

**Early-life Factors Associated with the Development of Youth Onset Type 2 Diabetes
Mellitus in Manitoba: A Retrospective Case Control Study**

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PRENATAL, OBSTETRICAL AND PERINATAL FACTORS ASSOCIATED WITH THE DEVELOPMENT OF YOUTH ONSET T2DM

Abstract

The purpose of this study was to explore associations between demographic variables and factors indicative of the intrauterine environment of a mother to the subsequent development of youth onset type 2 diabetes mellitus (T2DM). Until 1990, T2DM was seldom reported in youth, with the first pediatric case of T2DM in Canada reported in 1984. Unprecedented, the incidence of T2DM in youth exceeded that of newly diagnosed type 1 diabetes mellitus (T1DM) in Manitoba in 2011. Orem's Theory of Self-care and the Social Ecological Theory provided the guiding frameworks that directed the examination of a wide range of factors associated with youth onset T2DM.

This case-control study utilized repository data housed at the Manitoba Centre for Health Policy to facilitate a retrospective secondary data analysis to review the perinatal exposures of Manitoba youth with and without T2DM. De-identified health records were examined from a sample comprised of 270 youth (aged 10 – 17 years at the time of diagnosis) with T2DM and 1341 youth without T2DM, for a total number of cases of 1611 along with their de-identified biological mothers' health records. The mean age at time of diagnosis was 13.1 years and over 61% of youth onset T2DM cases are females. The majority (71.1%) of youth with T2DM resided in rural areas at time of diagnosis.

Univariate descriptions of associations were obtained and multiple conditional regression analysis were conducted to identify key factors associated with the development of T2DM in youth.

This study found a 14-fold increase in the risk of youth onset T2DM when the mother had pre-gestational diabetes, and 6.5-fold increase in that risk if the offspring's mother had gestational diabetes mellitus. Breastfeeding was found to be protective when compared with formula feeding, (OR=0.5175, 95% CI 0.3641-0.7354, $p=0.0002$). The effect of size for gestational age was determined to have a significant association on the development of youth onset T2DM ($p=0.0037$), with the largest association found in youth who were born in the “preterm-large for GA” category. A lower income quintile at time of birth was found to be more significantly associated with the development of youth onset T2DM than increasingly higher income quintiles ($p= <0.0001$).

The findings of this study emphasize that efforts aimed at preventing a pandemic of T2DM in the youth of our country must begin in the pre-conception period. Efforts need to continue throughout pregnancy and early life of the offspring if we are to re-route the current path of increasing rates of youth onset T2DM around the globe. The results of this study indicate that public awareness campaigns and targeted health care interventions are urgently needed to educate women with T2DM in the childbearing years about the importance of breastfeeding in the immediate postpartum period.

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Chapter 1: Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder of glucose homeostasis characterised by hyperglycemia and altered lipid metabolism caused by varying degrees of insulin resistance in the context of an inability to compensate with increased insulin secretion (Nolan, Damm & Prentki, 2011). T2DM has a heterogeneous etiology with social, behavioural and environmental risk factors exposing the effects of genetic susceptibility (Reinehr, 2013). With increasing global prevalence, the burden of T2DM is far reaching with its impact on both short and long term health, as well as the huge direct and indirect costs to society. It is estimated that by 2016, direct health care costs associated with diabetes in Canada will exceed \$8 billion annually (Ohinmaa, Jacobs, Simpson & Johnson, 2004).

Youth onset T2DM was first described in First Nations children in Canada in the 1980s (Dean & Moffat, 1988), and has since been reported in children around the world including the United States of America, Australia, Japan, India, and the United Kingdom (Kitagawa, Owada, Urakami & Yamauchi, 1998). Youth onset T2DM is a complex condition defined by hyperglycemia and is compounded by the numerous elements including obesity, insulin resistance, adolescence, poverty, and family beliefs or myths (Dean & Sellers, 2007).

This chapter will introduce the epidemiology of youth onset T2DM, as well as examine the incidence and prevalence of this disease. The differences between T2DM, gestational diabetes and type 1 diabetes will be addressed. In addition, the risk factors associated with youth onset T2DM will be reviewed. This backdrop will foreground the statement of the research problem. The chapter concludes with a statement of the research problem, the study's purpose and objectives.

Epidemiology of Youth Onset Type 2 Diabetes Mellitus

Worldwide, T2DM is increasing in epidemic proportions (Fetita, Sobngwi, Seradas, Calvo & Gautier, 2006). In the year 2000, the global prevalence of diabetes mellitus was estimated at 2.8%, translating into 171 million individuals, while the projected prevalence for the year 2030 is 4.4%, translating into 366 million individuals living with diabetes worldwide (McIntyre, Thoma, Wong, Idris & Callaway, 2009). It is the predominant form of diabetes and accounts for 90% of all cases of diabetes.

Until 1990, T2DM was seldom reported in children or adolescents (Nolan et al., 2011). In Canada, the first pediatric case of T2DM was reported in 1984 (Dean, Mundy & Moffat, 1992). In the early 1990s, T2DM accounted for approximately 2-3% of cases of newly diagnosed diabetes in children and adolescents (Karabouta, Barnett, Shield, Ryan & Crowne, 2008); however, T2DM is no longer a disease primarily of adulthood. It now represents up to 45% of all newly diagnosed diabetes in children (Pinhas-Hamiel & Zeitler, 2007). In some areas of the world, the incidence of T2DM exceeds that of type 1 diabetes mellitus (T1DM) in youth. In Taiwan, for example, where youth onset T2DM was once unheard of – the results of a nationwide screening program showed that T2DM has replaced T1DM as the leading cause of diabetes mellitus in children with incident rates of 6.5 per 100,000 (Wei et al., 2003). In Manitoba, Canada the annual incidence of youth onset T2DM increased dramatically from 9.03 to 20.55 per 100,000 youth/year between the years of 2006 to 2011 (Sellers, Wicklow & Dean, 2012). In 2011, the incidence of new cases of T2DM in youth in Manitoba exceeded that of T1DM (71 versus 55 new cases respectively) for the first time (Sellers, Wicklow & Dean, 2012).

