	Congenital malformations of adrenal gland
Q89.2	Congenital malformations of other endocrine glands
Q89.3	Situs inversus
Q89.4	Conjoined twins
Q89.7	Multiple congenital malformations, not elsewhere classified
Q89.8	Other specified congenital malformations
Q90.0	Trisomy 21, meiotic nondisjunction
Q90.1	Trisomy 21, mosaicism (mitotic nondisjunction)
Q90.2	Trisomy 21, translocation
Q90.9	Down syndrome, unspecified
Q91.0	Trisomy 18, meiotic nondisjunction
Q91.1	Trisomy 18, mosaicism (mitotic nondisjunction)
Q91.2	Trisomy 18, translocation
Q91.3	Edwards syndrome, unspecified
Q91.4	Trisomy 13, meiotic nondisjunction
Q91.5	Trisomy 13, mosaicism (mitotic nondisjunction)
Q91.6	Trisomy 13, translocation
Q91.7	Patau syndrome, unspecified
Q92.0	Whole chromosome trisomy, meiotic nondisjunction

Q92.1	Whole chromosome trisomy, mosaicism (mitotic nondisjunction)
Q92.2	Major partial trisomy
Q92.3	Minor partial trisomy
Q92.4	Duplications seen only at prometaphase
Q92.5	Duplications with other complex rearrangements
Q92.6	Extra marker chromosomes
Q92.7	Triploidy and polyploidy
Q92.8	Other specified trisomies and partial trisomies of autosomes
Q92.9	Trisomy and partial trisomy of autosomes, unspecified
Q93.0	Whole chromosome monosomy, meiotic nondisjunction
Q93.1	Whole chromosome monosomy, mosaicism (mitotic nondisjunction)
Q93.2	Chromosome replaced with ring or dicentric
Q93.3	Deletion of short arm of chromosome 4
Q93.4	Deletion of short arm of chromosome 5
Q93.5	Other deletions of part of a chromosome
Q93.6	Deletions seen only at prometaphase
Q93.7	Deletions with other complex rearrangements
Q93.8	Other deletions from the autosomes
Q93.9	Deletion from autosomes, unspecified
Q95.2	Balanced autosomal rearrangement in abnormal individual
Q95.3	Balanced sex/autosomal rearrangement in abnormal individual
Q95.4	Individuals with marker heterochromatin
Q95.5	Individuals with autosomal fragile site
Q95.8	Other balanced rearrangements and structural markers
Q95.9	Balanced rearrangement and structural marker, unspecified
Q96.0	Karyotype 45,X
Q96.1	Karyotype 46,X iso (Xq)
Q96.2	Karyotype 46,X with abnormal sex chromosome, except iso (Xq)
Q96.3	Mosaicism, 45,X/46,XX or XY
Q96.4	Mosaicism, 45,X/other cell line(s) with abnormal sex chromosome
Q96.8	Other variants of Turner syndrome
Q96.9	Turner syndrome, unspecified
Q97.0	Karyotype 47,XXX
Q97.1	Female with more than three X chromosomes
Q97.2	Mosaicism, lines with various numbers of X chromosomes
Q97.3	Female with 46,XY karyotype
Q97.8	Other specified sex chromosome abnormalities, female phenotype
Q97.9	Sex chromosome abnormality, female phenotype, unspecified
Q98.0	Klinefelter syndrome karyotype 47,XXY

Q98.1	Klinefelter syndrome, male with more than two X chromosomes
Q98.2	Klinefelter syndrome, male with 46,XX karyotype
Q98.3	Other male with 46,XX karyotype
Q98.4	Klinefelter syndrome, unspecified
Q98.5	Karyotype 47,XYY
Q98.6	Male with structurally abnormal sex chromosome
Q98.7	Male with sex chromosome mosaicism
Q98.8	Other specified sex chromosome abnormalities, male phenotype
Q98.9	Sex chromosome abnormality, male phenotype, unspecified
Q99.0	Chimera 46,XX/46,XY
Q99.1	46,XX true hermaphrodite
Q99.2	Fragile X chromosome
Q99.8	Other specified chromosome abnormalities
Q99.9	Chromosomal abnormality, unspecified
D21.5	Benign neoplasms of connective and other soft tissue of pelvis
P35.0	Congenital rubella syndrome
P35.1	Congenital cytomegalovirus infection
P37.1	Congenital toxoplasmosis
D82.1	Di George syndrome

