# MATERNAL AND NEONATAL RISK FACTORS FOR TYPE 1 DIABETES MELLITUS AMONG CHILDREN IN NEWFOUNDLAND AND LABRADOR

by

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# ABSTRACT

This population-based case-control study was carried out to investigate mother and infant risk factors for diabetes among children aged 0 to 15 years. Maternal risk factors of interest included mother's age, delivery method, marital status, education, mother's T1DM status and hypertension. Infant risk factors included birth order, prematurity or full-term birth, size-for-gestational-age and birth weight.

Diabetes cases were identified using the Newfoundland & Labrador Diabetes Database (NLDD) for childhood diabetes maintained by the Janeway Pediatric Research Unit. The Newfoundland and Labrador Centre for Health Information's Live Birth System (LBS) was used to obtain mother's demographic and clinical data related to the pregnancy and birth. Two-hundred and sixty-six cases identified from the NLDD were linked to the LBS. Three control subjects were selected for each case.

Multivariate conditional logistic regression was carried out to assess the risk factors associated with the development of T1DM. C-section delivery was associated with increased risk of T1DM (HR 1.41, p=0.015) when birth weight and gestational age were included in the regression model.

This study presented a unique opportunity to use clinical and administrative data to examine risk factors associated with T1DM, a health issue of great significance in Newfoundland and Labrador. Findings may have an impact on health practice, health care planning and future research related to T1DM among children.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| **AGA** | Appropriate for gestational age |
| **C-Section** | Caesarean section |
| **CA** | Canadian Diabetes Association |
| **HLA** | Human leukocyte antigen |
| **LGA** | Large for gestational age |
| **MHC** | Major histocompatibility complex |
| **NL** | Newfoundland and Labrador |
| **NLDD** | Newfoundland and Labrador Diabetes Database |
| **LBS** | Live Birth Notification System |
| **NLCHI** | Newfoundland and Labrador Centre for Health |
| **SGA** | Information Small for gestational age |
| **T1DM** | Type 1 Diabetes Mellitus |

# LIST OF APPENDICES

# CHAPTER 1 INTRODUCTION

## 1.1 Background of Study

Diabetes mellitus is a metabolic disorder distinguished by the occurrence of hyperglycemia, or high blood sugar. Hyperglycemia can be due to defective insulin secretion, insulin action or a combination of the two and can be a very dangerous condition as it may cause damage to various organs. The two primary types of diabetes mellitus are type 1 and type 2. There are several other types of diabetes, such as gestational diabetes and others related to pancreatic diseases, drug or chemical exposure, and genetic syndromes (Ly et al, 2014).

Type 1 diabetes mellitus (T1DM) in childhood and adolescence is characterized by four phases: prediabetes, presentation of diabetes, partial remission and permanent insulin dependency. Prediabetes is characterized by the presence of antibodies to some islet cell antigens which frequently implicate the development of T1DM. The presentation phase is characterized by the sudden onset of polyuria (frequent urination) and/or polydipsia (excessive thirst). The first sign of the disease for many patients is ketoacidosis. Ketoacidosis is characterized by high levels of ketones in the blood. The body compensates for the lack of insulin needed to breakdown glucose as energy by breaking down fat which results in the buildup of ketones. In the partial remission or 'honeymoon' phase, patients often need very little insulin to maintain glycemic control as their bodies are still effectively secreting endogenous insulin. Between 30-60% of children and adolescents exhibit a partial remission phase during the first 1-6 months after starting insulin injections. In the final phase of the disease, the patient is completely dependent on insulin injections. Diabetes that

is well established is often associated with various acute and chronic conditions and may result in premature death. Serious complications of the disease include: retinopathy, nephropathy, cardiovascular disease, neuropathy, and vascular diseases (Ly et al, 2014).

T1DM is one of the most widespread chronic diseases in childhood and often results in acute and even life-threatening medical conditions (Ly et al, 2014). T1DM results from autoimmune destruction of pancreatic β-cells. This destruction often leads to insulin deficiency. T1DM is thought to originate through a combination of genetic and environmental factors, however environmental factors remain poorly defined (Ly et al, 2014).

### 1.2 Rationale

Both type 1 and type 2 diabetes are major health concerns for the people of Newfoundland and Labrador (NL). NL is recognized as having the highest rates of diabetes in Canada among both adults and children (Statistics Canada, 2016). A study published by Newhook et al. in 2012 found the incidence of T1DM in NL children aged 0-14 years was 37.7 per 100, 000. Despite the fact that children in Newfoundland and Labrador have an alarming rate of T1DM, little research has been conducted with respect to the maternal and neonatal risk factors that may be associated with the onset of the disease. Identification of these risk factors is a critical first step toward addressing the high incidence of T1DM in NL and protecting the health of our population. This study aimed to understand the factors related to T1DM among children in NL.

## 1.3 Research Questions

This study addressed the following **research questions**:

1. Is there an association between maternal and or neonatal risk factors (specifically maternal age at delivery, C-section delivery, and birth order) and T1DM among children in NL?
2. Are there additional perinatal risk factors for T1DM in NL which have not been previously identified?

## 1.4 Outline

The current chapter serves as an introduction to the study. Chapter 2 summarizes the literature related to T1DM and maternal and neonatal risk factors. Chapter 3 details the study methodology including data sources, study population and statistical analysis. Chapter 4 presents the results including a description of the population and results of the conditional logistic regression models. Chapter 5 will follow with a discussion of the results in the context of previous work in this area, as well as a discussion of the strengths and limitations of the study. The final chapter, Chapter 6 will provide a brief conclusion to the study.

Part of the results of this work has been previously published in the Journal of Environmental and Public Health (Appendix A).

# CHAPTER 2 LITERATURE REVIEW

## 2.1 Epidemiology of Type 1 Diabetes Mellitus

The incidence of T1DM is highly variable worldwide (Soltesz et al., 2007). The Zunyi region of China has the lowest reported incidence (0.1/100,000 per year) and Finland has the highest reported incidence at 40/100,000 per year (Soltesz et al., 2007). More recently, in Finland the incidence rate for children age 0-14 years was reported as 64.9 per 100,000 persons years in 2011 (Harjutsalo et al., 2013). The rate of T1DM in North America is also quite variable. For example, Mexico has an incidence of 1.5/100,000 per year whereas the Unites States has an incidence of 16.1/100,000 per year; the reported incidence for Canada is 21.7/100,000 per year (Soltesz et al., 2007). In Newfoundland and Labrador, the incidence of T1DM is much higher than the Canadian rate. A 2004 study reported an incidence of 35.93 per 100,000 persons per year over the period 1987–2002 for the Avalon Peninsula, which is located in the island portion of NL (Newhook et al., 2004). In addition, a province-wide study showed that the incidence of T1DM is very high across all regions of the province and this incidence is increasing over time. The incidence of T1DM for the period of 1987-2005 was reported as 35.08/100,000. This is the highest incidence rate of T1DM reported in North America (Newhook et al., 2008). A study published by Newhook et al. in 2012 found the incidence of T1DM in children aged 0-14 years was 37.7 per 100, 000. Furthermore, this study found that the incidence from 2007-2010 was an alarming 49.9 per 100,000 in the same age group. Newhook and colleagues found that throughout the study period, the incidence of T1DM in children

increase by a factor of 1.03 per 100,000 each year. A further study conducted in NL in 2005 reported an increase in diabetes-related hospitalizations among children aged 0-19 years during the period 1995 to 2002 (Alaghehbandan et al., 2006).

According to the Canadian Community Health Survey (2016), the percentage of the population aged 12 and over that report having been diagnosed by a health professional as having type 1 or type 2 diabetes in Canada is 7.0 percent. In Newfoundland and Labrador, that percentage is 9.6 and is the highest of the ten provinces (Statistics Canada, 2016).

## 2.2 Genetics and Type 1 Diabetes Mellitus

The link between genetic factors and the development of T1DM has been well documented. This link has been demonstrated by identical (monozygotic) twin studies where by age 60, 65% of siblings of TIDM cases will develop TIDM (Redondo et al., 2009). Additionally, the risk of a child born to a family who has a history of diabetes, has a 5% chance of developing the disease. Comparatively, the risk for a child born to a family without a history of the disease is 0.3% (Bonifacio and Ziegler, 2010).

It has been well established that the major histocompatibility complex (MHC), also known as the HLA complex, is involved in the family aggregation of TIDM (Noble et al., 1996; Lambert et al., 2004). There are two susceptibility haplotypes in the HLA class II region of chromosome 6 (Mehers and Gillespie, 2008).

Interestingly, Newfoundland and Labrador has been described as a genetically isolated population (Rahman et al., 2003). Many studies have demonstrated the founder effect in this province (Olufemi et al., 1998; Spirio et al., 1999; Young et al., 1999; Xie et al., 2002; Warden et al., 2013; Zhai et al., 2016).

Family history of T1DM has been shown to be linked to the development of T1DM in children. A 2007 population-based cohort study of childhood T1DM in Western Australia examined this relationship and found a significantly higher incidence of T1DM in children with mothers who had pre-existing diabetes (Haynes, Bowert, Bulsara et al., 2007). In addition, a case-control study conducted in Denmark found that a history of T1DM either for the mother or father were significant risk factors of T1DM in children (Svensson et al., 2005).

### 2.3 Sex and Type 1 Diabetes Mellitus

In general, males and females have a similar risk for developing T1DM. A NL study found that the incidence of T1DM among boys aged 0-4 years was higher than among girls who were the same age; however, the overall sex ratio for children aged 0-14 years was essentially one (Newhook et al., 2004). An updated study by Newhook and colleagues (2012), confirmed the findings of the previous study. Boys aged 0-4 years had a higher incidence of T1DM than their female counterparts (IR=32.7, CI 27.1-39.1 for males and IR=21.7 CI 17.1-27.1 for females). This may suggest that males are developing

the disease at an earlier age because of unknown perinatal, early childhood environmental and/or genetic risk factors.

In another very high incidence area, Sardinia, a male excess was identified in the 0-14 years age group (Casu et al., 2004). Bruno and colleagues (2013) conducted a more recent study in Sardinia using 20 years of data. This study also found a higher incidence rate for boys (IR=50.6, 95% CI 48.0-53.4) compared to girls (IR=38.7, 95% CI 36.4-41.2). In the same study, the rate ratio for boys was found to be significantly higher than girls (RR= 1.31, 95% CI 1.21-1.42) (Bruno et al., 2013). It was confirmed that the bias in male incidence was largely confined to patients with the DR3/nonDR4 genotype, however they did not find a significant involvement of the Y chromosome (Contu et al., 2002).

"The Danish Study Group of Diabetes in Childhood" found an increased risk of neonatal infections in boys with type 1 diabetes. They hypothesized that there may be a gender difference in susceptibility to T cell-mediated autoimmune diabetes and gender differences in response to infections (Svensson et al., 2003).

### 2.4 Perinatal Factors and T1DM

The following section examines the current literature related to perinatal factors and T1DM in children.

### 2.4.1 Gestational Age

Research findings on gestational age and T1DM have been inconsistent. An Austrian case-control study conducted by Waldhoer and colleagues (2008) examined whether the observed increase in incidence of T1DM in children could be explained by perinatal factors. The study included all Austrian children with T1DM that were born after 1988 and less than 5 years of age at diagnosis, and found a significant relationship between gestational age and risk of T1DM. Using 40 weeks gestation as the reference, they found that babies born at 34-39 weeks had a significantly higher risk of T1DM than those born at 33 or 40 weeks' gestation.

Cardwell et al (2005) examined perinatal risk factors for T1DM in a cohort of children in Northern Ireland. The study included all children diagnosed with T1DM at 15 years of age or younger from 1971-2001 that had been born between 1971 and 1986. In contrast to the study by Waldhoer and colleagues (2008), this study found a significant inverse relationship between gestational age and T1DM risk. The relative risk for children born after 40 weeks was 0.73 compared to babies born prior to 39 weeks (Cardwell et al., 2005).

Furthermore, a 2015 cohort and case control study involving 11,403 diabetes cases and 17,920 sibling controls found that gestational age of pre-term (33 to 36 weeks) (RR=1.18, 95% CI 1.09-1.28) and early term (37 to 38 weeks) (RR=1.12, 95% CI 1.07-1.17) were associated with an increased relative risk of T1DM (Khashan et al., 2015). Similarly, to

Cardwell and colleagues (2005), this study also found that babies born postterm (at 41 weeks or later) had a decreased relative risk of T1DM.

### 2.4.2 Birth Weight

Similar to gestational age, findings related to birth weight and T1DM are not consistent. Khasan and colleagues (2015) also examined birth weight and T1DM. Birth weight of less than 1,500 grams was associated with a lower risk of T1DM (RR=0.50, 95% CI 0.31-0.80). No association was found with respect to other birth weight categories.

A 2010 matched case control study of 316 cases and 1083 controls found no significant association between birth weight categories or birth weight as a continuous variable and T1DM (Robertson and Harrild, 2010). This study included children born at the Aberdeen Maternity Hospital in Scotland from 1972 to 2002. The controls were randomly selected and matched on year of birth. The authors acknowledge that the study may have lacked power to detect associations that had been observed in other studies.

A meta-analysis published in 2009 examined 12 studies related to birth weight and T1DM in childhood (Harder et al., 2009). This pooled study included 10 case-control and 2 cohort studies with a total of 2, 398, 150 participants. The authors determined that high birth weight (greater than 4000 grams) was associated with increased odds of T1DM (OR=1.17, 95% CI 1.09-1.26).

### 2.4.3 Size-for-gestational age

Size for-gestational age and T1DM was examined by Khassan et al. (2015). This study as described previously, also assessed birth weight and gestational age. With respect to size-for gestational age, the authors found that both small for gestational age (SGA) and large for gestational age (LGA) were associated with diabetes risk using appropriate for gestational age (AGA) as the reference category. SGA babies had a decreased risk of diabetes in the cohort study (RR=0.83, 95% CI 0.75-0.93). An increased risk was observed for LGA (RR=1.14, 95% CI 1.04-1.24). This decreased risk with respect to SGA remained significant in the sibling case control study. However, the increased risk for LGA did not remain.

Algert and colleagues (2009) found that SGA was associated with a decreased risk of hospitalization related to T1DM (RR=0.48, 95% CI 0.28-0.84). This studied examined children born between 2000 and 2005 in Australia. The authors followed the children until they were 6 years of age or until 2007, whichever came first.

### 2.4.4 Parity

Research findings on parity and diabetes have been inconsistent. Results of a retrospective cohort study in the United Kingdom suggest that there is a relationship between parity (or birth order) and risk of TIDM. When data was adjusted for confounders, the researchers found a significant decrease in risk of diabetes with increasing birth order (Cardwell, Carson & Patterson, 2004). Similarly, a Western Australia case-control study published in 2006 also found that incidence of type 1

diabetes in children decreased with increasing birth order (Haynes, Bowert, Bulsara et al., 2007).

A 2011 pooled analysis published by Cardwell and colleagues, examined 6 cohort studies and 25 case control studies. Prior to adjusting for maternal age, the authors found no association with diabetes risk and birth order. However, once adjusted for maternal age, the risk of type 1 diabetes in the third born was observed to be less than that of the first born (OR=0.86, 95% CI 0.76-0.97)

### 2.4.5 Caesarean Section and T1DM

2.3 out between 1992 and 2007. The authors observed a significant increase in risk of T1DM after C-section delivery (OR=1.23, 95% CI 1.15-1.32; $p<0.0001$) (Cardwell et al., 2007).