The increasing rate of youth onset T2DM is a major health concern. In addition, the early age of onset will result in increasing numbers of pregnant women who have T2DM pre-dating

their pregnancies (Nolan et al., 2011). This has resulted in increasing numbers of pregnancies complicated by pre-gestational diabetes. For the purpose of this thesis, youth onset T2DM will be defined as those cases of T2DM diagnosed in individuals prior to the age of 18 years.

For the purpose of this thesis, Indigenous Peoples of Canada are commonly referred to as Aboriginal. In 1996, the Royal Commission of Aboriginal Peoples defined Aboriginal to encompass all individuals with First Nation (registered and non-registered Indians), Metis, and Inuit ancestry. I acknowledge that the terminology and language are influenced by the historical and sociopolitical context. Indigenous is a term used to refer to individuals officially recorded as the first inhabitants of an area or country prior to colonization and/or invasion (Dakubo, 2010). Although there is no accepted definition of Indigenous, common elements of indigeneity include: self-identification and acceptance as such by their community, historical continuity and land occupation before invasion and colonization, strong links to natural resources, land and water along with a distinct language, culture, religion, ceremonies and beliefs (Gracey & King, 2009). While it is more respectful to refer to Indigenous Peoples by the name of their Tribe, in this thesis the term used by authors is included. In addition, it is commonly understood that there is more diversity within a culture than between cultures.

Pathophysiology: Type 1 Diabetes, Type 2 Diabetes, and Gestational Diabetes

Type 1 diabetes mellitus. Despite similarities in nomenclature, T1DM and T2DM differ significantly in underlying pathophysiology. Type 1 diabetes mellitus (T1DM), once termed “juvenile diabetes”, tends to be diagnosed in early life and results from the autoimmune destruction of the insulin producing beta cells of the pancreas. Left with the inability to produce insulin, the person with T1DM is required to take exogenous insulin for survival (Cnop et al., 2005).

Type 2 diabetes mellitus. Type 2 diabetes mellitus (T2DM) is defined as diabetes resulting from insulin resistance with a concomitant insulin secretory defect, and in the past, was typically diagnosed within the adult years (Nadeau & Dabelea, 2008). Although T2DM has traditionally been viewed as an adult disease, it is now being diagnosed in children and adolescents in all parts of the world (Nadeau & Dabelea, 2008). Management strategies in this disease are aimed at decreasing insulin resistance and/or increasing insulin secretory capacity and range from lifestyle therapy including diet and exercise, to oral medications and/or insulin therapy. Risk factors for the development of T2DM include poverty, obesity, sedentary lifestyle, family history of diabetes and belonging to an ethnic minority or a marginalized racial group – particularly First Nations Peoples in Canada, American Indians, Alaskan Natives, Indo-Asians and African-Americans (Adelson, 2005; Fagot-Campagna et al., 2000; Nadeau & Dabelea, 2008). In addition to the aforementioned risk factors, exposure to pre-gestational diabetes in utero is a significant risk factor for the development of youth onset T2DM (Dabelea et al., 2008; Pettitt et al., 2008; Young et al., 2002).

Puberty is said to play a major role in the development of T2DM in children, with mid-puberty age group (i.e. age 13) commonly being reported as the mean age for diagnosis (Reinehr, 2013; Sellers, Wicklow & Dean, 2012). The time of puberty has been described as the ‘perfect storm’ whereby there is increased insulin resistance as a result of increased growth hormone secretion, which results in hyperinsulinemia (Reinehr, 2013). Add to that puberty ‘mix’ a degree of obesity and family history of diabetes, perhaps compounded by rapid weight gain in the pubertal youth – and indeed the ‘perfect storm’ for insulin resistance and/or youth onset T2DM is created.

Gestational diabetes mellitus. Gestational diabetes mellitus (GDM) is defined as glucose intolerance with its onset or first recognition occurring during pregnancy (Metzger et al., 2008). It is estimated to affect approximately 3.5% of all pregnancies worldwide (Anna, Vander Ploeg, Cheung, Huxley & Bauman, 2008), with higher rates noted in Aboriginal populations. A Manitoba study found that GDM was detected in 2.9% of pregnancies between the years 1985 and 2004, which was 2.3% in 1985-1989 and 37% in 1999-2004 (Aljohani et al., 2008a). In this condition, women remain normoglycemic when not pregnant, however, with the increased insulin resistance of pregnancy, they develop abnormal glucose metabolism. Management within pregnancy varies and depends on the degree of hyperglycemia, ranging from diet and exercise to multiple dose insulin therapy. If abnormal glucose tolerance persists beyond pregnancy, then the diagnosis of T2DM is established.

Pregnancy itself is a 'diabetogenic' state (Plagemann, 2011). This diabetogenic state stems from the metabolic adaptations established by the mother in an effort to ensure optimal fetal food supply – a physiological state of insulin resistance thereby is created (Plagemann). Women with risk factors for the development of T2DM (i.e. obesity, family history, sedentary lifestyle), may not have the insulin secretory capacity to overcome the additional insulin resistance of pregnancy and may thus develop GDM. GDM itself is a risk factor for the subsequent development of T2DM (Osgood, Dyck & Grassman, 2011).

The diagnostic criteria for GDM is controversial. The Hyperglycemia and Adverse Pregnancy Outcomes Study (HAPO) provided empirical evidence about perinatal outcomes and demonstrated that hyperglycemia in pregnancy was associated with adverse pregnancy outcomes (Metzger et al., 2008). The International Association of Diabetes in Pregnancy Study Group (IADPSG) set forth recommendations that include universal screening of all pregnant women at

24-28 weeks gestation with a 2-hour (fasting) oral glucose tolerance test (OGTT); if any one of the values obtained in that test exceed recommended thresholds then a diagnosis of GDM is made (Metzger et al., 2010). The IADPSG also recommended lower diagnostic values than previously accepted (Hardar & Yogev, 2013). The glucose thresholds set forth by the IADPSG are as follows: Fasting plasma glucose ≤ 5.1 mmol/L, 1 hour after 75g OGTT ≤ 10.0 mmol/L, and 2 hour after 75g OGTT ≤ 8.5 mmol/L (Metzger et al., 2010).