Note: If neonatal sex was identified as “other”, it was coded as a congenital anomaly

Appendix E – Definitions used to Identify Level of Hospital Service

Hospital Level of Service		Definition
Level 0		<10% of deliveries from catchment area per year
Level 1		>10% of deliveries from catchment area for neonates > 34 weeks gestational age
	a	Usually vaginal deliveries only (<5 C-sections/year)
	b	>5 C-sections per year by GP surgeon
	c	>5 C-sections per year by General Surgeon
	d	>5 C-sections per year by Obstetrician
Level 2		An average of 4 or greater deliveries of neonates 32-34 weeks gestational age inclusive, with length of stay > 5 days per year.
Level 3		Members of the Canadian Neonatal Network
	a	No major surgery
	b	Major surgery but no cardiac bypass or extra-corporeal membrane oxygenation
	c	Major cardiac surgery

Note: See Appendix F for the CCI and ICD-10 codes used to identify levels 3b and 3c.

Appendix F – ICD-10 Codes and CCI Codes used to Identify Level 3b and Level 3c Hospital Service

CCI Code	CCI Code Description	ICD-10	ICD-10 Code Description
For Level 3b			
1.SY.84.^^	Reconstruction, muscles of the chest and abdomen	Q79.2	Exomphalos
		Q79.3	Gastroschisis
1.GJ.86.^^	Closure of fistula, trachea	Q39.1	Atresia of oesophagus with tracheo-esophageal fistula
		Q39.2	Congenital tracheo-oesophageal fistula without atresia
1.NA.87.^^	Excision partial, esophagus	Q39.0	Atresia of oesophagus cout fistula
1.NA.89.^^	Excision total, esophagus	Q39.1	Atresia of oesophagus with
1.NA.91.^^	Excision radical, espohagus		tracheo-esophageal fistula
1.NA.84	Reconstruction, esophagus		
1.NK.80.^^	Repair, small intestine	P77	Necrotizing enterocolitis
1.NK.87.^^	Excision partial, small intestine	A04.7	Enterocolitis due to C. difficile
1.NM.80.^^	Repair, large intestine		
1.NM.87.^^	Excision partial, large intestine		
1.NM.91.^^	Excision radical, large intestine		
1.NQ.89.^^	Excision total, rectum		
1.NM.89.^^	Excision total, large intestine		
1.NM.91.^^	Excision radical, large intestine		
1.IM.51	Ligation of PDA	Q25.0	Patent ductus arteriosus
1.AC.52.ME-SJ 1.AC.52.MF-SJ 1.AC.52.MJ-SJ	Drainage, ventricles of brain with shunt terminating in ^^ – ^^ approach	Q05.-	Spina Bifida

1.AC.52.MP-SJ 1.AC.52.MQ-SJ 1.AC.52.GN-SJ 1.AC.52.GI-SJ 1.AC.52.GK-SJ 1.AC.52.GJ-SJ		Q03.-	Congenital hydrocephalus
For Level 3c			
1.LZ.37.GP-GB 1.LZ.37.LA-GB	Cardiopulmonary bypass	Q20.-	Congenital malformations of cardiac chambers and connections
1.LZ.37.GP-QM	Extracorporeal membrane oxygenator (ECMO)	Q21.-	Congenital malformations of cardiac septa
		Q22.-	Congenital malformations of pulmonary and tricuspid valves
		Q23.-	Congenital malformations of aortic and mitral valves
		Q24.-	Other congenital malformations of heart

Note: At least 5 records from a given hospital including a given CCI code and a compatible ICD-10 code (compatible codes are grouped between horizontal gridlines in the table below) must be present to meet the criterion.