A 2015 study published after the meta-analysis described above found a dramatic increased risk of T1DM in children delivered by C-section (Lee et al., 2015). This nested case control study included 632 cases and 6320 controls born from 2000 to 2005. Compared to vaginal delivery, children born by C-section were approximately 2.5 times more likely to develop T1DM (OR=2.43, 95% CI 1.54-3.84).

### 2.4.6 Maternal Age

Maternal age at birth has also been shown to be associated with childhood T1DM. A pooled analysis of 11 observational studies found that for each 5-year increase in maternal age at delivery, the child's odds of developing T1DM increased by about 5% (Cardwell et al., 2009); The analysis included 30 studies with 14,752 cases of T1DM, and showed that children of mothers over 35 years of age had on average a 10% greater odds of developing T1DM compared to children born to mothers aged 25-30 years. No significant difference was observed when mothers aged 30-34 compared to the reference category of those mothers aged 25-30. Finally, an Australian study published in 2009, found that as maternal age increased the risk of T1DM increased (Algert et al., 2009). The relative risk increased by 1.13 for every 5-year increase in maternal age.

Not all studies have found maternal age to lead to an increased risk of diabetes. A matched case control study in Scotland, found no significant increased risk of T1DM and maternal age (Robertson and Harrild, 2010). This study included 361 cases and 1083 controls born between 1984 and 2005.

A further study published in 2015, found babies born to younger mothers to have an increased risk of T1DM (Lee et al., 2015). The adjusted odds ratio for mothers under 25 was 1.94 compared to mothers aged 25 to 29 years.

### 2.4.7 Sociodemographic Factors

Education level of parents has also been examined with respect to T1DM risk in children. A case-control study in Belgrade included children 16 years of age and under that had been hospitalized with T1DM, and found that there was no significant association between the educational level of mothers and T1DM in children. However, a significantly higher proportion of fathers of T1DM children had higher levels of education compared to fathers of children that did not have T1DM (Šipetić et al., 2004). A population-based case control study carried out in Washington State also examined the relationship between mother's education level and T1DM. Unlike the study by Šipetić and colleagues (2004), this study found an association between mother's education level and T1DM. Mothers of children without diabetes were more likely to have not graduated high school than mothers of cases (OR=0.57 95% CI 0.43-0.75) (D'Angeli et al., 2010).

Another parental factor considered by researchers is marital status. A population-based study by Waldhoer and colleagues (2008) included 444 newly diagnosed cases of children aged 0-15 years with T1DM. The study found that children of unmarried couples have a lower risk of having T1DM than children of married couples (HR=0.73 95% CI 0.57-0.90; p=0.0034).

# CHAPTER 3 METHODS

## 3.1 Data Sources

This study was a case control design involving the linkage of data extracted from the *Newfoundland and Labrador Diabetes Database* (NLDD) with the *Live Birth Notification System* (LBS). A list of variables available in the NLDD and the LBS are presented in Appendix B and Appendix C, respectively. Cases included children born in NL from 1992 onwards to 2010 that have been diagnosed with T1DM by 15 years of age. Children with type 2 diabetes, maturity-onset diabetes of youth, transient hyperglycemia, and diabetes caused by chemotherapy or cystic fibrosis are excluded from the NLDD and thus were not included in the study. Children born prior to 1992 were not included in the study because there are no electronic birth notification data available before this date.

The NLDD is maintained by the Janeway Pediatric Research Unit at the Janeway Child Health Care Centre. This registry includes the majority of cases of T1DM diagnosed in NL from 1987 to present for children at time of diagnosis. The Janeway Child Health Care Centre is the only tertiary care pediatric hospital in the province and therefore, the vast majority of children who develop diabetes in the province would be seen there. Children are included in the register as part of a prospective provincial study on the

epidemiology of T1DM in NL. They have a confirmed diagnosis of T1DM according to Canadian Diabetes Association (CDA) criteria for T1DM.

The LBS is maintained by the Newfoundland and Labrador Centre for Health Information (NLCHI). Data for this system is acquired from Live Birth Notification forms that are completed in provincial health care facilities. A notification form must be completed by staff at the time of the birth and provided to the Vital Statistics Divisions, Service NL. The forms are provided to NLCHI by the Vital Statistics Division, Service NL, and contain both clinical and demographic data for all births (resident and non-resident) in the province. At the time of the study, the LBS contained information from 1992-2010.

Standardization of the Live Birth System had to occur prior to analysis. Over the course of the study, mother's education was collected in two different ways. From 1992 to 2001, mother's education was captured as the number of school years completed and was entered as a numeric value in the Live Birth System. From 2002 onward, mother's education was captured categorically as one of the following: not graduated high school, graduated high school, beyond high school, or college or university degree. For the purposes of this study, education was grouped into three categories: has not graduated high school, graduated high school, and education beyond high school. Recoding of the education variable for 1992 to 2001 required consideration of mother's age and length of school at that time. For example, mothers/women born before 1966 would have graduated high school after completing Grade 11. For the analysis, 11 years of education was considered completed high school for women born before 1966 and 12 years of education

was considered completed high school for women born in 1966 or after. Number of years of education less than or greater than these numbers was considered less than high school and beyond high school, respectively. Assumptions had to be made in order to recode this variable for analysis. These include the assumption that all mothers went to school in Newfoundland and Labrador and does not account for those who may have been held back or skipped ahead a grade.

### 3.2 Data Linkage

Patient records were individually linked across datasets. A unique identifier, such as health care number, was not available for all children in the NLDD. As a result, case subjects were linked to the LBS using child's date of birth and mother's maiden name. Where available, child's name was used to verify the linkage. Of the 301 cases in the NLDD, 23 were excluded because they were born out of province and birth records were not available through the LBS. Of the remaining 278, 6 were excluded as duplicate records based on available information. Linkage was possible for all but six children due to missing information. This resulted in a total of 266 cases included in the study. Three control subjects (N=798) were randomly selected from the LBS for each case matched on month and year of birth, sex and health authority of mother's residence at time of delivery. During the study period (1992 - 2010), the number of health authorities in the province changed. Health authorities were recoded to reflect the current Eastern Health, Central Health, Western Health and Labrador-Grenfell Health regions.

### 3.3 Power Analysis

Power analysis was performed to determine whether the proposed sample size for this study would be sufficient to detect statistically significant associations between T1DM and the risk factors of interest. The power analysis was conducted considering an overall rate of birth by C-section in NL as 30.9% (Canadian Institute for Health Information, 2007), in order to achieve a power of 80% with a desired odds ratio of 1.5. Using the method described by Kelsey et al. (1996) the power analysis confirmed that a sample size of 266 cases and 798 controls is sufficient to detect statistically significant relationships between T1DM and delivery by C-section.

### 3.4 Study Variables

Cases and controls were grouped into two gestational age categories: preterm (less than 37 weeks) and term/post-term (37 weeks or greater). Birth weight in grams was used to classify cases and controls as high birth weight (>4,000 grams) or not (≤4,000 grams). Cases and controls were also classified as small/appropriate-for-gestational-age or large-for-gestational-age using the method described by Kramer et al. (2001). Method of delivery was categorized as vaginal or C-section. Cases and controls were grouped according to parity, or birth order, as either 1 and 2 or more. Mother's age in years was classified as ≤34 years or >34 years. Mothers were also classified by their T1DM status and hypertension status. Mother's marital status was categorized as married, single, separated, widowed, or divorced. Mother's education level was classified into three

categories: not graduated high school, graduated high school, and education beyond high school.

### 3.5 Data Analysis

The Statistical Package for the Social Sciences (SPSS) 17.0 (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc.) was used to generate descriptive statistics and chi square tests. Conditional multivariate logistic regressions were conducted using SAS 9.2 of the SAS System for Windows. Copyright © 2007 SAS Institute Inc.

Cases and controls were described by sex, place of residence, age of onset, length of gestation, type of delivery, birth weight, birth order, birth month, and Apgar score (i.e., an evaluation of the physical condition of newborns after delivery). Demographic and clinical factors of mothers, including age, marital status, education, place of residence, birth place, parity (number of live born children delivered), and complications of pregnancy were examined. Paternal factors including age and birth place were considered. The LBS and NLDD did not include any further information on paternal factors.

Exploratory analysis considered measures of association, including chi square test, followed by conditional logistic regression to determine whether these factors were significantly associated with the diagnosis of T1DM among children. The hazard ratio

was applied to test and measure the association between T1DM status and each of the exposure variables. The logistic regression model was used to predict diabetes status on the basis of the independent variables. Model fitting determined the percent of variance in diabetes status explained by the exposure variables.

Chi-square tests were used to examine significant differences between cases and controls. Fisher exact tests were used for expected counts less than five. Conditional multiple logistic regression was used to assess the relationship between T1DM risk and the variables of interest. Conditional logistic analysis was chosen as this was a matched case control study. The regression produced hazard ratios with 95% confidence intervals and corresponding P-values.

Two conditional logistic regression models were carried out for this study. The first model contained birth weight, gestational age, parity, delivery method, mother's marital status, mother's education level, mother's age, maternal hypertension and mother's T1DM status. The second model included parity, delivery method, mother's marital status, mother's education level, mother's age, maternal hypertension and mother's T1DM status and size-for-gestational-age. Birth weight and gestational age were not included in the same model as size-for-gestational-age as they are components of this variable and would have been collinear.

### 3.6 Ethical Considerations

This study received approvals from the Health Research Ethics Authority (formerly the Human Investigation Committee) of Memorial University (Appendix D), and from the Secondary Uses Committee of the Newfoundland and Labrador Centre for Health Information (NLCHI) (Appendix E) prior to commencement.

# CHAPTER 4 RESULTS

## 4.1 Introduction

The following chapter presents the results of the study. The results are presented as follows: descriptive characteristics, chi square analysis and multivariate regression analysis.

## 4.2 Descriptive Results

The NLDD contained 301 cases of T1DM that met inclusion criteria for this study on initial examination. Twenty-three cases were removed based on out of province birthplace and thus would not link to the LBS. A further 6 cases were removed as they were determined to be duplicates based on MCP. Of the remaining 272, six did not have enough available information to be linked to their birth records. A total of 266 cases were linked to their birth records.

Table 1 presents the descriptive characteristic of the diabetes cases. The percentages of male and female cases were similar (50.8 and 49.2, respectively). Approximately one-third (35.0%) were diagnosed with T1DM between the ages of 0-4 years, 40.4% were diagnosed between the ages of 5-9 years, and about a quarter (24.6%) were diagnosed between the ages of 10-15 years. Just over 80% of mothers resided within the Eastern Health Authority at time of delivery.

**Table 1: Characteristics of children diagnosed with T1DM in Newfoundland and Labrador, 1993-2010**

| | n | % |
|---|---|---|
| **Sex** | | |
| Male | 135 | 50.8 |
| Female | 131 | 49.2 |
| **Age at diagnosis (years)** | | |
| 0-4 | 91 | 35.0 |
| 5-9 | 105 | 40.4 |
| 10-15 | 64 | 24.6 |
| **Mother's health region of residence at time of delivery** | | |
| Eastern | 215 | 80.8 |
| Central | 19 | 7.1 |
| Western | 14 | 5.3 |
| Lab/Grenfell | 18 | 6.8 |

Table 2 presents year of birth, year of diagnosis and age at diagnosis of cases by sex. More than 40% (41.7%) of males diagnosed with T1DM were diagnosed before the age of five years, about a third (36.4%) were diagnosed between the ages five and nine years and the remaining 22.0% were diagnosed between the ages of 10 and 15 years. The distribution of age of diagnosis for females is notably different with less than a quarter (21.8%) of cases diagnosed before five years of age, 44.5% diagnosed between the ages of five and nine years of age. Furthermore, just over a quarter (27.3%) diagnosed between 10 and 15 years of age.

**Table 2: Year of birth, year of diagnosis and age at diagnosis of children with T1DM, Newfoundland and Labrador**

| | **Males** | | **Females** | | **Total** | |
|---|---|---|---|---|---|---|
| **Year of birth** | n | % | n | % | n | % |
| 1992-1995 | 59 | 43.7 | 54 | 41.2 | 113 | 42.5 |
| 1996-1999 | 34 | 25.2 | 43 | 32.8 | 77 | 28.9 |
| 2000-2003 | 17 | 12.6 | 13 | 9.9 | 30 | 11.3 |
| 2004-2007 | 25 | 18.5 | 21 | 16.0 | 46 | 17.3 |
| **Year of diagnosis** | n | % | n | % | n | % |
| 1993-1997 | 12 | 9.1 | 6 | 4.7 | 18 | 6.9 |
| 1998-2002 | 39 | 29.5 | 32 | 25.0 | 71 | 27.3 |
| 2003-2006 | 33 | 25.0 | 31 | 24.2 | 64 | 24.6 |
| 2007-2010 | 48 | 36.4 | 59 | 46.1 | 107 | 41.2 |
| **Age at diagnosis (completed years)** | n | % | n | % | n | % |
| 0-4 | 55 | 41.7 | 36 | 28.1 | 91 | 35.0 |
| 5-9 | 48 | 36.4 | 57 | 44.5 | 105 | 40.4 |
| 10-15 | 29 | 22.0 | 35 | 27.3 | 64 | 24.6 |

Table 3 presents the results of the Chi Square analysis. A higher percentage of cases than controls were born pre-term (9.8% versus 6.8%, respectively, p-value 0.073). While there was no significant difference observed between birth weight of the cases and controls, there was a significant difference observed for size-for-gestational-age with a higher percentage of cases than controls born large for gestational age (18.2% versus 12.8%, respectively, p-value 0.024). It was more common for cases to be delivered by C-section than controls (30.8% versus 22.1%, p-value 0.009). Distribution of cases and controls was similar for mother's age at birth, mother's marital status, mother's education level, mother having hypertension or type 1 diabetes during pregnancy.

**Table 3: Maternal and perinatal characteristics of the study population**

| | # Cases (N=266) | | # Controls (N=798) | | p-value[1] |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Gestational age (completed weeks) | | | | | |
| Pre-Term | 26 | 9.8 | 54 | 6.8 | |
| Term/Post-Tern | 240 | 90.2 | 743 | 93.2 | 0.073 |
| Birth weight (grams) | | | | | |
| <2,500 | 16 | 6.0 | 43 | 5.4 | |
| 2,500-4,000 | 204 | 76.7 | 622 | 78.1 | 0.873 |
| >4,000 | 46 | 17.3 | 131 | 16.5 | |
| Size-for-Gestational-Age | | | | | |
| Small/Appropriate | 207 | 81.8 | 679 | 87.2 | 0.024* |
| Large-for-gestational-age | 46 | 18.2 | 100 | 12.8 | |
| Method of Delivery | | | | | |
| Vaginal Spontaneous | 147 | 55.3 | 519 | 65.0 | |
| Vaginal Assisted | 37 | 13.9 | 103 | 12.9 | 0.009* |
| C-section | 82 | 30.8 | 176 | 22.1 | |
| Mother's age (years) | | | | | |
| ≤34 | 235 | 88.3 | 725 | 90.9 | 0.142 |
| >34 | 31 | 11.7 | 73 | 9.1 | |
| Mother has T1DM at time of birth | | | | | |
| Yes | 4 | 1.5 | 9 | 1.1 | 0.416 |
| No | 262 | 98.5 | 789 | 98.9 | |
| Mother has hypertension | | | | | |
| Yes | 18 | 6.8 | 56 | 7.0 | 0.508 |
| No | 248 | 93.2 | 742 | 93.0 | |
| Mother's marital status | | | | | |
| Married | 181 | 68.0 | 499 | 62.5 | 0.060 |
| Single, Separated, Widowed, Divorced | 85 | 32.0 | 299 | 37.5 | |
| Birth order (including current live birth) | | | | | |
| 1 | 124 | 46.6 | 386 | 48.4 | |
| 2 | 110 | 41.4 | 267 | 33.5 | 0.017* |
| 3+ | 32 | 12.0 | 145 | 18.2 | |
| Education | | | | | |
| Not graduated high school | 39 | 15.1 | 138 | 17.7 | |
| Graduated high school | 49 | 18.9 | 166 | 21.3 | 0.344 |
| Education beyond high school | 171 | 66.0 | 475 | 61.0 | |

[1]p-value of less than 0.05 was considered significant

Table 4 presents the results of the conditional logistic regression model "Birth Weight/Gestational Age." In the model which included birth weight and gestational age, delivery by C-section was associated with increased risk of T1DM (Odds ratio (OR) 1.14, p=0.015). All other factors were not significantly associated with increased risk of T1DM.