The debate within the obstetrical and diabetes community lay not in whether or not women should be screened for GDM, but rather at what threshold and with which screening test. The 2 hour fasting 75g OGTT is both costly and timely; it requires fasting, a potentially uncomfortable state for pregnant women. Additional resource issues are presented with lower diagnostic criteria as likely more women would be diagnosed with GDM, creating increased need for high risk obstetrical care and follow-up (i.e. additional fetal assessments, monitoring in labour) – all of these increased costs continue to be debated as there is no current evidence that the identification and treatment of women based on the IADPSG criteria would lead to clinically significant improvements in maternal and/or neonatal health, though would significantly increase health care costs (Hadar & Yogev, 2013).

The Canadian Diabetes Association has not adapted the criteria recommended by the IADSPG; rather, they recommend two choices in their latest edition of Clinical Practice Guidelines (Thompson et al., 2013). The “preferred approach” is to begin with a 50g glucose challenge test (GCT), and if abnormal proceed with a 75g OGTT. The diagnosis of GDM is made if one or more values are abnormal (Fasting ≥ 5.3 , 1 hour ≥ 10.6 , or 2 hour ≥ 9.0 mmol/L) (Thompson et al.).

The “alternate approach” is the one step 75g OGTT with diagnosis of GDM made if one or more value exceeds recommended thresholds (Fasting ≥ 5.1 , 1 hour ≥ 10.0 , and 2 hour ≥ 8.5 mmol/L (Thompson et al., 2013). The authors of those recommendations acknowledge that GDM, if untreated, leads to increased maternal and perinatal morbidity, while treatment is associated with outcomes similar to control populations.

Both GDM and T2DM are associated with significant adverse outcomes - not only for the mother, but also for the fetus, neonate, child, and adult offspring of the diabetic mother (Hadar & Yogev, 2013). Examples of adverse maternal outcomes include an increased rate of caesarean and operative deliveries, polyhydramnios, preeclampsia and an increased risk of future T2DM for the mother with GDM. Fetal and neonatal consequences include shoulder dystocia, pre-term delivery, macrosomia, birth trauma and congenital malformations (i.e. cleft lip) (Harder & Yogev).

Maternal GDM and maternal T2DM have been shown to significantly increase the risk of obesity and contribute to the development of GDM and/or T2DM in both childhood and adulthood in the offspring (Dabelea et al., 2000; Dabelea, 2007; Hadar & Yogev, 2013; Metzger et al., 2008; Wroblewska-Seniuk, Wender-Ozegowska & Szczapa, 2009). The highest prevalence of T2DM in a cohort of offspring born to mothers with youth onset T2DM was reported as 25% of all offspring (7/28), and more specifically the rate of 43% of offspring (6/14) when the age range was kept to those offspring of 10-19 years (Mendelson et al., 2011).

Incidence and Prevalence of Youth Onset T2DM

The incidence of T2DM in children, though variable around the globe, has increased dramatically in recent years (Wei et al., 2003). Prevalence rates ranging from 0.4 per 1000 in

Israeli youth at age 17 years, to rates as high as 50.9 per 1000 in the Pima Indians aged 15-19 years have been reported (Nadeau & Dabelea, 2008). The SEARCH for Diabetes in Youth is an observational, multicenter study conducting population-based ascertainment of diabetes in youth with onset at prior to 20 years of age. These researchers reported a prevalence rate of 2.22/1000 in their study population with an increase from rates originally published by this group in 2001 and 2009 (Pettitt et al., 2014). Further details of the SEARCH for Diabetes study will be offered in Chapter 2 of this paper.

A recently published Canadian surveillance program estimated that the minimum incidence of T2DM in Canada is 1.54 cases per 100,000 youth under age 18 years, with the highest incidence reported in the province of Manitoba at 12.35 per 100,000 (Amed et al., 2010). Significant regional variation in the incidence of youth onset T2DM was noted in this study, with incidence rates ranging from 0.4 to 12.45 cases per 100,000. A more recent publication describing the youth onset T2DM population in Manitoba reported incident rates as high as 20.55 per 100,000 youth in 2011 (Sellers, Wicklow & Dean, 2012). In 2011, the number of newly diagnosed youth onset T2DM outnumbered cases of newly diagnosed T1DM for the first time ever in Manitoba (Sellers, Wicklow & Dean, 2012).

The differentiation of T1DM versus T2DM in youth is not always easily assessed at diagnosis for the two diseases are not completely distinct (Reinehr, 2013). Those youth presenting in diabetic ketoacidosis and/or requiring insulin at presentation, may be initially classified as having T1DM and subsequently re-classified as T2DM. Similarly, youth having lost weight due to hyperglycemia may not be overweight and therefore more likely to be classified as T1DM at diagnosis. As well, youth having T1DM may present as overweight at diagnosis (Reinehr, 2013). However, with heightened awareness and more robust literature available which

documents increased incidence of youth onset T2DM, it is more likely that increased surveillance efforts and a greater tendency to classify the disorder accurately as T2DM may contribute to reported rises in incidence (Nadeau & Dabelea, 2008).

Risk Factors for Development of Youth Onset T2DM

Multiple risk factors for the development of youth onset T2DM have been identified. These include membership in particular groups (e.g. people of , Hispanic, South Asian, Asian or African descent), family history of diabetes, obesity, exposure to T2DM in utero, impaired glucose tolerance, evidence of insulin resistance, hypertension, polycystic ovarian syndrome (PCOS), acanthosis nigricans, non-alcoholic fatty liver disease (NAFLD), dyslipidemia, and the use of atypical antipsychotic medications (Panagiotopoulos, Riddell & Sellers, 2013). While only some of the above risk factors are modifiable for the youth themselves, numerous intervention trials and diabetes prevention efforts have been designed to target lifestyle modification and behaviour change aimed at minimizing those modifiable risk factors. Many of these programs were aimed at targeting prevention and/or glycemic control at the family history stage.

In contrast to the majority of empirical evidence, the SEARCH for Diabetes study found that T2DM occurred in youth from all racial and ethnic groups (Pettitt et al., 2014) and therefore was not race specific. Canadian data gathered in a national surveillance study concluded that ethnic minorities were indeed overrepresented, but 25% of children with T2DM were Caucasian (Amed et al., 2010). In a recent Manitoba study which included youth from Northwestern Ontario and Manitoba who were all followed in the same Pediatric Diabetes clinic, 87.7% of children with T2DM were of self-declared First Nations heritage (Sellers, Wicklow & Dean, 2012).

The role of genetics in T2DM, specific to maternal inheritance in T2DM, was first suggested by epidemiologists, whereby adults with T2DM had a higher prevalence of T2DM on the maternal side in comparison with the paternal side (Fetita et al., 2006). There is growing acceptance of the concept that even a mild alteration in the intrauterine environment can influence the infant's health prospects not only in the perinatal period but over the entire life course (Gluckman, Hanson, Cooper & Thornburg, 2008). "Fetal programming" is the term used to describe the process that occurs in utero which influences long-term fetal outcomes (Yajnik, 2010). Numerous articles, which will be reviewed in Chapter 2, have discussed the effect of fetal exposure to maternal diabetes and their conclusions range from the causal factor being either the genetic effect, the environmental effect or a combination. Though the exact pathophysiology continues to be explored, there is consensus that intrauterine exposures to maternal diabetes and obesity are strongly associated with T2DM in youth (Dabelea, et al., 2008).

Statement of the Research Problem: A Significant Burden of Illness

As a relatively new phenomenon, the body of research pertaining to the burden of illness and the natural history of youth onset T2DM is in its infancy. Recently, numerous reports have emerged that indicate that T2DM in children and adolescents is a serious concern because of the increased duration of the disease, microvascular and macrovascular complications (Young et al., 2002), and the potential for future offspring to be exposed to diabetes in utero – a vicious cycle perpetuating the risks of subsequent T2DM in those offspring (Dabelea, 2007). Complications may occur at earlier ages for this population with a shorter duration of diabetes than those with type 1 diabetes, and may be more aggressive than in adult onset T2DM (Dart et al., 2012; Dart et al., 2014; Karabouta et al., 2008; Pinhas-Hamiel & Zeitler, 2007;).

In particular, one burden of T2DM is associated with microvascular complications including nephropathy, retinopathy and neuropathy. Furthermore, macro vascular complications include cardiovascular, cerebrovascular and peripheral vascular disease (Pinhas-Hamiel & Zeitler, 2007). Two review articles examined both acute and long-term comorbidities and presented convincing evidence that those with youth onset T2DM could be at an increased risk of early development of complications (Dean & Sellers, 2007; Pinhas-Hamiel & Zeitler, 2007). Acute complications of T2DM include diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar state, and malignant hyperthermia-like syndrome with rhabdomyolysis (Pinhas-Hamiel & Zeitler, 2007).

Renal disease is the most frequently described chronic complication of youth onset T2DM (Dart et al., 2014). Concerning rates of renal complications in the form of microalbuminuria (26.9% of youth) and macroalbuminuria (4.7% of youth) have been documented (Dart et al, 2012), with microalbuminuria frequently noted as being present at diagnosis (Pinhas-Hamiel & Zeitler, 2007). Additionally, Dart et al. (2012) found that youth with T2DM were four times more likely to develop end stage renal disease than their counterparts with T1DM for the same duration of disease (2012).

Commonly reported chronic comorbidities of youth onset T2DM include hypertension, dyslipidemia, non-alcoholic fatty liver disease, and obesity. In a study exploring treatment options for T2DM in adolescents and youth -the TODAY study, 14% of adolescents with T2DM were found to have hypertension, 80% had low HDL concentrations and 10% had hypertriglyceridemia (Copeland et al., 2011). The Canadian Pediatric Surveillance Program found that 37% of children with T2DM had at least one comorbidity at diagnosis, and 13% had three or more co-morbidities at diagnosis (Amed et al., 2010). As the body of evidence grows,

health care providers are encouraged to more effectively document the natural history of youth onset T2DM with its comorbidities and complications. Therefore, it will be imperative to conduct intervention trials aimed at lessening comorbidities and preventing youth onset T2DM.

While primary intervention trials, lifestyle modification trials and pharmacologic treatment interventions have been attempted, the precipitously increasing incidence of T2DM in youth demands prompt attention by all interested and affected parties and policy makers. Despite public health interventions at all levels – including at the community, provincial and national jurisdictions, prevention efforts have not been successful and incidence rates continue to escalate (Sellers, Wicklow & Dean, 2012). With further evidence and knowledge about the increased risk of rapid progression to complications of T2DM in youth grows, it is imperative that efforts are continued and intensified to attempt to lessen the incidence of youth onset T2DM and its complications.

Research Objectives and Significance

Optimal prevention of youth onset T2DM requires identification of the early-life modifiable risk factors (Franks et al., 2006). As stated by Young et al. (2002), the strongest known risk factor for T2DM in children is maternal diabetes. This study explored associations between demographic variables and factors that reflected the intrauterine environment of a mother, with the subsequent development of T2DM in the mother's offspring. Unless prevention and intervention efforts are successful, it can be anticipated that the burden of T2DM and its complications will continue to affect many more individuals and their families, the result of which will convey enormous human and financial costs to society (Reinehr, 2013). The research

question for this thesis is - What are the early-life factors that are associated with the development of youth onset type 2 diabetes?

The significance of this research was rooted in its determination of demographic variables and perinatal factors associated with T2DM in youth. The study is important because it adds to the knowledge about the effect poverty, geographic location, the intrauterine environment of mothers with pre-gestational diabetes, and any amount of breastfeeding on youth onset T2DM. Based upon this information, interventions and/or primary prevention initiatives may be developed, implemented, and evaluated to prevent T2DM in children and ultimately improve health in this population for current and future generations.