**Table 4: Risk of T1DM associated with specified maternal and perinatal factors, birth weight model**

| | Birth Weight/Gestational Age Model | | |
|---|---|---|---|
| | **Odds Ratio** | **95% Confidence Interval** | **P-Value** |
| **Birth Weight** | | | |
| ≤4,000 | REF | | |
| >4,000 | 1.07 | 0.10-0.91 | 0.692 |
| **Gestational Age** | | | |
| Pre-term | REF | | |
| Term | 0.777 | 0.78-1.47 | 0.282 |
| **Delivery Method** | | | |
| Vaginal | REF | | |
| C-section | 1.41 | 0.49-1.23 | 0.015 |
| **Mother's Age (years)** | | | |
| ≤34 | REF | | |
| >34 | 1.14 | 1.07-1.86 | 0.531 |
| **Mother has T1DM** | | | |
| No | REF | | |
| Yes | 1.16 | 0.76-1.70 | 0.795 |
| **Mother has hypertension** | | | |
| No | REF | | |
| Yes | 0.836 | 0.45-2.89 | 0.502 |
| **Mother's Marital Status** | | | |
| Married | REF | | |
| Single, separated, widowed, divorced | 0.880 | 0.50-1.39 | 0.654 |
| **Parity** | | | |
| 1 | REF | | |
| 2+ | 1.04 | 0.51-1.51 | 0.787 |
| **Mother's Education** | | | |
| Has not graduated high school | 0.880 | 0.60-1.29 | 0.520 |
| Graduated high school | 0.889 | 0.63-1.25 | 0.506 |
| Education beyond high school | REF | | |

In the second model, which included size-for-gestational-age, C-section delivery was not associated with increased risk of T1DM (OR 1.3, p=0.076). Both parity and size-for-gestational-age were found to be significant risk factors for T1DM from chi square analysis; these factors did not remain significant in the conditional logistic regression models.

**Table 5: Risk of T1DM associated with specified maternal and perinatal factors, Size for-gestational age model**

| | Size for-Gestational Age Model | | |
|---|---|---|---|
| | **Odds Ratio** | **95% Confidence Interval** | **P-Value** |
| **Size for-Gestational Age** | | | |
| Small/appropriate | REF | | |
| Large | 1.33 | 0.94-1.89 | 0.112 |
| **Delivery Method** | | | |
| Vaginal | REF | | |
| C-section | 1.304 | 0.97-1.75 | 0.076 |
| **Mother's Age (years)** | | | |
| ≤34 | REF | | |
| >34 | 1.15 | 0.76-1.74 | 0.5199 |
| **Mother has T1DM** | | | |
| No | REF | | |
| Yes | 1.129 | 0.86-1.48 | 0.388 |
| **Mother has hypertension** | | | |
| No | REF | | |
| Yes | 0.930 | 0.74-1.17 | 0.552 |
| **Mother's Marital Status** | | | |
| Married | REF | | |
| Single, separated, widowed, divorced | 0.849 | 0.62-1.15 | 0.3003 |
| **Parity** | | | |
| 1 | REF | | |
| 2+ | 1.010 | 0.79-1.29 | 0.942 |
| **Mother's Education** | | | |
| Has not graduated high school | 0.898 | 0.61-1.32 | 0.597 |
| Graduated high school | 0.907 | 0.64-1.28 | 0.592 |
| Education beyond high school | REF | | |

# CHAPTER 5 DISCUSSION

Findings of this study indicate that C-section delivery was a significant risk factor for T1DM in children aged 0-15 years. This finding is in line with a meta-analysis of 20 studies which found that the combined effect of C-section delivery was 1.23 (95% CI 1.15-1.32) (Cardwell et al., 2008), however there is no definitive explanation for the observed relationship.

One theory involves the role of gut bacteria in the development of the immune system (Penders et al., 2006). Studies have shown a difference between the compositions of gut microbiota in vaginally delivered children and those delivered by C-section. Children delivered by C-section may be primarily exposed to bacteria in the hospital and not maternal bacteria. Children born vaginally have contact with the mother's vaginal and intestinal flora (Neu and Rushing, 2011). The increased risk of T1DM may be linked to a different composition of gut flora (Penders et al., 2006).

A study by Gronlund and colleagues (1999) demonstrated that the gut flora of babies born by C-section to have been altered for up to six months after delivery. Furthermore, intestinal flora has been shown to vary for as long as seven years after birth (Salmenen et al., 2004).

Another possible explanation is related to the hygiene hypothesis which proposes that the risk of diabetes may be increased when children are not exposed to infections in early life (Gale, 2002). This theory posits that children delivered by C-section have decreased exposures to infections compared to children born vaginally and, in turn, have increased risk for diabetes (Gale, 2002).

Furthermore, it is important to highlight that lactation may be delayed by C-section delivery. Therefore, this delay in breastfeeding of babies born by C-section may also lead to differences in gut flora (Neu and Rushing, 2011).

A further difference noted between vaginal delivery and C-section delivery are the microbes that are found to colonize the babies. Those delivered vaginally were found to be colonized with *Lactobacillus.* However, babies delivered by C-section were found to be colonized with bacteria commonly found in hospitals and health care facilities (Dominguez-Bello et al., 2010).

In the present study, maternal age at time of birth was not found to be significantly associated with T1DM; other studies have found significant relationships between mother's age and T1DM. A meta-analysis of 37 studies found that the odds of T1DM increased by 10% for children whose mothers were over 35 years of age at time of birth (OR=1.10 95% CI 1.01, 1.20; p=0.03) (Cardwell et al., 2009). Conversely, a matched case-control study of 196 cases in the United Kingdom by Marshall and colleagues

(2004) found that mothers of control children were older than mothers of cases (OR=0.900 95% CI 0.854, 0.948; p<0.001).

For other maternal factors, such as education level and marital status, that were considered in this study, there were no associations found; this is consistent with other similar studies (Šipetić et al., 2004; Šipetić et al., 2005).

Additionally, the present study did not find any associations with maternal hypertension and risk of T1DM. Other studies have found an increased risk of T1DM with maternal history of T1DM (Svensson et al., 2005; Marshall et al., 2004; Haynes, Bowert, Bulsara et al., 2007); however, these studies also had information on paternal history of T1DM. A 2009 study by Algert and colleagues (Algert et al., 2009) did not find an association between maternal T1DM and risk of T1DM in children. Similar to the present study, the study by Algert et al. (2009) did not contain information on paternal T1DM.

There was no significant relationship between parity and T1DM risk found in the current study. This is different than a Western Australia population base cohort study of 835 cases of T1DM diagnosed by the age of 15 that found a significant decrease in T1DM with increasing birth order (Haynes, Bowert, Bulsara et al., 2007).

Birth weight, gestational age and size-for-gestational-age were not found to be associated with T1DM in the present study. A meta-analysis of 11 studies examining birth weight found that a birth weight greater than 4,000 grams was associated with increased odds of

T1DM (OR=1.17 95%CI 1.09, 1.26; p<0.05) (Harder et al, 2009). The present study did not find birth weight was associated with increased risk of diabetes. However, it is important to consider that it was not powered to detect an odds ratio of 1.30.

Findings related to the association between gestational age and T1DM appear to be mixed. A case-control study conducted in Austria found that babies born at 34-39 weeks had a significantly higher risk for T1DM compared to those born before 33 or after 40 weeks (Waldhoer et al., 2008). However, a study by Cardwell et al (2005) found that children born after 40 weeks' gestation had a significantly lower risk of T1DM than children born prior to 40 weeks.

While size-for-gestational-age has not been extensively studied, some studies have found significant associations. A cohort study of 272 children in New South Wales, Australia with T1DM found that children who were small-for-gestational-age had a significantly decreased risk of T1DM compared to children born appropriate-for-gestational age (Algert et al., 2009).

The findings of this study should be considered in the context of its strengths and weaknesses. An important strength is the use of a record linkage case-control study design eliminates recall bias that is apparent in cross-sectional study designs. Secondly, data contained in the LBS were collected at time of birth by healthcare professionals, and the NLDD data were collected from physician charts at time of T1DM diagnosis. The quality of the databases contributes to the study as data from these sources would likely

be more reliable than data gathered from interviews with mothers. In addition, missing data was minimal. Data collected in the LBS is subject to verification and data quality checks which results in a very complete dataset.

Although the NLDD is a reliable source of data, it should be noted that it is not a registry. The NLDD may not include all cases of T1DM. This study found that 80% of cases were from the Eastern Health region of NL. According to the 2011 Census, Eastern Health accounts for about 60% of the population. This could mean that the study population was not representative of the population of NL.

A limitation of this study is that there was very little information available pertaining to fathers. The majority of the information collected at the time of birth is related to the mother and child. Thus, paternal factors could not be considered. In addition, family history of diabetes was not available and thus could not be accounted for in the present study.

A further limitation is that the reason for C-section was not available in this study and may be a potential confounder. Antibiotic use during labour and delivery may also be associated with delivery method (Neu and Rushing, 2011). Therefore, further studies should aim to include antibiotic data related to the mother and baby.

# CHAPTER 6 CONCLUSIONS

This study explored potential maternal and neonatal risk factors for T1DM in children in Newfoundland and Labrador. Data was extracted from the NLDD and the LBS. C-section delivery was associated with increased risk of T1DM (HR 1.41, p=0.015) when birth weight and gestational age were included in the regression model.

This study presented a unique opportunity to use clinical and administrative data to examine risk factors associated with T1DM, a health issue of great significance in Newfoundland and Labrador. These findings may have an impact on health practice, health care planning and future research related to T1DM among children. Further investigation, including a chart review to obtain more information related to C-section delivery, should be undertaken to understand the nature of this association. Additional exploration into this topic may lead to a change in practice related to elective C-section delivery.

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# REFERENCES


Alaghehbandan R, Collins KD, Newhook LA, MacDonald D. Childhood type 1 diabetes mellitus in Newfoundland and Labrador, Canada. Diabetes Research and Clinical Practice 2006; 74:82-89.

Algert CS, McElduff A, Morris JM, Roberts CL. Perinatal risk factors for early onset of type 1 diabetes in a 2000-2005 birth cohort. Diabetic Medicine 2009;26;1193-1197.

Bingley P, Douek IF, Rogers CA, Gale EA. Influence of maternal age at delivery and birth order on risk of type 1 diabetes in childhood: prospective population based family study. Bart's-Oxford Family Study Group. BMJ 2000; 321(7258):420-424.

Blanchard JF, Dean H, Anderson K, Wadja A, Ludwig S, Depew N. Incidence and prevalence of diabetes in children aged 0-14 years in Manitoba, Canada, 1985-1993. Diabetes Care 1997; 20(4):512-517.

Blom L, Persson LA, Dahlquist G. A high linear growth is associated with an increased risk of childhood diabetes mellitus. Diabetologia 1992; 35:528-533.

Bonifacio E, Ziegler AG. Advances in the prediction and natural history of type 1 diabetes. Endocrinol Metab Clin North Am. 2010; 39:513-525.

Bruno G, Merletti F, Biggeri A et al. Increasing trend of type I diabetes in children and young adults in the province of Turin (Italy). Analysis of age, period and birth cohort effects from 1984 to 1996. Diabetologia 2001; 44:22-25.

Bruno G, Maule M, Biggeri A et al. More than 20 years of registration of type 1 diabetes in Sardanian children. Temporal variations of incidence with age, period of diagnosis and year of birth. Diabetes 2013; 62:3542-3546.

Canadian Institute for Health Information, Giving Birth in Canada: Regional Trends from 2001-2002 to 2005-2006, Canadian Institute for Health Information, 2007.

Canadian Institute for Health Information. Discharge Abstract Database (DAD) 2015.

Cardwell CR, Carson DJ, Patterson C. Parental age at delivery, birth order, birth weight and gestational age are associated with the risk of childhood Type 1 diabetes: a UK regional retrospective cohort study. Diabet Med 2005; 22(2):200-206.

Cardwell CR, Stene LC, Joner G, Bulsara MK, Cinek O, Rosenbauer J, et al. Maternal age at birth and childhood type 1 diabetes: A pooled analysis of 30 observational studies. Diabetes 2009; 10: 2337.

Cardwell CR. Stene LC, Joner G, Bulsara MK, Cinek O, Rosenbauer J, et al. Birth order and childhood type 1 diabetes risk: A pooled analysis of 31observational studies. International Journal of Epidemiology 2011; 40: 363-374.

Cardwell CR. Stene LC, Joner G, Cinek O, Svensson J, Goldacre M J, et al.Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: A meta-analysis of observational studies. Diabetologia 2007; 51(5), 726-735.

Casu A, Pascutto C, Bernardinelli L, Songini M. Type 1 diabetes among Sardinian children is increasing. Diabetes Care 2004; 27(7):1623-1629.

CDA 2008. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Canadian Journal of Diabetes 2008; 32:s150-s161.

Cinek O, Kolouskova S, Lanska V et al. Type 1 diabetes mellitus in Czech children diagnosed in 1990-1997: a significant increase in incidence and male predominance in the age group 0-4 years. Collaborators of the Czech Childhood Diabetes Registry. Diabetic Med 2000; 17:64-69.

Contu D, Morelli L, Zavattari P et al. Sex-related bias and exclusion mapping of the nonrecombinant portion of chromosome Y in human type 1 diabetes in the isolated founder population of Sardinia. Diabetes 2002; 51:3573-3576.

Christau B, Kromann H, Ortved Anderson O et al. Incidence, seasons and geographic patterns of juvenile onset insulin-dependent diabetes mellitus in Denmark. Diabetologia 1977; 13:281-284.Gamble DR. The epidemiology of insulin-dependent diabetes, with particular reference to the relationship of virus infection to its etiology. Epidemiol Rev 1980; 2:49-70.

Dahlquist G, Gustavsson KH, Holmgren G et al. The incidence of diabetes mellitus in Swedish children 0-14 years of age. A prospective study 1977-1980. Acta Paediatr Scand 1982; 71:7-14.

Dahlquist G, Kallen B. Maternal-child blood group incompatibility and other perinatal events increase the risk for early onset type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1992; 35:671-675.

D'Angeli MA, Merzon E, Valbuena LF, Tirschwell D, Paris CA, Mueller BA. Environmental factors associated with childhood-onset type 1 diabetes mellitus: an exploration of the hygiene and overload hypotheses. Archives of pediatrics & adolescent medicine. 2010;164(8):732-738.

Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med 1993; 329(14):977-986.

Diabetes Epidemiology Research International Group. Secular trends in incidence of childhood IDDM in 10 countries. Diabetes 1990; 39:858-864.

Dokheel TM. An epidemic of childhood diabetes in the United States? Diabetes Care 1993; 16:1606-1611.

Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, Knight R. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci 2010; 107(26): 11971-11975.

Ehrlich RM, Walsh LJ, Falk JA, Middleton PJ, Simpson NE. The incidence of type 1 (insulin dependent) diabetes in Toronto. Diabetologia 1982; 22:289-291.

EURODIAB ACE Study Group. Variation and trends in incidence of childhood diabetes in Europe. Lancet 2000; 355:873-876.

Gale EA. A missing link in the hygiene hypothesis. Diabetologia 2002; 45:588-594.

Gardner SG, Bingley PJ, Sawtell PA, Weeks S, Gale EA. Rising incidence of insulin dependent diabetes in children aged under 5 years in the Oxford region: time trend analysis. The Bart's-Oxford Study Group. British Medical Journal 1997; 315:713-717.

Gronlund MM, Lehtonen OP, Eerola E, Kero P. Fecal microflora in healthy infants born by different methods of delivery: permanent changes in intestinal flora after cesarean delivery. Journal of Pediatric Gastroenterology and Nutrition 1999; 28(1):19-25.

Harder T, Roepke K, Diller N, Stechling Y, Dudenhause JW, Plagemann A. Birth weight, early weight gain, and subsequent risk of type 1 diabetes: systematic review and meta-analysis. American Journal of Epidemiology 2009; 169:1428-1436.

Harjutsalo V, Sund R, Knip M, Groop P. Incidence of Type 1 Diabetes in Finland. JAMA 2013; 310(4):427–428.

Haynes A, Bower C, Bulsara MK, Finn J, Jones TW, Davis EA. Perinatal risk factors for childhood Type 1 diabetes in Western Australia—a population-based study (1980–2002). Diabetic Medicine 2007; 24(5):564-570.

Helgason T, Jonasson MR. Evidence for a food additive as a cause of ketosis-prone diabetes. Lancet 1981; 2:716-720.

Karvonen M, Vuk-Kajander M, Moltchanova E, Libman I, LaPorte R, Tuomilehto J. Incidence of childhood Type 1 Diabetes Worldwide. Diabetes Care 2000; 23:1516-1526.

Kelsey JL, Whittemore AS, Evans AS, Thomson WD. Methods in Observational Epidemiology. Second ed. Oxford NY: Oxford University Press; 1996 p. 327-335.

Khashan AS, Kenny LC, Lundholm C, Kearney PM, Gong T, McNamee R, Almqvist C. Gestational age and birth weight and the risk of childhood type 1 diabetes: a population-based cohort and sibling design study. Diabetes Care 2015 ; 38 :2308-2315.

Kostraba JN, Gay EC, Cai Y et al. Incidence of insulin-dependent diabetes mellitus in Colorado. Epidemiology 1992; 3:232-238.

Kramer MS, Platt RW, Evans AS, Thomson WD. A new and improved population-based Canadian reference for birth weight and gestational age. Pediatrics 2001; 108(2):E35.

Lambert AP, Gillespie KM, Thomson G, Cordell HJ, Todd JA, Gale EA, Bingley PJ. Absolute risk of childhood-onset type 1 diabetes defined by human leukocyte antigen class II genotype: a population-based study in the United Kingdom. J Clin Endocrinal Metab. 2004; 89:4037-4043.

LaPorte RE, Orchard TJ, Kuller LH et al. The Pittsburgh insulin dependent diabetes mellitus registry. An J Epidemiol 1981; 114:379-384.

Lee HY, Lu CY, Chen HF, Su HF, Li CY. Perinatal and childhood risk factors for early-onset type 1 diabetes: a population-based case-control study in Taiwan. European Journal of Public Health 2015; 25:1024-1029.

Ly TT, Maahs DM , Rewers A , et al. ISPAD Clinical Practice Consensus Guidelines 2014. Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatr Diabetes. 2014;15(Suppl 20):180-192.

Marshall AL, Chetwynd A, Morris JA et al. Type 1 diabetes mellitus in childhood: a matched case control study in Lancashire and Cumbria, UK. Diabet Med. 2004; 25:1035-1040.

Mehers KL, Gillespie KM. The genetic basis for type 1 diabetes. Br Med Bull 2008; 88:115-129.

McKinney PA, Parslow R, Gurney K, Law G, Bodansky HJ, Williams DRR. Antenatal risk factors for childhood diabetes mellitus; a case-control study of medical data in Yorkshire, UK. Diabetologia 1997; 40:933-939.

Newhook LA, Curtis J, Hagerty D et al. High Incidence of Childhood Type 1 Diabetes in the Avalon Peninsula, Newfoundland, Canada. Diabetes Care 2004; 27:885-888.

Newhook LA, Grant M, Sloka S et al. Very high and increasing incidence of Type 1 Diabetes Mellitus in Newfoundland and Labrador, Canada climbs to over 45/100,000: a retrospective time trend study. BMC Research Notes 2012; 5:628.

Newhook LA, Penney M, Fiander J, Dowden J. Recent incidence of type 1 diabetes mellitus in Newfoundland and Labrador, Canada. Pediatric Diabetes 2008; 9(3 Pt 2):62-68.

Noble JA, Valdes AM, Cook M, Klitz W, Thomson G, Erlich HA. The role of HLA class genes in insulin-dependent diabetes mellitus: molecular analysis of 180 Caucasian, multiplex families. Am J Hum Genet. 1996; 59:1134-1148.

Neu J, Rushing J. Cesarean versus vaginal delivery: long tern infant outcomes and the hygiene hypothesis. NIH Public Access 2011; 38(2):321-331.

Nystrom L, Dahlquist G, Rewers M, Wall S. The Swedish childhood diabetes study: an analysis of the temporal variation in diabetes incidence, 1978-1987. Int J Epidemiol 1990; 19:141-146.

Olufemi SE, Green JS, Manickam P, Guru SC, Agarwal SK, Kester MB, Dong Q, Burn AL, Spiegel AM, Marx SJ, Collins FS, Chandrasekharappa SC. Common ancestral mutation in the MEN1 gene is likely responsible for the prolactinoma variant of MEN1 (MEN1Burin) in four kindreds from Newfoundland. Hum. Mutat. 1998; 11:264-269.

Onkamo P, Vaananen S, Karvonen M, Tuomilehto J. Worldwide increase in incidence of type 1 diabetes: the analysis of the data on published incidence trends. Diabetologia 1999; 42:1395-1403.

Penders J, Thijs C, Vink C, Stelma FF, Snijders B, Kummeling I, van den Brandt PA, Stobberingh EE. Factors influencing the composition of the intestinal microbiota in early infancy. Pediatrics 2006;118(2):511-521.

Rewers M, LaPorte R, Walczak M, Dmochowski K, Bogaczynska E. Apparent epidemic of insulin-dependent diabetes mellitus in midwestern Poland. Diabetes 1987; 36:106-113.

Rewers M, Norris J, Dabelea D. Epidemiology of Type I Diabetes. Second Edition Edited by George S.Eisenbarth, editor. Type 1 Diabetes: Molecular, Cellular & Clinical Immunology. BDC Type 1 Diabetes Book [9]. 2004.

Rahman P, Jones A, Curtis J et al. The Newfoundland population: a unique resource for genetic investigation of complex diseases. Hum Mol Genet 2003; 12 Spec No 2: R167–R172.

Robertson L, Harrild K. Maternal and neonatal risk factors for childhood type 1 diabetes: a matched case-control study. BMC Public Health 2010;10:281.

Redondo MJ, Jeffrey J, Fain PR, Eisenbarth GS, Orban T. Concordance for islet autoimmunity among monozygotic twins. N Engl J Med. 2009; 359:2849-2850.

Rosenbauer J, Herzig P, von Kries R, Neu A, Giani G. Temporal, seasonal, and geographical incidence patterns of type I diabetes mellitus in children under 5 years of age in Germany. Diabetologia 1999; 42:1055-1059.

Salminen S, Gibson GR, McCartney AL, Isolauri E. Influence of mode of delivery on gut microbiota composition in seven year old children. Gut 2004;53(9)1388-1389.

Schoenle EJ, Lang-Muritano M, Gschwend S et al. Epidemiology of type I diabetes mellitus in Switzerland: steep rise in incidence in under 5 year old children in the past decade . Diabetologia 2001; 44:286-289.

Siemiatycki J, Colle E, Aubert D, Cambell S, Belmonte M. The distribution of Type 1(Insulin-Dependent) Diabetes Mellitus by age, sex, secular trend, seasonality, time clusters, and space-time clusters: evidence from Montreal, 1971-1983. American Journal of Epidemiology 1986; 124:545-560.

Šipetić S, Vlajinac H, Kocev N, Saji´ S. The Belgrade childhood diabetes study: prenatal and social associations for type 1 diabetes. Paediatric and Perinatal Epidemiology. 2004; 18: 33–39.

Soltesz G, Patterson CC, Dahlquist G, & EURODIAB Study Group. Worldwide childhood type 1 diabetes incidence--what can we learn from epidemiology? Pediatric Diabetes 2009; 8(6): 6-14.

Spirio L, Green J, Robertson J, Robertson M, Otterud B, Sheldon J, Howse E, Green R, Groden J, White R, Leppert M. The identical 5′ splice-site acceptor mutation in five attenuated APC families from Newfoundland demonstrates a founder effect. Hum. Genet. 1999; 105:388-389.

Statistics Canada. Census of the population 2011.

Statistics Canada. Table 105-0508 - Canadian health characteristics, annual estimates, by age group and sex, Canada (excluding territories) and provinces, occasional (number unless otherwise noted), CANSIM (database). (accessed: November 25, 2017)

Stene LC, Magnus P, Lie RT, Sovik O, Joner G. Maternal and paternal age at delivery, birth order, and risk of childhood onset type 1 diabetes: population based cohort study. BMJ 2001; 323(7309):369.

Sumnik Z, Drevinek P, Lanska V, Malcova H, Vavrinec J, Cinek O. Sumnik Z, Drevinek P, Lanska V, Malcova H, Vavrinec J, Cinek O. Higher maternal age at delivery, and lower birth orders are associated with increased risk of childhood type 1 diabetes mellitus. Exp Clin Endocrinol Diabetes 2004; 112(116):294-297.

Svensson B, Carstensen B, Mortensen B, Borch-Johnsen K. Gender-associated differences in Type 1 diabetes risk factors? Diabetologia 2003;442-443.

Svensson J, Carstensen B, Mortensen HB, Borch-Johnsen K. Danish Study Group of Childhood Diabetes. Early childhood risk factors associated with type 1 diabetes--is gender important? Eur J Endocrinol 2005; 20(5):429-434.

Tarn AC, Gorsuch AN, Spencer KM, Bottazzo GF, Lister J. Diabetes and social class. Lancet 1983;631-632.

Toth EL, Lee KC, Couch RM, Martin LF. High incidence of IDDM over 6 years in Edmonton, Alberta, Canada. Diabetes Care 1993; 16:796-800.

Tuomilehto J, Karvonen M, Pitkaniemi J et al. Record-high incidence of Type 1 (insulin-dependent) diabetes mellitus in Finnish children. Diabetologia 1999; 42(6):655-660.

Tuomilehto J, Rewers M, Reunanen A et al. Increasing trend in type I (insulin-dependent) diabetes mellitus in childhood in Finland. Analysis of age, calendar time, and birth cohort effects during 1965 to 1984. Diabetologia 1991; 34:282-287.

Wagener DK, LaPorte R, Orchard TJ, Cavender DE, Kuller LH, Drash AL. The Pittsburgh diabetes mellitus study 3: an increased prevalence with older maternal age. Diabetologia 1983; 25:82-85.

Waldhoer, T, Rami, B, Schober, E, & Austrian Diabetes Incidence Study Group. Perinatal risk factors for early childhood onset type 1 diabetes in austria - a population-based study (1989-2005). Pediatric Diabetes 2008, 9: 178-181.

Warden G, Harnett D, Green J et al: A population-based study of hereditary non-polyposis colorectal cancer: evidence of pathologic and genetic heterogeneity. Clin Genet 2013; 84: 522–530

Xie, YG, Zheng, H, Leggo, J, Scullym, MF, Lillicrap, D. A founder factor VIII mutation, valine 2016 to alanine, in a population with an extraordinarily high prevalence of mild hemophilia A. Thromb. Haemost. 2002; 87:178-179.

Young, T.L., Penney, L., Woods, M.O., Parfrey, P.S., Green, J.S., Hefferton, D. and Davidson, W.S. A fifth locus for Bardet–Biedl syndrome maps to chromosome 2q31. Am. J. Hum. Genet. 1999; 64:900-904.

Zhai G, Zhou J, Woods MO, et al. Genetic structure of the Newfoundland and Labrador population: founder effects modulate variability. European Journal of Human Genetics. 2016; 24(7):1063-1070.

**Appendix A: A published manuscript in a peer-reviewed journal resulted from this study**

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*Research Article*

# History of Cesarean Section Associated with Childhood Onset of T1DM in Newfoundland and Labrador, Canada

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*Objectives*. Newfoundland and Labrador (NL) has one of the highest incidences of Type 1 diabetes mellitus (T1DM) worldwide. Rates of T1DM are increasing and the search for environmental factors that may be contributing to this increase is continuing. *Methods*. This was a population-based case control design involving the linkage of data from a diabetes database with live birth registration data. 266 children aged 0–15 years with T1DM were compared to age- and gender-matched controls. Chi-square analysis and multivariate conditional logistic regression were carried out to assess maternal and infant factors (including maternal age, marital status, education, T1DM, hypertension, birth order, delivery method, gestational age, size-for-gestational-age, and birth weight). *Results*. Cases of T1DM were more likely to be large-for-gestational-age ($P = 0.024$) and delivered by C-section ($P = 0.009$) as compared to controls. C-section delivery was associated with increased risk of T1DM (HR 1.41, $P = 0.015$) when birth weight and gestational age were included in the model, but not when size-for-gestational-age was included (HR 1.3, $P = 0.076$). *Conclusions*. Birth by C-section was found to be a risk factor for the development of T1DM in a region with high rates of T1DM and birth by C-section. These findings may have an impact on health practice, health care planning, and future research.

## 1. Introduction

Type 1 diabetes mellitus (T1DM) is one of the most common chronic diseases in childhood and results from autoimmune destruction of pancreatic $\beta$-cells, leading to insulin deficiency. T1DM is thought to originate through a combination of genetic and unknown environmental factors, of which environmental factors remain poorly defined. Newfoundland and Labrador (NL), Canada, is recognized as having one of the highest rates of T1DM worldwide [1]. A study on hospitalizations of children in NL reported an increase in diabetes-related hospitalizations among children aged 0–19 years [2]. T1DM is a significant disease in NL with its associated acute and chronic complications as well as the economic costs to both families and the health care system. Identification of potential perinatal environmental risk factors is examined in this study to try and elucidate potential reasons of why the disease is so common in this region of North America.