Chapter 2: Review of the Literature

The incidence of T2DM in children, though variable around the globe, has increased dramatically in recent years (Wei et al., 2003). Research exploring the cause of this sudden rise in T2DM in youth has pointed to a variety of complex influences including rapid environmental and behavioural changes, possible genetic contributors and more recently, the role of diabetic pregnancies and their effect on fetal programming (Osgood, Dyck & Grassman, 2011). Among factors predisposing a child to youth onset T2DM, the health and behavior of the mother has been said to be critical (Bartz & Freemark, 2012). An association between intrauterine exposure to maternal diabetes and T2DM in youth has been described; however, few studies have examined specific factors of pregnancy to focus on the root cause of this reported association. The goal of this study was to explore associations between demographic variables and perinatal factors to the subsequent development of youth onset T2DM.

This chapter will summarize the current literature in relation to those factors which are most commonly reported as being associated with the development of youth onset T2DM. In this chapter, a review of literature will be provided to ground this study, enhance understanding of the topic presented and its' associated issues, and argue for the need for this study. Special emphasis will be afforded to examining the body of literature that focuses on the association of youth onset T2DM with intrauterine exposures, including maternal diabetes and each of the potential pregnancy factors that may or may not be associated with the development of childhood T2DM in children of women with T2DM pre-dating their pregnancy. In addition, evidence about the prevalence of this disease will be examined.

Given the focus of this study, this chapter is divided into two sections. The first section examines the literature describing factors associated with the development of T2DM, including

those related to the intrauterine environment as well as those that are not – such as genetic predisposition, ethnicity and early feeding patterns. The second section of this chapter will draw attention to two theoretical frameworks that have been chosen to support this study, namely Orem's Theory of Self-care and the Social Ecological Theory. This chapter closes with a summary of the information reviewed, a discussion identifying knowledge gaps within the current body of research and then discusses the potential contributions of this study in filling those identified knowledge gaps.

Race and Ethnicity

Race and ethnicity have been recognized as important factors in the development of T2DM in adults and according to Nadeau and Dabelea (2008), the influence of race and ethnicity appears to be even stronger for youth-onset T2DM. The vast majority of cases of youth onset T2DM are of non-European backgrounds; for example, T2DM is prevalent among Asians, Hispanics and African-Americans (Acton et al., 2002; Fagot-Campagna et al., 2000; Scott, Smith, Cradock & Pihoker, 1997). Moreover, disturbingly high prevalence rates have been reported in Indigenous people of Canada, Australia, New Zealand and the United States of America, as well as being seen in Asians, Hispanics and African-Americans (Acton et al.; Fagot-Campagna et al.; Scott, Smith, Cradock & Pihoker). In particular, high rates of both youth and adult onset T2DM among the Pima Indians of the United States of America are described in numerous population-based reports (Nadeau & Dabelea, 2008). Several key studies conducted within the Pima Indians will be reviewed in this chapter, with emphasis on individual factors contributing to the onset of T2DM.

In a recent Canadian study, the majority of children (87.7%) with T2DM were reported as having First Nation ancestry (Sellers, Wicklow & Dean, 2012). Sellers, Wicklow and Dean used

a retrospective review of the clinical presentation of all youth diagnosed with T2DM in a 5 year period (2006-2011) at the Diabetes Education Resource for Children and Adolescence (DER-CA) located in Winnipeg, Manitoba. Since 1985, the DER-CA has been following and providing care for children with diabetes who reside in Manitoba or northwestern Ontario. Incidence rates (per 100,000 children) have continued to escalate over the 5 year study period from 9.03 in 2006-2007, to 16.25 in 2009-2010, to 20.58 in 2010-2011 (Sellers, Wicklow & Dean).

Genetic Predisposition

A strong family history of T2DM among youth diagnosed with T2DM has been described in the literature, leading scholars to conclude that a genetic predisposition to T2DM exists. Reports stated that 45-80% of children with T2DM have at least one affected parent and 70-100% had a first or second degree relative affected with T2DM (Sinha et al., 2002). Studies conducted with the Pima Indians have consistently shown a family history of diabetes as a risk factor for T2DM and particularly youth onset T2DM (Dabelea et al., 2000; Dabelea et al., 2008; Franks et al., 2006).

Pertinent to this study is an emerging discussion about the unique hepatic nuclear factor (HNF)-1alpha G319S polymorphism. In the Oji-Cree First Nation peoples of northwestern Ontario and northeastern Manitoba, a polymorphism in the HNF-1 alpha gene has been identified involving a serine for glycine substitution at codon 319. This polymorphism results in an insulin secretory defect and is positively associated with diabetes in this population, though these individuals often lacked some characteristic features of insulin resistance – obesity and acanthosis nigricans (Hegele et al., 2003; Sellers, Triggs-Raine, Rockman-Greenberg & Dean, 2002).

Acanthosis nigricans is described as a cutaneous finding characterized by velvety hyperpigmented patches which are most prominent in areas where two skins may touch or rub together, for example the neck folds, arm pits and groin areas. *Acanthosis nigricans* has been noted as present in 50% of Caucasian children and 90% of non-Caucasian children diagnosed with T2DM; it is recognized more easily on darker-skinned, obese individuals (Reinehr, 2013).