## 2. Methodology

This study was a case control design involving the linkage of data extracted from the Newfoundland and Labrador Diabetes Database (NLDD) with the Live Birth System (LBS). The NLDD is maintained by the Janeway Pediatric Research Unit at the Janeway Child Health Care Centre (JCHCC) in St. John's, NL. The JCHCC is the only tertiary care pediatric hospital in the province. The NLDD includes data for the majority of cases of T1DM diagnosed in NL from 1987 to present. Children are included in the database as part of a prospective provincial study on the epidemiology of T1DM in NL. They have a confirmed diagnosis of T1DM according to Canadian Diabetes Association (CDA) criteria [3]. The LBS is maintained by the Newfoundland and Labrador Centre for Health Information (NLCHI). Data for this system are acquired from Live Birth Notification forms that are completed in all provincial health care facilities. The forms are provided to NLCHI by the Vital Statistics Division,

Service NL, and contain clinical and demographic data for all births (resident and nonresident) in the province. The system currently contains data on all births from 1992 to 2011.

Patient records were individually linked across datasets. Cases included children born in NL from 1992 onwards which have been diagnosed with T1DM before 15 years of age. Children with type 2 diabetes, maturity-onset diabetes of youth, transient hyperglycemia, and diabetes caused by chemotherapy or cystic fibrosis are excluded from the NLDD and thus were not included in the study. Children born prior to 1992 were not included in the study because there are no electronic birth notification data available before this date.

A unique identifier, such as the provincial health insurance plan number, was not available for all children in the NLDD. As a result case subjects were linked to the LBS using child's date of birth and mother's maiden name. Where available, child's name was used to verify the linkage. Of the 301 cases in the NLDD, 23 were excluded because they were born out of province. Of the remaining 278, 6 were excluded as duplicate records. Linkage was possible for all but six children resulting in a total of 266 cases included in the study. Three control subjects ($N = 798$) were selected for each case matched on year of birth, sex, and health authority of mother's residence at time of delivery. Power analysis was performed to determine whether this sample size would be sufficient to detect statistical significant associations between T1DM and the risk factors of interest. The power analysis was conducted considering an overall rate of birth by C-section in NL as 30.9% [4], in order to achieve a power of 80% with a desired odds ratio of 1.5. Using the method described by Kelsey et al. [5] the power analysis confirmed that a sample size of 266 cases and 798 controls is sufficient to detect statistically significant relationships between T1DM and delivery by C-section.

Cases and controls were grouped into two gestational age categories: preterm and term/postterm. Birth weight in grams was used to classify cases and controls as high birth weight (>4,000 grams) or not (≤4,000 grams). Cases and controls were also classified as small/appropriate-for-gestational-age or large-for-gestational-age using the method described by Kramer et al. [6]. Method of delivery was categorized as vaginal or C-section. Cases and controls were grouped according to parity or birth order as either 1 and 2 or more. Mother's age in years was classified as ≤34 years or >34 years. Mothers were also classified by their T1DM status and hypertension status. Mother's marital status was categorized as married, single, separated, widowed, or divorced. Mother's education level was classified into three categories: not graduated high school, graduated high school, and education beyond high school.

Descriptive statistics were generated to describe the distribution of cases and controls. Demographic and clinical factors of mothers, including age, marital status, education, place of residence, parity (number of live born children delivered), and complications of pregnancy, were included. Cases and controls were analyzed by sex, place of residence, age of onset, length of gestation, type of delivery, birth weight, size for gestational age, and birth order.

Chi-square tests were used to predict diabetes status on the basis of the independent variables. Conditional multiple logistic regression was used to assess the relationship between T1DM risk and the variables of interest. Two conditional logistic regression models were employed. The first model contained birth weight, gestational age, parity, delivery method, mother's marital status, mother's education level, mother's age, maternal hypertension, and mother's T1DM status. The second model incorporated all variables in the first model with the exception of birth weight and gestational age which were replaced with size-for-gestational-age. Birth weight and gestational age were not included in the same model as size-for-gestational-age as they are components of this variable.

The Statistical Package for the Social Sciences (SPSS) 17.0 was used to generate descriptive statistics and chi-squares. SAS 9.2 was used to conduct the conditional multivariate logistic regressions.

This study received approvals from the Human Investigation Committee of Memorial University, from each of the hospital boards and the Secondary Uses Committee of the Newfoundland and Labrador Centre for Health Information (NLCHI) prior to commencement.

## 3. Results

Table 1 presents the descriptive characteristics of the cases of T1DM. The percentages of male and female cases were similar (50.8 and 49.2, resp.). Table 1 also demonstrates the age distribution of cases as well as their age of diagnosis. There were more males than females diagnosed in the 0–4 age group; however, this finding was not statistically significant.

Table 2 presents maternal and perinatal characteristics of the study population. A higher percentage of cases than controls were born pre-term (9.8% versus 6.8%, resp.). While there was no significant difference observed between birth weight of the cases and controls, there was a significant difference observed for size-for-gestational-age with a higher percentage of cases than controls born large-for-gestational-age (18.2% versus 12.8%, resp., $P = 0.024$). It was more common for cases to be delivered by C-section than controls (30.8% versus 22.1%, $P = 0.009$). T1DM was more common among first or second born cases compared to those born third or higher ($P = 0.022$).

Table 3 presents the results of the conditional logistic regression models. In the model which included birth weight and gestational age, delivery by C-section was associated with increased risk of T1DM. Children delivered by C-section were 1.41 times as likely to develop T1DM (Hazard ratio (HR) 1.41, $P = 0.015$). In the second model, which included size-for-gestational-age, C-section delivery was not associated with increased risk of T1DM (HR 1.3, $P = 0.076$). Both parity and size-for-gestational-age were found to be significant risk factors for T1DM from chi-square analysis (Table 2); these factors did not remain statistically significant in the conditional logistic regression models.

Table 1: Characteristics of children diagnosed with T1DM in Newfoundland and Labrador, by sex, 1992–2010.

| Variables | Males | | Females | | Total | | $P$ value |
|---|---|---|---|---|---|---|---|
| | $n$ | % | $n$ | % | $n$ | % | |
| Year of birth | | | | | | | |
| 1992–1995 | 59 | 43.7 | 54 | 41.2 | 113 | 42.5 | 0.553 |
| 1996–1999 | 34 | 25.2 | 43 | 32.8 | 77 | 28.9 | |
| 2000–2003 | 25 | 18.5 | 21 | 16.0 | 46 | 17.3 | |
| 2004–2007 | 17 | 12.6 | 13 | 9.9 | 30 | 11.3 | |
| Year of diagnosis | | | | | | | |
| 1993–1997 | 12 | 9.1 | 6 | 4.7 | 18 | 6.9 | 0.263 |
| 1998–2002 | 39 | 29.5 | 32 | 25.0 | 72 | 27.6 | |
| 2003–2006 | 33 | 25.0 | 31 | 24.2 | 64 | 24.1 | |
| 2007–2010 | 48 | 36.4 | 59 | 46.1 | 107 | 41.0 | |
| Age at diagnosis | | | | | | | |
| 0–4 | 55 | 41.7 | 36 | 21.8 | 91 | 35.0 | 0.073 |
| 5–9 | 48 | 36.4 | 57 | 44.5 | 105 | 40.4 | |
| 10–15 | 29 | 22.0 | 35 | 27.3 | 64 | 24.6 | |

## 4. Discussion

Findings of this study indicate that C-section delivery was a significant risk factor for T1DM in children aged 0–15 years. This finding is in line with a recent meta-analysis of 20 studies which found that the combined effect of C-section delivery was 1.23 (95% CI 1.15–1.32) [7]. Theories of why this may be associated with the development of T1DM in offspring includes the involvement of the role of gut bacteria in the development of the immune system [8]. Studies have shown a difference between the compositions of gut microbiota in vaginally delivered children and those delivered by C-section. Children delivered by C-section may be primarily exposed to bacteria in the hospital and not maternal bacteria, hence the increased risk of T1DM may be linked to a different composition of gut flora [8]. Another possible explanation is related to the hygiene hypothesis which proposes that the risk of diabetes may be increased when children are not exposed to infections in early life [9]. Children delivered by C-section have decreased exposures to infections compared to children born vaginally and, in turn, have increased risk for diabetes [9]. Another theory suggests that the observed increased risk of diabetes after C-section may be related to perinatal stress [10]. NL has a high rate of birth by C-section as compared to other regions in Canada. The provincial rate of births by C-section was 30.9% in 2005-2006 versus the Canadian rate of 26.3% [4]. The rates of C-section have increased in NL to 33% in 2010 [11].

In the present study, maternal age at time of birth was not found to be significantly associated with risk of T1DM in offspring; other studies have found significant relationships between mother's age and T1DM risk. A recent meta-analysis of 37 studies found that the odds of T1DM increased by 10% for children whose mothers were over 35 years of age at time of birth (OR = 1.10 95% CI 1.01, 1.20; $P = 0.03$) [12]. Conversely, a matched case-control study of 196 cases in the United Kingdom [13] found that mothers of control children were older than mothers of cases (OR = 0.900 95% CI 0.854, 0.948; $P < 0.001$). For other maternal factors, such as education level and marital status, there were no associations found which is consistent with other similar studies [14, 15]. The present study also did not find any associations between maternal hypertension and risk of T1DM in offspring. Other studies have found an increased risk of T1DM in offspring with maternal history of T1DM [13, 16, 17]; however, these studies also included information on paternal history of T1DM. A 2009 study by Algert and colleagues [18] did not find an association between maternal T1DM and risk of T1DM in children. Similar to the present study, the study by Algert et al. did not contain information on paternal T1DM.

There was no significant relationship between parity and T1DM risk found in the current study. This is different than a Western Australia population based cohort study of 835 cases of T1DM diagnosed by the age of 15 that found a significant decrease in T1DM with increasing birth order [18].

Birth weight and gestational age were not found to be associated with risk of T1DM in the present study; however, chi-squared analysis revealed a significant difference between T1DM and size-for-gestational-age with a higher percentage of cases than controls born large-for-gestational-age, but this was no longer significant in the conditional logistic regression models. Our findings do not support the findings of a meta-analysis of 11 studies examining birth weight which found that a birth weight greater than 4,000 grams was associated with an increased odds of T1DM (OR = 1.17 95% CI 1.09, 1.26; $P < 0.05$) [19]. Findings related to the association between gestational age and T1DM appear to be mixed. A case-control study conducted in Austria found that babies born at 34–39 weeks had a significantly higher risk for T1DM compared to those born before 33 or after 40 weeks [20]. However, a study by Cardwell et al. [21] found that children born after 40 weeks gestation had a significantly lower risk of T1DM than children born prior to 40 weeks. While size-for-gestational-age has not been extensively studied,

Table 2: Maternal and perinatal characteristics of the study population.

| Variables | No. of cases ($N = 266$) | | No. of controls ($N = 798$) | | $P$ value |
|---|---|---|---|---|---|
| | $n$ | % | $n$ | % | |
| Gestational age (completed weeks) | | | | | |
| Preterm | 26 | 9.8 | 54 | 6.8 | |
| Term/postterm | 240 | 90.2 | 743 | 93.2 | 0.073 |
| Birth weight (grams) | | | | | |
| <2,500 | 16 | 6.0 | 43 | 5.4 | |
| 2,500–4,000 | 204 | 76.7 | 622 | 78.1 | |
| >4,000 | 46 | 17.3 | 131 | 16.5 | 0.873 |
| Size-for-gestational-age | | | | | |
| Small/appropriate | 207 | 81.8 | 679 | 87.2 | |
| Large-for-gestational-age | 46 | 18.2 | 100 | 12.8 | 0.024* |
| Method of delivery | | | | | |
| Vaginal spontaneous | 147 | 55.3 | 519 | 65.0 | |
| Vaginal assisted | 37 | 13.9 | 103 | 12.9 | |
| C-section | 82 | 30.8 | 176 | 22.1 | 0.009* |
| Mother's age (years) | | | | | |
| ≤34 | 235 | 88.3 | 725 | 90.9 | |
| >34 | 31 | 11.7 | 73 | 9.1 | 0.142 |
| Mother has T1DM | | | | | |
| Yes | 4 | 1.5 | 9 | 1.1 | |
| No | 262 | 98.5 | 789 | 98.9 | 0.416 |
| Mother has hypertension | | | | | |
| Yes | 18 | 6.8 | 56 | 7.0 | |
| No | 248 | 93.2 | 742 | 93.0 | 0.508 |
| Mother's marital status | | | | | |
| Married | 181 | 68.0 | 499 | 62.5 | |
| Single, separated, widowed, divorced | 85 | 32.0 | 299 | 37.5 | 0.060 |
| Birth order (including current live birth) | | | | | |
| 1-2 | 234 | 88.0 | 653 | 48.4 | |
| 3+ | 32 | 12.0 | 145 | 18.2 | 0.022* |
| Education | | | | | |
| Not graduated high school | 39 | 15.1 | 138 | 17.7 | |
| Graduated high school | 49 | 18.9 | 166 | 21.3 | |
| Education beyond high school | 171 | 66.0 | 475 | 61.0 | 0.344 |

* $P$ value of less than 0.05 was considered significant.

some studies have found significant associations. A cohort study of 272 children in New South Wales, Australia, with T1DM found that children who were small-for-gestational-age had a significantly decreased risk of T1DM compared to children born appropriate-for-gestational age [18].

The findings of this study should be considered in the context of its strengths and weaknesses. An important strength is that the use of a record linkage case-control study design eliminates recall bias that is apparent in cross-sectional study designs. Secondly, data contained in the LBS were collected at time of birth by healthcare professionals, and the NLDD data were collected from physician charts at time of T1DM diagnosis which contributes to the reliability of the data. A limitation of this study is that there was very little information available pertaining to fathers as the majority of the information collected at the time of birth for the LBS is related to the mother and child. Thus, paternal factors and family history could not be considered for analysis.

This study identified C-section as a significant risk factor for the development of T1DM among children aged 0–15 years in NL, a region with very high rates of T1DM. Findings may have an impact on health practice, health care planning and future research related to T1DM among children. Further research should be undertaken to understand the nature of this association.

## Authors' Contribution

L. A. Newhook is the senior investigator and was responsible for the intellectual conception and design of the study, funding application, paper preparation and is the guarantor of

Table 3: Risk of T1DM associated with specified maternal and perinatal factors.

| Variables | Birth weight/gestational age model | | Size-for-gestational-age model | |
|---|---|---|---|---|
| | HR | *P* value | HR | *P* value |
| Birth weight | | | | |
| ≤4,000 | REF | | — | — |
| >4,000 | 1.07 | 0.692 | — | — |
| Gestational age | | | | |
| Preterm | REF | | — | — |
| Term | 0.777 | 0.282 | — | — |
| Size-for-gestational age | | | | |
| Small/appropriate | — | — | REF | |
| Large | — | — | 1.33 | 0.112 |
| Delivery method | | | | |
| Vaginal | REF | | REF | |
| C-section | 1.41 | 0.015 | 1.304 | 0.076 |
| Mother's age (years) | | | | |
| ≤34 | REF | | REF | |
| >34 | 1.14 | 0.531 | 1.15 | 0.5199 |
| Mother has T1DM | | | | |
| No | REF | | REF | |
| Yes | 1.16 | 0.795 | 1.129 | 0.388 |
| Mother has hypertension | | | | |
| No | REF | | REF | |
| Yes | 0.836 | 0.502 | 0.930 | 0.552 |
| Mother's marital status | | | | |
| Married | REF | | REF | |
| Single, separated, widowed, divorced | 0.880 | 0.654 | 0.849 | 0.3003 |
| Parity | | | | |
| 1 | REF | | REF | |
| 2+ | 1.04 | 0.787 | 1.010 | 0.942 |
| Mother's education | | | | |
| Has not graduated high school | 0.880 | 0.520 | 0.898 | 0.597 |
| Graduated high school | 0.889 | 0.506 | 0.907 | 0.592 |
| Education beyond high school | REF | | REF | |

T1DM: type 1 diabetes mellitus.

the research. J. Phillips was responsible for overall coordination of the study and contributed intellectually to the methods, literature review, database development, analysis, logistics, paper preparation, and approvals. N. Gill contributed intellectually to the methods, database development, analysis, logistics, and approvals. S. Penney was the research nurse who was responsible for study approvals, as well as gathering, confirming, and entering of data and maintaining the NLDD. K. Sikdar was responsible for overseeing the statistical analysis. All authors contributed to and approved the final paper submission.