In a study conducted by Sellers, Triggs-Raine, Rockman-Greenberg and Dean (2002), 51 youth with T2DM participated. Participating youth were genotyped for the G319S mutation of the HNF-1 α gene. In this sample, 41.2% were found to have at least one copy of the mutant allele. The authors of this study noted that those without the mutant allele were more likely to present with symptoms of hyperglycemia, whereas those with one or two copies of the S319 heterozygotes and homozygotes were more likely to be asymptomatic, as well as having a lower BMI and decreased frequency of *acanthosis nigricans* (Sellers, Triggs-Raine, Rockman-Greenberg & Dean,). The authors conclude that the lack of symptoms of hyperglycemia and said markers of insulin resistance may be indicative of insulin-secretion and/or production that may be defective and contributing to hyperglycemia. Harries, Sloman, Sellers, Hattersley and Ellard (2008) state that “the clinical heterogeneity in the disease phenotype suggests that diabetes in the Oji-Cree may have both genetic and environmental components” (p. 1978). A recent study examined a birth cohort of First Nation children born to mothers with youth-onset T2DM; these researchers found the frequency of the S319 allele to be over 90% and over 40% of the offspring of this cohort had T2DM before the age of 19 years (Mendelson et al., 2011). The early onset of T2DM among these First Nations peoples is concerning.

This genetic polymorphism is a likely factor in the increased prevalence of youth onset T2DM in Manitoba as reported in Chapter 1 of this thesis. However, when youth of Oji-Cree

heritage are excluded from studies examining these Manitoba youth, the incidence of T2DM in youth remains higher in Manitoba than in other areas of Canada (Sellers, Wicklow & Dean, 2012). Therefore, the presence of this polymorphism may explain in part a predisposition to the development of T2DM. For instance, socioeconomic status may also contribute to the high prevalence rate of T2DM among the youth in this population. “Poverty remains a persistent reality for about 20% of children in Manitoba” (Social Planning Council of Winnipeg, 2014. p. 1).

The presence of T2DM within this cohort does not explain the rapid increase in prevalence which is reported around the globe. Though few would dispute that an inherited, genetic susceptibility to T2DM does indeed exist, the worldwide increase in T2DM cannot be attributed solely to a single gene defect or mutation (Joy, Lahiry, Pollex & Hegele, 2008).

Intrauterine Environment

Over the last few decades, evidence has been accumulating indicating that the risk of developing chronic diseases in adulthood is highly influenced by factors acting early in life in the intrauterine environment during specific developmental windows of tissue plasticity (Somm, Schwitzgebel, Vauthay, Aubert & Huppi, 2008). This section will examine the literature regarding key fetal exposures, namely maternal diabetes, maternal obesity, maternal dysglycemia, maternal smoking and birth weight, and their relationship with youth onset T2DM. Literature examining the relationship of early infant nutrition and maternal nutrition with youth onset T2DM will also be shared in this section.

Fetal exposure to maternal diabetes. Several recent studies now provide evidence supporting the association of exposure to maternal diabetes in utero to the development of childhood obesity (Dabelea, 2007; Krishnaveni et al., 2010). Having first been suggested in

1954, when observations that prenatal hyperinsulinemia seen in fetuses of diabetic pregnancies might lead to the development of diabetes in adulthood (Hoet & Lukens, 1954), an abundance of research in this area has ensued. The intrauterine environment experienced by offspring of diabetic mothers was found to provide an increased risk for obesity, adiposity, glucose intolerance and increased blood pressure (Krishnaveni et al., 2010).

In the Pima Indians of the southwestern United States, offspring exposed to maternal diabetes in utero have a 10-fold higher rate of childhood obesity, than those not exposed to maternal diabetes (Dabelea & Pettitt, 2001; Pettitt, Baird, Aleck, Bennett & Knowler, 1983). An abundance of work within the Pima Indian population strongly suggests that the effect of maternal diabetes in utero compounds genetic susceptibility.

This compounding effect relates to research reporting that a threefold higher risk of developing diabetes at an earlier age exists for siblings born after the mother's diagnosis of diabetes, when compared with siblings born before the mother's diagnosis of diabetes (Dabelea et al., 2000). These results were supported by a study conducted with a Manitoba population, where it was reported that Aboriginal children with T2DM were more likely to have experienced a "diabetes" intrauterine environment (Young et al., 2002). More recently, intrauterine exposure to maternal diabetes and overweight/obesity was found to be strongly associated with T2DM in youth (Dabelea et al., 2008).

Realizing that data obtained from the Pima Indians and Aboriginal children in Manitoba (as described above) may not be generalizable to a broader population, a study focusing on diabetes in pregnancy that recruited a large heterogeneous sample was retrieved. A large record-linkage prospective-cohort study was found, which examined records of 280,866 singleton-born Swedish men from 248,293 families. This study aimed to examine associations of diabetes mellitus in

pregnancy with offspring body mass index (BMI) at age 18 years (Lawlor, Lichtenstein & Langstrom, 2011). Men only, were chosen for this large study as all Swedish men must undergo a mandatory military conscription examination for which records were available that detailed current BMI, and the records detailing their birth and the mother's pregnancy that led to their birth were reviewed. Lawlor, Lichtenstein and Langstrom reported that maternal diabetes during pregnancy was associated with greater mean BMI at age 18 years in their sons, and that the difference in BMI of brothers born after their mother was diagnosed with diabetes versus those born before was on average 0.94kg/m² greater. Maternal diabetes was found to have long-term consequences for greater BMI in offspring, and that this association is likely related to intrauterine mechanisms, independent of maternal BMI in early pregnancy (Lawlor, Lichtenstein & Langstrom, 2011). One weakness in this study is that the authors were unable to clarify the type of diabetes (Type 1 vs Type 2 vs GDM) from maternal records. The main strengths of this study are its large sample size and the ability to examine sibling as well as unrelated individuals. Additionally, it is important to acknowledge that the noted effect of diabetes in pregnancy on offspring adiposity was similar in this European population to that of the findings reported in Aboriginal populations (Dabelea et al., 2008)

The SEARCH for Diabetes in Youth is an observational, multicenter study conducting population-based ascertainment of diabetes in youth with onset at prior to 20 years of age (Dabelea et al., 2008). Numerous ancillary studies were conducted from the data obtained within this large observational study conducted at 6 clinical sites within the United States of America. The SEARCH Case-Control Study is one such ancillary study, and is an important study offering sound evidence of a strong association between maternal diabetes and T2DM in youth (Dabelea et al., 2008). The SEARCH Case-Control Study is a retrospective and self-report study

contrasting 79 youth, aged 10 to 22 years having T2DM against 190 non-diabetic control youth of diverse ethnic background. Biological mothers were surveyed with regards to in utero exposures to maternal diabetes and obesity. Maternal diabetes during pregnancy, including both pre-gestational (defined in the current study as *prevalent diabetes*) and gestational diabetes, was reported by the biological mother during a research visit, as were self-reports of maternal pre-pregnancy weight and height (utilized by researchers to calculate body mass index or *BMI*). After adjusting for offspring age, sex, and race/ethnicity, both exposure to maternal diabetes and exposure to maternal obesity were independently associated with T2DM in youth. The researchers reported that 30.4% of youth with T2DM were exposed to maternal diabetes and 57% of T2DM to maternal overweight/obesity in utero, compared with 6.3% and 27.4% respectively in the non-diabetic control youth. T2DM was diagnosed at younger ages among those exposed to hyperglycemia in utero than those offspring who were not (Pettitt, et al., 2008).

Efforts made to decipher the genetic link of developing T2DM versus the risk added by the intrauterine environment were explored by Dabelea et al. (2000) when they examined sibling parameters within the context of intrauterine exposure to diabetes. Data was obtained for their longitudinal study of diabetes and its complications conducted since 1965 among the Pima Indians of Arizona. Families were included if they had at least one sibling born before and at least one sibling born after the mother was diagnosed with T2DM, and the final sample included 19 nuclear families with 58 siblings – 36 born pre-diabetes and 22 born to mothers with known diabetes (Dabelea et al., 2000). Exposure to diabetes in utero was assumed if the mother was diagnosed with T2DM prior to the delivery of the child and absent if diagnosed after delivery, although the researchers did not differentiate between GDM and prevalent (pre-existing) diabetes. Dabelea et al. (2008), showed in a separate study that the risk of obesity and diabetes

development was significantly higher, threefold higher risk in children born after the onset of maternal diabetes than in their siblings born prior to maternal diabetes, thus supporting the hypothesis that obesity and T2DM in the offspring of mothers with pre-gestational diabetes is stimulated not solely by genetic factors but by a complex cascade of factors stemming from the intrauterine environment (Dabelea et al., 2000). Potential limitations of these findings pertain to recall bias as information was obtained from the recollections of biological mothers, the fact that levels of maternal dysglycemia were not noted, and limited information pertaining to paternal diabetes as a contributing factor was unavailable. One aspect of this study that limits its generalizability is that the age range extends beyond the traditional pediatric age limit of less than 18 years old. Despite these limitations, the large data set achieved in this study makes the SEARCH study an important contributor to the understanding of youth onset T2DM.

A range of growth trajectories have been examined among diverse cohorts, with the conclusion that exposure to maternal diabetes in utero accelerates BMI growth in later childhood (Crume et al., 2011), thus increasing a long-term risk for obesity. These authors also argue that the risk of obesity may not manifest itself until after the first years of life, which reinforces a need for continued follow-up of growth as well as identifying the early childhood years as offering a possible target for interventions aimed at preventing obesity (Crume et al., 2011; Gillman et al., 2010).

The highest prevalence of T2DM in a cohort of offspring of mothers with youth onset T2DM was published in 2011, with rates of 25% of offspring (aged 7-19 years) having T2DM and 43% of offspring (aged 10-19 years) having already been diagnosed with T2DM (Mendelson et al., 2011). While results of this study may not be generalizable to the general population due to the documented relation of the genetic polymorphism (HNF1-alpha) as described earlier in this

chapter, the prevalence rates of obesity and T2DM in this cohort may provide useful insight to further research efforts.

Fetal exposure to maternal obesity. An association has been identified between maternal pre-pregnancy obesity and excessive neonatal growth and adiposity, independent of diabetes in pregnancy (Sebire et al., 2001). These results fostered a growing interest in the hypothesis that maternal obesity in pregnancy, even in the absence of diabetes, is also associated with lifelong metabolic abnormalities in the offspring, such as obesity (Salsberry & Reagan, 2005). Salsberry and Reagan examined a cohort of 2070 mothers and their 3022 children. These 3022 children were studied at 6 to 7 years of age, with significant results. Almost one quarter of the children of obese mothers were obese, in comparison with only 9% of offspring of the normal weight mothers, which was statistically significant ($p < 0.001$). However, no study was located that specifically examined an association between T2DM in youth with fetal exposure to maternal pre-pregnancy obesity in mothers without diabetes (Dabelea et al., 2008).

Fetal exposure to dysglycemia. Having diabetes in pregnancy does not guarantee that a fetus would be exposed to hyperglycemia in utero if the mother is able to achieve optimal glucose control during her pregnancy. However, it is unlikely that a mother with diabetes would achieve normo-glycemia throughout the entire pregnancy. Some studies have examined the effect of maternal glycemia during pregnancy in relation to the subsequent risk of childhood obesity. For example, Hillier et al. (2007) examined the relationship between the level of maternal glycemia during pregnancy and the risk of obesity in a multiethnic cohort with a sample size of 9,439 mother-child pairs. In this cohort, universal GDM screening using a 50g oral glucose challenge test (GCT) was performed routinely, and if indicated – GDM was diagnosed/treated using a three hour oral glucose tolerance test (OGTT). Weight was measured

for all offspring at 5-7 years of age, with those measurements then compared with the levels of maternal glycemia noted during both GCT and OGTT tests. A positive correlation was found between rising maternal glucose level and increased risk of obesity in the mothers' children (Hillier et al, 2007). These results were supported by several studies (Dabelea et al., 2000; Dabelea et al., 2008; Krishnaveni, et al., 2010). One weakness of this study was that it utilized a 3-hour OGTT of 100g, as opposed to the 2 hour 75g OGTT which is the current standard of measuring glucose tolerance in pregnancy that is recommended and utilized for most other studies.