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## References

[1] L. A. Newhook, M. Grant, A. Sloka et al., "Very high and increasing incidence of type 1 diabetes mellitus in Newfoundland and Labrador, Canada," *Pediatric Diabetes*, vol. 9, part 2, no. 3, pp. 62–68, 2008.

[2] R. Alaghehbandan, K. D. Collins, L. A. Newhook, and D. MacDonald, "Childhood type 1 diabetes mellitus in Newfoundland and Labrador, Canada," *Diabetes Research and Clinical Practice*, vol. 74, no. 1, pp. 82–89, 2006.

[3] Canadian Diabetes Association, *Canadian Diabetes Association 2008 Clinical Practice Guidelines*, Canadian Diabetes Association, 2008.

[4] Canadian Institute for Health Information, *Giving Birth in Canada: Regional Trends from 2001-2002 to 2005-2006*, Canadian Institute for Health Information, 2007.

[5] J. L. Kelsey, A. S. Whittemore, A. S. Evans, and W. D. Thomson, *Methods in Observational Epidemiology*, Oxford University Press, Oxford, UK, 2nd edition, 1996.

[6] M. S. Kramer, R. W. Platt, S. W. Wen et al., "A new and improved population-based Canadian reference for birth weight for gestational age," *Pediatrics*, vol. 108, no. 2, article E35, 2001.

[7] C. R. Cardwell, L. C. Stene, G. Joner et al., "Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies," *Diabetologia*, vol. 51, no. 5, pp. 726–735, 2008.

[8] J. Penders, C. Thijs, C. Vink et al., "Factors influencing the composition of the intestinal microbiota in early infancy," *Pediatrics*, vol. 118, no. 2, pp. 511–521, 2006.

[9] E. A. Gale, "A missing link in the hygiene hypothesis?" *Diabetologia*, vol. 45, no. 4, pp. 588–594, 2002.

[10] G. Dahlquist and B. Kallen, "Maternal-child blood group incompatibility and other perinatal events increase the risk for early-onset type 1 (insulin-dependent) diabetes mellitus," *Diabetologia*, vol. 35, no. 7, pp. 671–675, 1992.

[11] Research and Evaluation Department: Newfoundland Centre for Health Information, "Live Birth Trends 2006–2010," 2011.

[12] C. R. Cardwell, L. C. Stene, G. Joner et al., "Maternal age at birth and childhood type 1 diabetes: a pooled analysis of 30 observational studies," *Diabetes*, vol. 59, no. 2, pp. 486–494, 2010.

[13] A. L. Marshall, A. Chetwynd, J. A. Morris et al., "Type 1 diabetes mellitus in childhood: a matched case control study in Lancashire and Cumbria, UK," *Diabetic Medicine*, vol. 21, no. 9, pp. 1035–1040, 2004.

[14] S. Sipetic, H. Vlajinac, N. Kocev, and S. Saji, "The Belgrade childhood diabetes study: prenatal and social associations for type 1 diabetes," *Paediatric and Perinatal Epidemiology*, vol. 18, no. 1, pp. 33–39, 2004.

[15] S. B. Sipetic, H. D. Vlajinac, N. I. Kocev, J. M. Marinkovic, S. Z. Radmanovic, and M. D. Bjekic, "The Belgrade childhood diabetes study: a multivariate analysis of risk determinants for diabetes," *European Journal of Public Health*, vol. 15, no. 2, pp. 117–122, 2005.

[16] J. Svensson, B. Carstensen, H. B. Mortensen, and K. Borch-Johnsen, "Early childhood risk factors associated with type 1 diabetes—is gender important?" *European Journal of Epidemiology*, vol. 20, no. 5, pp. 429–434, 2005.

[17] A. Haynes, C. Bower, M. K. Bulsara, J. Finn, T. W. Jones, and E. A. Davis, "Perinatal risk factors for childhood type 1 diabetes in Western Australia—a population-based study (1980–2002)," *Diabetic Medicine*, vol. 24, no. 5, pp. 564–570, 2007.

[18] C. S. Algert, A. McElduff, J. M. Morris, and C. L. Roberts, "Perinatal risk factors for early onset of type 1 diabetes in a 2000–2005 birth cohort," *Diabetic Medicine*, vol. 26, no. 12, pp. 1193–1197, 2009.

[19] T. Harder, K. Roepke, N. Diller, Y. Stechling, J. W. Dudenhausen, and A. Plagemann, "Birth weight, early weight gain, and subsequent risk of type 1 diabetes: systematic review and meta-analysis," *American Journal of Epidemiology*, vol. 169, no. 12, pp. 1428–1436, 2009.

[20] T. Waldhoer, B. Rami, E. Schober et al., "Perinatal risk factors for early childhood onset type 1 diabetes in Austria—a population-based study (1989–2005)," *Pediatric Diabetes*, vol. 9, part 1, no. 3, pp. 178–181, 2008.

[21] C. R. Cardwell, D. J. Carson, and C. C. Patterson, "Parental age at delivery, birth order, birth weight and gestational age are associated with the risk of childhood type 1 diabetes: a UK regional retrospective cohort study," *Diabetic Medicine*, vol. 22, no. 2, pp. 200–206, 2005.

## Appendix B: Newfoundland and Labrador Diabetes Database variable list

## Variable requested from the Newfoundland and Labrador Diabetes Database

| ***Newfoundland and Labrador Diabetes Database*** | | |
|---|---|---|
| Patient's name: first | Patient's first name | Linkage |
| Last: | Patient's last name | Linkage |
| Gender label | Gender | Linkage |
| Date of birth | Date of Birth | Linkage |
| diagdate | Date of Dx | Data Analysis |
| mother | Mother's Name | Linkage |
| maiden | Mother's maiden name | Linkage |

## Appendix C: Live Birth Notification System variable list

# Appendix 1

## NLCHI Live Birth System Data Dictionary

**Note:** Items in grey are variables which are no longer collected and/or valid.

| NLCHI LIVE BIRTH SYSTEM DATA DICTIONARY | | | | | | |
|---|---|---|---|---|---|---|
| **Variable Name** | **Label** | **Value/Example** | **Type** | **Length** | **Applicable Year** | **Comments** |
| year | Year of Birth | Value: YYYY | Numeric | 4 | 1992-2016 | Derived from Registration # |
| reg_num | Registration Number | Year-Province - Accession Number<br>YYYY/NL/1234…<br>NL = 10 for Newfoundland and Labrador | Numeric | 11 | 1992-2016 | |
| c_name | Infant's Surname, Full Given Name(s) | Full name of infant, if available | String | 40 | 1997-2016 | No punctuation used e.g. O'Leary is entered as OLeary |
| c_sex | Infant's Sex | 1 = Male<br>2 = Female<br>3 = Unknown | Numeric | 1 | 1992-2016 | |
| c_dob | Infant's Date of Birth | MM/DD/YYYY | Date | 10 | 1992-2016 | |
| c_locbir | Locality of Birth | 1 = Hospital<br>2 = Private Home<br>3 = Other Health Care Facility (Clinical)<br>4 = Unknown<br>5 = Other (e.g. Ambulance)<br>9= System Missing | Numeric | 1 | 2002-2016 | |
| c_locoth | Other Location (Specify) | Specify other location of birth | String | 15 | 2002-2016 | |
| hospital | Hospital | Name of Facility where birth occurred. | String | 15 | 1992-2016 | Hospital name auto-populated on data entry. |
| hospcode | Hospital Code | Institution number assigned to the facility with appropriate alpha accompaniment<br>e.g. H60 = born at Carbonear General Hospital<br>e.g. R01=Born at home but admitted to HSC. | String | 4 | 1992-2016 | |
| c_locat | Place of Occurrence | City/Town where birth occurred | String | 20 | 1992-2016 | Derived from hospital code |
| c_plcode | SGC code for Place of Occurrence | SGC for city/town of occurrence | String | 7 | 1992-2016 | Derived from hospital code |
| c_admnum | Infant's Hospital Admit Number | Admission # assigned by facility | String | 11 | 1992-2006 | |

| NLCHI LIVE BIRTH SYSTEM DATA DICTIONARY | | | | | | |
|---|---|---|---|---|---|---|
| **Variable Name** | **Label** | **Value/Example** | **Type** | **Length** | **Applicable Year** | **Comments** |
| c_chanum | Infant's Hospital Chart Number | Chart number as recorded on LBN form – format is facility-driven. | String | 12 | 2002-2016 | |
| crelcode | Infant's Religious Denomination | 0 = None<br>1= Anglican<br>2 = Roman Catholic<br>3 = United Church<br>4 = Pentecostal<br>5=Salvation Army<br>6=Seventh Day Adventist<br>7=Mormon<br>8=Jewish<br>9=Apostolic Faith<br>10=Plymouth Brethren<br>11=Baptist<br>12=Jehovah Witness<br>13=East Indian<br>14=Moravian<br>15=Christian Scientist<br>16=Other<br>98=Refusal<br>99=Unknown | Numeric | 2 | 1992-2001 | |
| m_name | Mother's Surname, Full Given Name(s) | Mother's full name | String | 40 | 1997-2016 | No punctuation used e.g. O'Leary is entered: OLeary |
| m_maiden | Mother's Maiden Name & Initials | Mother's maiden name | String | 20 | 1997-2016 | No punctuation used e.g. O'Leary is entered: OLeary |
| mcp_validated | Validate MCP Number | MCP # checked and verified by NLCHI | Numeric | 12 | 2009-2016 | New for 2009, but all MCP #s in Longitudinal File validated also. |
| m_admnum | Mother's Hospital Admission Number | Admission number generated by health care facility | String | 12 | 1992-2006 | |
| m_chanum | Mother's Hospital Chart Number | Chart number as recorded on LBN form. | String | 12 | 1997-2016 | |
| m_dob_derived | Mother's DOB from MCP | Mother's Date of Birth from validated MCP | Date | 10 | 1992-2016 | Derived from validated MCP |
| m_age_derived | Mother's Age from MCP | Mother's age derived from validated MCP # | Numeric | 8 | 1992-2016 | Derived from validated MCP |

| NLCHI LIVE BIRTH SYSTEM DATA DICTIONARY | | | | | | |
|---|---|---|---|---|---|---|
| **Variable Name** | **Label** | **Value/Example** | **Type** | **Length** | **Applicable Year** | **Comments** |
| m_age_derived2 | Mother's Age from MCP | Mother's age derived from validated MCP # (to 1 decimal) | Numeric | 8<br>+1 decimal | 1992-2016 | Derived from validated MCP |
| m_brcode | Mother's Birth Place Residence Code | Code used to identify Mother's birth place | String | 3 | 1992-2002 | |
| maddres1<br>maddres2<br>maddres3<br>maddres4 | Mother's Address (Street) | Completed if permanent residence is different than mailing address. | String | 25 | 1992-1995<br>1997-2001 | |
| m_pcode | Postal Code | Mother's postal code for place of residence | String | 6 | 1992-2016 | |
| m_addcod | Mother's Address Code | Mother's current home residence code<br>(7-digit SGC code) | String | 7 | 1992-2016 | |
| sgc<br>Office use only | SGC Code | Shortened SGC code for Mother's residence<br>4-5 digits. | Numeric | 8 | 1992-2016 | Derived from mother's residence code. |
| hth_auth | Regional Health Authority | 1 = Eastern<br>2 = Central<br>3 = Western<br>4 = Lab/Grenfell<br>9 = Out/Province<br>99 = Unknown | Numeric | 8 | 1992-2016 | Derived from SGC |
| m_marsta | Legal Marital Status of Birth Mother | 1 = Never Married<br>2 = Legally Married and Not Separated<br>3 = Legally Married but Separated<br>4 = Divorced<br>5 = Widowed<br>6= Unknown<br>9= System Missing | Numeric | 1 | 1992-2016 | |
| laparent | Living Arrangements of Birth Parents | 1 = Living Together as a Couple<br>2 = Not Living Together as a Couple<br>3 = Unknown<br>9= System Missing | Numeric | 1 | 2002-2016 | |
| mrparent | Birth Parents Legally Married to Each Other | 1=Yes<br>2=No<br>3=Unknown<br>9=System Missing | Numeric | 1 | 2002-2006 | |

| NLCHI LIVE BIRTH SYSTEM DATA DICTIONARY | | | | | | |
|---|---|---|---|---|---|---|
| **Variable Name** | **Label** | **Value/Example** | **Type** | **Length** | **Applicable Year** | **Comments** |
| m_educ | Mother's Education | 1 = Has not Graduated High School<br>2 = Graduated High School<br>3 = Beyond High School<br>4 = College/University Degree<br>5 = Unknown<br>9= System Missing | Numeric | 1 | 2002-2016 | |
| meduc | Mother's Education | Mother's education – Actual number of years | Numeric | 1 | 1992-2001 | |
| f_name | Father's Name | See comment | String | 45 | 1997-2002 | No punctuation used e.g. O'Leary is entered: OLeary |
| f_dob | Other Parent's Date of Birth | MM/DD/YYYY | Date | 10 | 1992-2002<br>2006-2016 | *in 2009, variable label changed to "Other Parent" |
| f_age | Other Parent's Age | Other Parent's Age as recorded on LBN | Numeric | 2 | 1992-2002<br>2006-2016 | Derived from f_dob |
| f_age2 | Other Parent's Age (+ 1 decimal place) | Other Parent's Age to one decimal place | Numeric | 2<br>+1 decimal | 1992-2002<br>2006-2016 | Derived from f_dob |
| f_brcode | Father's Birth Residence Code | Code used to identify Father's birth place | String | 3 | 1992-2002 | |
| feduc | Father's education | Father's education – actual number of years. | Numeric | 2 | 1992-2001 | |
| live | Total No. of children born to this mother (including this delivery) Live born | Enter numeric value for number of live born children ever born to this mother, which includes current delivery | Numeric | 2 | 1992-2016 | |
| still | Total No. of children born to this mother (including this delivery) Stillborn | Enter numeric value for number of stillborn children ever born to this mother, which includes current delivery | Numeric | 2 | 1992-2016 | |
| lastdate | Date of Last Delivery | MM/DD/YYYY | Date | 10 | 1992-2016 | |
| livestil | Last Delivery Live or Still Birth | 1=Live<br>2=Still | Numeric | 2 | 1992-2001 | |
| prevcsec | Prior C-Section | 1 = Yes<br>2 = No<br>3= Unknown<br>9= System Missing | Numeric | 2 | 2002-2016 | |
| lstyle1 | Substance Use During Pregnancy: NONE | 1 = None<br>0 = Substance Use<br>2 = Unknown<br>9= System Missing | Numeric | 1 | 2002-2016 | Check box for "None". |

| NLCHI LIVE BIRTH SYSTEM DATA DICTIONARY | | | | | | |
|---|---|---|---|---|---|---|
| **Variable Name** | **Label** | **Value/Example** | **Type** | **Length** | **Applicable Year** | **Comments** |
| lstyle2 | Substance Use During Pregnancy: DRUGS | 1 = Yes<br>0 = No<br>2 = Unknown<br>9= System Missing | Numeric | 1 | 2002-2016 | |
| lstyle3 | Substance Use During Pregnancy: UNKNOWN | 1 = Unknown<br>0 = Known<br>9= System Missing | Numeric | 1 | 2002-2016 | |
| lstyle4 | Substance Use During Pregnancy: ALCOHOL | 1 = Yes<br>0 = No<br>2 = Unknown<br>9= System Missing | Numeric | 1 | 2002-2016 | |
| lstyle5 | Substance Use During Pregnancy: SMOKING | 1 = Yes<br>0 = No<br>2 = Unknown<br>9= System Missing | Numeric | 1 | 2002-2016 | |
| lstyle6 | Number of Cigarettes / Day | Enter numeric value | Numeric | 2 | 2002-2016 | |
| support1 | Support Available – Husband / Partner | 1 = Yes<br>0 = No<br>2 = Unknown<br>9 = System Missing | Numeric | 1 | 2002-2016 | |
| support2 | Support Available - Living With Parents / Other Supports | 1 = Yes<br>0 = No<br>2 = Unknown<br>9 = System Missing | Numeric | 1 | 2002-2016 | |
| support3 | Support Available - Lives Alone | 1 = Yes<br>0 = No<br>2 = Unknown<br>9 = System Missing | Numeric | 1 | 2002-2016 | |
| pncspec | Physician Specialist for Prenatal Care | 1 = None<br>2 = OB/GYN<br>3 = Other<br>4 = Unknown<br>9 = System Missing | Numeric | 1 | 2002-2016 | |
| other1<br>other2<br>other3 | Specialist for Prenatal Care – Other | Specify “Other” | String | 20 | 2002-2016 | |
| speccare | Specialist for Prenatal Care | 1 = Yes<br>2 = No<br>3 = Unknown<br>9 = System Missing | Numeric | 1 | 1992-2001 | |
| trimest1 | Trimester 1 | 1 = Yes<br>2 = No<br>3 = Unknown<br>9 = System Missing | | | 1992-2001 | |
| trimest2 | Trimester 2 | 1 = Yes<br>2 = No<br>3 = Unknown | | | 1992-2001 | |

| NLCHI LIVE BIRTH SYSTEM DATA DICTIONARY | | | | | | |
|---|---|---|---|---|---|---|
| **Variable Name** | **Label** | **Value/Example** | **Type** | **Length** | **Applicable Year** | **Comments** |
| | | 9 = System Missing | | | | |
| trimest3 | Trimester 3 | 1 = Yes<br>2 = No<br>3 = Unknown<br>9 = System Missing | | | 1992-2001 | |
| pncbegan | Prenatal Care Began At (# Weeks) | 01-43 | Numeric | 2 | 2002<br>2006-2016 | |
| pnctrime | Prenatal Care Began At (Trimester) | 1 = None<br>2= First Trimester<br>3= Second Trimester<br>4= Third Trimester<br>5= Unknown<br>9= System Missing | Numeric | 2 | 1992-2001 | |
| provnum | Physician Provider Number | 6 digit Provider number | Numeric | 6 | 1992-2001 | |
| famdis1 | Familial Diseases - YES/NO | 1= None<br>2= Yes<br>3= Unknown<br>9= System Missing | Numeric | 1 | 1992-2001 | |
| famdis2 | Familial Diseases - Deafness | 1 = Yes<br>2 = No<br>3 = Unknown<br>9 = System Missing | Numeric | 1 | 1992-2001 | |
| famdis3 | - Other | 1 = Yes<br>2 = No<br>3 = Unknown<br>9 = System Missing | Numeric | 1 | 1992-2001 | |
| famicd1<br>famicd2<br>famicd3<br>famicd4<br>famicd5<br>famicd6 | Familial Diseases ICD Code(s) | Code used to identify familial disease | String | 4 | 1992-2001 | |
| numdeliv | Total Number of Infants in <u>THIS Delivery</u> | 1 = Single Birth<br>2 = Twins<br>3 = Triplets<br>4 = Quadruplets<br>5 = Quintuplets<br>9 = System Missing | Numeric | 1 | 1992-2016 | |
| Nonestil<br>Only on HRA's list | Stillborn <u>this</u> delivery <u>NONE</u> | 0 = Stillborn occurred <u>in this event</u><br>1 = No Stillborn in this event | | | "nonestil" is for editing purposes only & is deleted following the edit process. | Checkbox for "None" – if checked, it means no stillbirths in this delivery. " |

| NLCHI LIVE BIRTH SYSTEM DATA DICTIONARY | | | | | | |
|---|---|---|---|---|---|---|
| **Variable Name** | **Label** | **Value/Example** | **Type** | **Length** | **Applicable Year** | **Comments** |
| numstill | Number of Stillborn in ***this*** delivery | Left blank if none; or populated with numeric value, if stillbirth occurred during this delivery. | Numeric | 1 | 1992-2002<br>2006-2016 | |
| multiple | Multiple Birth - Birth Order | 1=1st<br>2=2nd<br>3=3rd<br>4=4th<br>8 = Unknown<br>9 = System Missing | Numeric | 1 | 1992-2002<br>2006-2016 | |
| medterm | Was this birth due to medical termination? | 1 = Yes<br>2 = No<br>9 = System Missing | Numeric | 2 | 2008 - 2016 | |
| mr_none | Medical Risk Factors – NONE | 0 = Medical Risk Factors-Existed<br>1 = No Medical Risk Factors<br>2 = Unknown<br>9 = System Missing | Numeric | 1 | 2006-2016 | Checkbox for "None" – if checked, it means no medical risk factor existed. |
| anemia | Anemia (< 100G/L) | 0 = No<br>1= Yes<br>2 = Unknown<br>9 = Systems Missing | Numeric | 1 | 1992-2002<br>2006-201 | |
| hyper_c | Hypertension (Chronic) | 0 = No<br>1= Yes<br>2 = Unknown<br>9 = Systems Missing | Numeric | 1 | 1992-2002<br>2006-2016 | |
| hyper_p | Hypertension (Associated with Pregnancy) | 0 = No<br>1= Yes<br>2 = Unknown<br>9 = Systems Missing | Numeric | 1 | 1992-2002<br>2006-2016 | |
| uti | UTI (Urinary Tract Infection) | 0 = No<br>1= Yes<br>2 = Unknown<br>9 = Systems Missing | Numeric | 1 | 1992-2002<br>2006-2016 | |
| iugr | IUGR (Intrauterine Growth Restriction) | 0 = No<br>1= Yes<br>2 = Unknown<br>9 = Systems Missing | Numeric | 1 | 1992-2002<br>2006-2016 | |
| iddm | Insulin Dependent Diabetes | 0 = No<br>1= Yes<br>2 = Unknown<br>9 = Systems Missing | Numeric | 1 | 1992-2002<br>2006-2016 | |

| NLCHI LIVE BIRTH SYSTEM DATA DICTIONARY | | | | | | |
|---|---|---|---|---|---|---|
| **Variable Name** | **Label** | **Value/Example** | **Type** | **Length** | **Applicable Year** | **Comments** |
| violence | Violence During Pregnancy | 0 = No<br>1= Yes<br>2 = Unknown<br>9 = Systems Missing | Numeric | 1 | 1992-2002<br>2006-2016 | |
| depress | Depression | 0 = No<br>1= Yes<br>2 = Unknown<br>9 = Systems Missing | Numeric | 1 | 1992-2002<br>2006-2016 | |
| isoimmun | Isoimmunization | 0 = No<br>1= Yes<br>2 = Unknown<br>9 = Systems Missing | Numeric | 1 | 1992-2002<br>2006-2016 | |
| gestdiab | Gestational Diabetes | 0 = No<br>1= Yes<br>2 = Unknown<br>9 = Systems Missing | Numeric | 1 | 1992-2002<br>2006-2016 | |
| hemmorr | Antepartum Hemorrhage | 0 = No<br>1= Yes<br>2 = Unknown<br>9 = Systems Missing | Numeric | 1 | 1992-2002<br>2006-2016 | |
| mr_other | Other Medical Risk Factor | 0 = No<br>1= Yes<br>2 = Unknown<br>9 = Systems Missing | Numeric | 1 | 1992-2002<br>2006-2016 | |
| mrficd1<br>mrficd2<br>mrficd3<br>mrficd4<br>mrficd5 | Medical Risk Factors (Other): ICD code(s) | ICD-10 Codes to identify risk factor | String | 8 | 1992-2002<br>2006-2016 | Mrficd4 and mrficd5 added in 2016 |
| mr_clari<br>(Office use only) | Medical Risk Factors (Other) CLARIFY | C = Clarification Required | String | 1 | Deleted after edit process. | |
| infect | Infectious Disease | 1=Yes<br>2=No<br>3=Unknown<br>9=System Missing | Numeric | 1 | 2002 | |
| tox_hyp | Toxaemia or Hypertension | 1=Yes<br>2=No<br>3=Unknown<br>9=System Missing | Numeric | 1 | 1992-2001 | |
| labour | Labour - YES / NO | 1 = Yes (spontaneous)<br>2 = No (induced)<br>3 = Unknown<br>9 = System Missing | Numeric | 1 | 1995-2016 | |
| spontan | Spontaneous Labour | 1=Yes<br>2=No<br>3=Unknown | Numeric | 1 | 1994-2016 | Derived from 'labour onset' |

| NLCHI LIVE BIRTH SYSTEM DATA DICTIONARY | | | | | | |
|---|---|---|---|---|---|---|
| **Variable Name** | **Label** | **Value/Example** | **Type** | **Length** | **Applicable Year** | **Comments** |
| | | 9=System Missing | | | | |
| augment | Labour Augmented After Onset | 1=Yes<br>2=No<br>3=Unknown<br>9=System Missing | Numeric | 1 | 2003-2007 | |
| induced | Induced Labour | 1=Yes<br>2=No<br>3=Unknown<br>9 = System Missing | Numeric | 1 | 1992-2016 | Derived from 'labour onset' |
| vbac | Vaginal Birth After C/Section Offered | 1=Yes | Numeric | 1 | 1994-2001 | |
| labcomp | Complications of Labour YES/NO | 1=Yes<br>2=No<br>9=System Missing | Numeric | 1 | 1992-2001 | |
| compicd1<br>compicd2<br>compicd3<br>compicd4 | Complications of Labour ICD | ICD Codes to identify complications of labour | String | 5 | 1992-2001 | |
| delpres | Delivery Presentation | 1 = Vertex<br>2 = Breech<br>3 = Other<br>4 = Unknown<br>9 = System Missing | Numeric | 1 | 1994-2016 | |
| dpresoth | Delivery Presentation Other (Specify) | Specify other type of delivery presentation | String | 30 | 1994-2005 | Text |
| dpresicd | Delivery Presentation (Other): ICD-10 | ICD code for "Other" type of delivery presentation | String | 6 | 2002-2016 | |
| dprescla<br><br>(Office use only) | Delivery Presentation 'Other" clarify | C = Clarification Required | | | | Variable deleted after edit process. |
| dmethod | Method of Delivery | 1= Vaginal Spontaneous<br>2= Vaginal Assisted<br>3= C/Section | Numeric | 1 | 1992-2016 | |
| csecicd1<br>csecicd2<br>csecicd3<br>csecicd4 | C / S Indications: ICD | ICD code to provide reason for C/Section | String | 6 | 1994-2016 | |
| dmethcla<br><br>(Office use only) | Delivery Method "Other" - Clarify | C = Clarification Required | | | | Variable deleted after edit process. |
| interven | Interventions During Delivery - NONE | 0=Yes<br>1=None<br>2=Unknown<br>9=System Missing | Numeric | 1 | 2002-2016 | |

| NLCHI LIVE BIRTH SYSTEM DATA DICTIONARY | | | | | | |
|---|---|---|---|---|---|---|
| **Variable Name** | **Label** | **Value/Example** | **Type** | **Length** | **Applicable Year** | **Comments** |
| lowforcp | Interventions - Low Forceps | 0=No<br>1=Yes<br>2=Unknown<br>9=System Missing | Numeric | 1 | 2002-2011 | |
| midforcp | Interventions - Mid Forceps | 0=No<br>1=Yes<br>2=Unknown<br>9=System Missing | Numeric | 1 | 2002-2011 | |
| vacuum | Interventions - Vacuum Extraction | 0=No<br>1=Yes<br>2=Unknown<br>9=System Missing | Numeric | 1 | 2002-2016 | |
| episiot | Interventions - Episiotomy | 0=No<br>1=Yes<br>2=Unknown<br>9=System Missing | Numeric | 1 | 2002-2016 | |
| medicat | Interventions - Medications | 0=No<br>1=Yes<br>2=Unknown<br>9=System Missing | Numeric | 1 | 2002-2009 | |
| ic_other | Other Interventions-Complications | 0=No<br>1=Yes<br>2=Unknown<br>9=System Missing | Numeric | 1 | 2008-2011 | In 2010, this field used for Other Interventions only. |
| icicd1<br>icicd2<br>icicd3<br>icicd4 | Complication (Other): ICD | ICD code to identify 'Other' Complication(s). | String | 6 | 2008-2016 | |
| comp | Complications of Delivery - NONE | 0=Yes<br>1=None<br>2=Unknown<br>9=System Missing | Numeric | 1 | 2010 - 2016 | |
| tear | Interventions - Tear | 0=No<br>1=Yes<br>2=Unknown<br>9=System Missing | Numeric | 1 | 2002-2016 | |
| teardeg | Tear (Specify degree) | 1=1st<br>2=2nd<br>9=System Missing<br>3=3rd<br>4=4th | Numeric | 1 | 2002<br>2006-2016 | 2010 onward, *only* 3rd & 4th degree tears were collected. |
| tearicd | Tear (Specify degree): ICD-10 | None | String | 6 | 2002 | |
| postpart | Post-partum Hemorrhage | 0=No<br>1=Yes<br>2=Unknown<br>9=System Missing | Numeric | 1 | 2010 - 2016 | |

| NLCHI LIVE BIRTH SYSTEM DATA DICTIONARY | | | | | | |
|---|---|---|---|---|---|---|
| **Variable Name** | **Label** | **Value/Example** | **Type** | **Length** | **Applicable Year** | **Comments** |
| comp_oth | Complication of Delivery-Other | 0=No<br>1=Yes<br>2=Unknown<br>9=System Missing | Numeric | 1 | 2010 - 2016 | |
| ic_clari<br><br>(Office Use Only) | Intervention – Complication 'Other' – clarify | C = Clarification Required | | | 2008-2016 | Variable deleted after edit process. |
| gestagew | Gestational Age Completed - Weeks | Value 01-43 | Numeric | 2 | 1992-2016 | |
| gestaged | Gestational Age Completed - Days | Value 1-6 | Numeric | 1 | 2002<br>2007-2016 | |
| gaconfrm | G/A confirmed by antenatal U/S? | 1=Yes<br>2=No | Numeric | 1 | 2002 | |
| gagew_us | Gestation Age - Weeks (based on U/S) | Value 01-43 | Numeric | 2 | 2003-2006 | |
| gaged_us | Gestation Age - Days (based on U/S) | Value 1-6 | Numeric | 1 | 2003-2006 | |
| gagew_lp | Gestation Age - Weeks (based on LMP) | Value 01-43 | Numeric | 2 | 2003-2006 | |
| gaged_lp | Gestation Age - Days (based on LMP) | Value 1-6 | Numeric | 1 | 2003-2006 | |
| gestbase | Gestational Age Based on US or LMP | 1=U/S<br>2=LMP<br>3=Unknown<br>9=System Missing | Numeric | 8 | 2002-2016 | |
| birthwgt | Birth Weight | Weight in Grams | Numeric | 4 | 1992-2016 | 9999 default value for missing birth weight(2017) |
| AGA | Appropriate size for Gestational Age | 0=No<br>1=Yes<br>2=Unknown<br>3=Not Applicable | Numeric | 8 | 1992-2016 | Derived from Gestational Age & Birth Weight |
| SGA | Small for Gestational Age | 0=No<br>1=Yes<br>2=Unknown<br>3=Not Applicable | Numeric | 8 | 1992-2016 | Derived from Gestational Age & Birth Weight |
| LGA | Large for Gestational Age | 0=No<br>1=Yes<br>2=Unknown<br>3=Not Applicable | Numeric | 8 | 1992-2016 | Derived from Gestational Age & Birth Weight |
| SFGA | Size for Gestational Age | 1 = Appropriate for GA<br>2 = Small For GA<br>3 =Large for GA<br>4 =Unknown<br>5 =Not Applicable | Numeric | 8 | 1992-2016 | Derived from Gestational Age & Birth Weight |

| NLCHI LIVE BIRTH SYSTEM DATA DICTIONARY | | | | | | |
|---|---|---|---|---|---|---|
| **Variable Name** | **Label** | **Value/Example** | **Type** | **Length** | **Applicable Year** | **Comments** |
| apgar1 | Apgar Score 1 | Vale 01-10 | Numeric | 2 | 1992-2016 | |
| apgar5 | Apgar Score 5 | Vale 01-10 | Numeric | 2 | 1992-2016 | |
| apgar10 | Apgar Score 10 | Vale 01-10 | Numeric | 2 | 1992-2001 | |
| apgar15 | Apgar Score 15 | Vale 01-10 | Numeric | 2 | 1992-2001 | |
| neocond | Neonatal Conditions / Birth Injuries noted at Birth | 1 = Yes<br>2 = No<br>9 = System Missing | Numeric | 1 | 1992-2001 | |
| neoicd1 | Neonatal Conditions-ICD | ICD code to identify condition | String | 4 | 1992-2001 | |
| neoicd2 | Neonatal Conditions: ICD | ICD code to identify condition | String | 4 | 1992-2001 | |
| anomaly | Congenital Anomalies - Yes/No | 1 = Yes<br>2 = No<br>3 = Unknown<br>9 = System Missing | Numeric | 1 | 1992-2002, 2008-2016 | |
| cephalus | Anencephalus | X= Yes | String | 1 | 1992-2001 | |
| spinabif | Spina Bifida | X= Yes | String | 1 | 1992-2001 | |
| hydrocef | Hydrocephalus | X= Yes | String | 1 | 1992-2001 | |
| cranio | Craniofacial | X= Yes | String | 1 | 1992-2001 | |
| fetalalc | Fetal Alcohol Syndrome | X= Yes | String | 1 | 1992-2001 | |
| fistula | T E Fistula | X= Yes | String | 1 | 1992-2001 | |
| hypospad | Hypospadis-Epispadias | X= Yes | String | 1 | 1992-2001 | |
| reducdef | Reduction Deformity | X= Yes | String | 1 | 1992-2001 | |
| atresia | Rectal/Anal Atresia/Stenosi | X= Yes | String | 1 | 1992-2001 | |
| omphal | Omphalocele-Gastroschisis | X= Yes | String | 1 | 1992-2001 | |
| chromo | Chromosomal Anomalies | X= Yes | String | 1 | 1992-2001 | |
| chromo1 | Chromosomal Anomalies ICD9 | ICD code to identify condition | String | 6 | 1992-2001 | |
| chromo2 | Chromosomal Anomalies ICD9 | ICD code to identify condition | String | 6 | 1992-2001 | |
| chromo3 | Chromosomal Anomalies ICD9 | ICD code to identify condition | String | 6 | 1992-2001 | |
| otherca | Other Congenital Anomalies | X= Yes | String | 1 | 1992-2001 | |
| anomicd1<br>anomicd2<br>anomicd3 | Other Congenital Anomalies ICD codes | ICD codes to identify conditions | String | 6 | 1992-2001 | |
| ntd | NTD (Neural Tube Defect) | 1=Yes<br>2=No<br>3=Unknown<br>4= Diagnosed Prenatally<br>5= Suspected at Birth | Numeric | 1 | 2002<br>2008-2016 | This was changed in 2013 to add variables 1, 2, and 3. |

| NLCHI LIVE BIRTH SYSTEM DATA DICTIONARY | | | | | | |
|---|---|---|---|---|---|---|
| **Variable Name** | **Label** | **Value/Example** | **Type** | **Length** | **Applicable Year** | **Comments** |
| heart | Congenital Heart Defect | 1=Yes<br>2=No<br>3=Unknown<br>4= Diagnosed Prenatally<br>5= Suspected at Birth | Numeric | 1 | 2002<br>2008-2016 | This was changed in 2013 to add variables 1, 2, and 3. |
| hearticd | Congenital Heart Defect - ICD-10 | ICD code to identify condition | String | 6 | 2002 | |
| heart_sp | Congenital Heart Defect (Specify) | Specify condition | String | 40 | 2008-2009 | |
| cran | Craniofacial | 1=Yes<br>2=No<br>3=Unknown<br>4= Diagnosed Prenatally<br>5= Suspected at Birth | Numeric | 1 | 2002<br>2008-2016 | This was changed in 2013 to add variables 1, 2, and 3. |
| cranicd | Craniofacial - ICD-10 | ICD code to identify condition | String | 6 | 2002 | |
| cran_sp | Craniofacial (Specify) | Specify condition | String | 40 | 2008-2009 | |
| gi | Gastrointestinal | 1=Yes<br>2=No<br>3=Unknown<br>4= Diagnosed Prenatally<br>5= Suspected at Birth | Numeric | 1 | 2002<br>2008-2016 | This was changed in 2013 to add variables 1, 2, and 3. |
| giicd | Gastrointestinal - ICD-10 | ICD code to identify condition | String | 6 | 2002 | |
| gi_sp | Gastrointestinal (Specify) | Specify condition | String | 40 | 2008-2009 | |
| msk | Musculoskeletal | 1=Yes<br>2=No<br>3=Unknown<br>4= Diagnosed Prenatally<br>5= Suspected at Birth | Numeric | 1 | 2002<br>2008-2016 | This was changed in 2013 to add variables 1, 2, and 3. |
| mskicd | Musculoskeletal - ICD-10 | ICD code to identify condition | String | 6 | 2002 | |
| msk_sp | Musculoskeletal (Specify) | Specify condition | String | 40 | 2008-2009 | |
| gu | Genitourinary | 1=Yes<br>2=No<br>3=Unknown<br>4= Diagnosed Prenatally<br>5= Suspected at Birth | Numeric | 1 | 2002<br>2008-2016 | This was changed in 2013 to add variables 1, 2, and 3. |
| guicd | Genitourinary - ICD-10 | ICD code to identify condition | String | 6 | 2002 | |

| NLCHI LIVE BIRTH SYSTEM DATA DICTIONARY | | | | | | |
|---|---|---|---|---|---|---|
| **Variable Name** | **Label** | **Value/Example** | **Type** | **Length** | **Applicable Year** | **Comments** |
| gu_sp | Genitourinary (Specify) | Specify condition | String | 40 | 2008-2009 | |
| chrom | Chromosomal | 1=Yes<br>2=No<br>3=Unknown<br>4= Diagnosed Prenatally<br>5= Suspected at Birth | Numeric | 1 | 2002<br>2008-2016 | This was changed in 2013 to add variables 1, 2, and 3. |
| chromicd | Chromosomal - ICD-10 | ICD code to identify condition | String | 6 | 2002 | |
| chrom_sp | Chromosomal (Specify) | Specify condition | String | 40 | 2008-2009 | |
| othcong | Other Congenital Anomalies | 1= Diagnosed Prenatally<br>2= Suspected at Birth | Numeric | 1 | 2002 | |
| othicd1 | Other Congenital Anomalies ICD-10 | ICD code to identify condition | String | 6 | 2002 | |
| othicd2 | Other Congenital Anomalies ICD-10 | ICD code to identify condition | String | 6 | 2002 | |
| othicd3 | Other Congenital Anomalies ICD-10 | ICD code to identify condition | String | 6 | 2002 | |
| othicd4 | Other Congenital Anomalies ICD-10 | ICD code to identify condition | String | 6 | 2002 | |
| anomocon1<br>anomocon2<br>anomocon3 | Other Congenital Anomaly Confirmed (Specify) | ICD codes to identify conditions | String | 40 | 2008 | |
| provider | Delivered By (Provider Code) | Physician's provider number | String | 6 | 1992-2002 | |
| attend | Designation of Attendant | 1= Medical Doctor<br>2= Nurse<br>3= Midwife<br>4= Unknown<br>5= Other<br>9= System Missing | Numeric | 1 | 2002-2016 | |
| attendot | Designation of Attendant Other (Specify) | Completed if "Other" selected for Designation of Attendant | String | 20 | 2008-2016 | |
| forceps | Interventions – Forceps | 0=No<br>1=Yes<br>2=Unknown<br>9=System Missing | Numeric | 1 | 2016 | New field for 2012 to replace mid and low forceps |
| comments | Comments | Comments/Clarifications by HRA or DBA | String | 40 | 1994<br>1997-2000<br>2011-2016 | Free text |
| m_mcp | Mother's MCP Number | Mother's Health Care Number, for NL residents it is a 12-digit MCP number | Numeric | 12 | 1997-2016 | This variable is kept in Master File, but no longer appears in Longitudinal File. |

| NLCHI LIVE BIRTH SYSTEM DATA DICTIONARY | | | | | | |
|---|---|---|---|---|---|---|
| **Variable Name** | **Label** | **Value/Example** | **Type** | **Length** | **Applicable Year** | **Comments** |
| m_mcp2 | Mother's corrected MCP Number | Mother's Health Care Number if corrected or revised | Numeric | 12 | 1999-2001 | If at time of delivery or if a revised MCP number was issued since delivery. |
| m_dob | Date of Birth | Mother's Date of Birth MM/DD/YYYY | Date | 10 | 1992-2016 | This variable is kept in Master File, but no longer appears in Longitudinal File. |
| m_age | Mother's Age | Age of Mother at time of delivery | Numeric | 8 | 1992-2016 | In 2010: auto-calculated on data entry. |
| m_age2 | Mother's age (+1 decimal place) | Mother's age to 1 decimal | Numeric | 8 +1 decimal | 1992-2016 | |
| ntdicd | NTD - ICD-10 | ICD code to identify condition | String | 6 | 2002 | |
| ntd_sp | NTD (Specify) | Specify condition | String | 40 | 2008-2009 | |
| medinjury | Was death due to maternal injury | 1 = Yes<br>2 = No<br>9 = System Missing | Numeric | 2 | 2016 | |

## Appendix D: Human Investigation Committee approval letter

MEMORIAL UNIVERSITY

Faculty of Medicine

Human Investigation Committee
Suite 200, Bonaventure Place
95 Bonaventure Avenue
St. John's, NL Canada A1B 2X5
Tel: 709 777 6974 Fax: 709 777 8776
hic@mun.ca www.med.mun.ca/hic

August 25, 2009

**Reference #09.154**

Dr. Leigh Anne Newhook
Pediatrics
Faculty of Medicine
Janeway Child Heath Centre

Dear Dr. Newhook:

RE: "Maternal and neonatal risk factors for type 1 diabetes mellitus among children aged 0 to 15 years in Newfoundland and Labrador: A case control study"

Your application received an expedited review by a Sub-Committee of the Human Investigation Committee and **full approval** was granted effective August 24, 2009.

This approval will lapse on **August 24, 2010**. It is your responsibility to ensure that the Ethics Renewal form is forwarded to the HIC office prior to the renewal date. *The information provided in this form must be **current to the time of submission** and submitted to the HIC **not less than 30 nor more than 45 days** of the anniversary of your approval date.* The Ethics Renewal form can be downloaded from the HIC website http://www.med.mun.ca/hic/downloads/Annual%20Update%20Form.doc

*The Human Investigation Committee advises THAT IF YOU DO NOT return the completed Ethics Renewal form prior to date of renewal:*

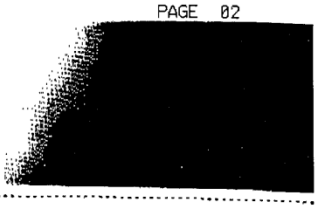
- *Your ethics approval will lapse*
- *You will be required to stop research activity immediately*
- *You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again*

*Lapse in ethics approval may result in interruption or termination of funding*

For a hospital-based study, it is **your responsibility to seek the necessary approval from Eastern Health and/or other hospital boards as appropriate.**

**Modifications of the protocol/consent are not permitted without prior approval from the Human Investigation Committee. Implementing changes in the protocol/consent without HIC approval may result in the approval of your research study being revoked, necessitating cessation of all related**

## Appendix E: Secondary Uses Committee of the Centre for Health Information approval letter



Centre for Health Information
Newfoundland & Labrador

70 O'Leary Avenue, St. John's, NL A1B 2C7
Telephone: 709-752-6000 • Facsimile: 709-752-6011

Registry Integrity Unit, 41 Conception Bay Highway
E. K Jerrett & Associate Building, Bay Roberts NL A0A 1G0
Telephone: 866-279-1198 • Facsimile: 709-786-5337

July 20, 2009

Dr. Leigh Ann Newhook, MD, MSc, FRCPC
Faculty of Medicine
Memorial University
300 Prince Phillip Drive
St. John's Nl A1B 3V6

Dear Dr. Newhook:

This is to advise you that the Secondary Uses Committee of the Centre for Health Information reviewed and conditionally approved your application on June 29th for access to data for the study **Maternal and neonatal risk factors for type 1 diabetes mellitus among children aged 0 to 15 years in Newfoundland and Labrador: A case-control study.**, which will link data from the Newfoundland and Labrador Diabetes Database maintained by the Janeway Pediatric Diabetes Team and the Live Birth System maintained by the Centre.

The use of the Live Birth System is conditional upon:

- Approval from the Human Investigation Committee of Memorial University
- You and the Centre will enter into an Information Management Agreement that specifies the conditions under which the Centre will maintain the database for the Janeway Pediatric Diabetes Team
- The Centre is provided with copies of all relevant signed consent forms, and
- Another employee of the Centre who is not a member of the project team links and de-identifies the dataset of record specific information

While not a condition of approval, the Centre recommends that because the Janeway Pediatric Diabetes Team used a broad consent to authorize this research, that they make available to the public either through a website or other general means of notification the research activities associated with the NLDD.

When you have received approval from the Human Investigations Committee please forward me a copy of their letter to you.

Yours sincerely

Lucy McDonald.

Lucy McDonald
Chief Privacy Officer/Corporate Secretary

Cc Kayla Collins