Maternal glycemia during pregnancy has been shown to be associated with increased birth weight and risk of diabetes in youth among the Pima Indians, even when mothers had normal glucose levels (Franks et al., 2006). Franks et al. drew this conclusion after having studied 911 non-diabetic Pima Indian mothers and 1436 of their children in a study that explored for associations between maternal third trimester glucose tolerances and measures of glycemic control and body composition in their children. A strong association between third trimester glucose levels and the offspring's risk of T2DM in young adulthood was demonstrated, which remained statistically significant even when only offspring of normal glucose tolerant mothers were examined (Franks et al.). The mean follow-up of 15.9 years in this study strengthens its reported findings.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study was an important study in examining associations of obesity and GDM with adverse pregnancy outcomes, having a sample of 23,316 women from 15 centers in nine countries between 2000 and 2006 (Catalano et al., 2012). One strength of this study lay in its design as an observational study in which neither caregivers nor participants were blinded to maternal glucose values; participants received neither

recommendations nor treatment for either glucose intolerance or obesity. All participants received a 2-hour 75g OGTT, and relationships between those test results and the primary perinatal outcomes were explored. The results demonstrated strong, continuous associations of maternal glucose levels below those diagnostic of diabetes with increased birth weight and increased cord-blood serum C-peptide levels even in women who did not meet diagnostic criteria for diabetes. As this was an observational study, a causal relationship cannot be established (Metzger et al., 2008) but the findings support the work of Franks et al. (2006). The HAPO study drew further attention to the question as to whether clinical interventions to improve maternal glycemia were warranted at levels below the current diagnostic threshold levels (Catalano et al.).

Not many years later, that question was repeated when new guidelines were proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) in 2010. The IADPSG recommended new and lower blood glucose values to formulate the diagnosis of GDM and emphasizes the importance of the treatment of even mild hyperglycemia within pregnancy (Metzger et al., 2010). These new thresholds for diagnosing have been chastised as having increased health care costs associated with the increased resources that are needed in GDM patients, and not necessarily with positive health gains (Ryan, 2011). Despite the scholarly debates surrounding the new guidelines, studies such as the HAPO study (Catalano et al., 2012) described above and that by Franks et al. (2006) garner support for these new guidelines.

Fetal exposure to maternal smoking. Although tobacco use is known to induce multiple health problems, more than one third of the world's population continues to smoke (Mackay, 2003). Within a long list of health problems caused by smoking, a growing body of evidence now exists linking cigarette smoking with the subsequent development of T2DM. Despite cigarette smoking being a known risk factor for numerous complications in pregnancy, 20-30%

of female smokers continue this addictive behaviour during pregnancy, representing approximately 10% of all pregnancies around the world (Somm et al., 2008).

The majority of located studies focus on the association between cigarette smoking and development of T2DM in the adult smoker. Previous studies have suggested that smoking is a risk factor for T2DM in middle-aged men (Feskens & Kromhout, 1989; Manson, Ajani, Liu, Nathan & Hennekens, 2000; Rimm, Chan, Stampfer, Colditz & Willet, 1995). However, few studies about smoking and T2DM have been conducted with women (Rimm, Manson, Stampfer, Colditz & Willet, 1993).

The MONICA/KORA Augsburg Cohort Study examined gender-specific associations between cigarette smoking and the incidence of T2DM in Germany in a cohort of 5,470 men and 5,422 women, all without diabetes aged 25-74 years (Meisinger, Doring, Thorand & Lowel, 2006). These researchers found that regular smoking was associated with a significantly increased risk of T2DM among men. Meisinger et al. (2006) also reported that the risk of T2DM increased with increasing nicotine and tar consumption per day in a graded manner, as was also reported in a systematic review and meta-analysis published by Willi, Bodemann, Gahali, Faris and Cornuz (2007). Although results were adjusted for a variety of confounders, one limitation in this study was that no data relating to body distribution or diet was included in this analysis. One merit of this study was that a diagnosis of T2DM was based on a physician-validated diagnosis. In the SEARCH Case-Control Study, maternal smoking during pregnancy had no effect on youth onset T2DM, with rates of 11.4% in the youth with T2DM and 11.1% in the non-T2DM youth control group (Dabelea et al., 2008).

In a mini-review (of an unstated number of studies), Xie, Liu, Wu and Wakui (2009) confirm that the underlying mechanism of how cigarette smoking increases the risk of T2DM is not

entirely clear. However, studies have suggested that smoking may contribute to the development of insulin resistance by altering the distribution of body fat (Borggreve, De Vries & Dullaart, 2003; Shimokota, Muller & Andres, 1989), or that agents in tobacco smoke may have direct toxic effects on the pancreas and insulin receptor sensitivity (Chowdhury, Rayford & Chang, 1998; Hartwig, Werner & Ryshich, 2000).

In an effort to examine the research pertaining directly to prenatal exposure to cigarette smoking and its subsequent link to the development of T2DM, the literature was further examined. No human studies linking maternal cigarette smoking to youth onset T2DM were found. However, some studies reported a link between prenatal cigarette smoking and elevated risk of metabolic syndrome and glucose metabolism later in life. Most located studies were either epidemiological surveys or experimental animal studies. More commonly found, were epidemiological studies concluding an increased risk of obesity in children born to women who smoked during pregnancy (Gao et al., 2005; Mokdad, Ford & Bowman, 2000; Yeh & Shelton, 2005), which in turn has been noted as a factor in the development of youth onset T2DM. One study presented an alarming prediction, whereby if estimates are correct that 11% of pregnant women in America smoke during pregnancy, then 715,000 children will be overweight as a result of maternal smoking (Oken, Huh, Taveras, Rich-Edwards & Gillman, 2005).

An experimental study, using rats exposed prenatally to levels of nicotine relevant to human exposure, did not find a deleterious effect on the offspring's ability to secrete insulin or maintain glucose homeostasis at early ages. However, a marked increase in body fat mass in infancy and adulthood was found as well as glucose intolerance with insulin resistance in adulthood (Somm et al., 2008). A group of the aforementioned authors completed a review on the topic of prenatal exposure to nicotine. They concluded that maternal smoking during pregnancy was associated

with the offspring's development of hypertension, obesity, dysglycemia and dyslipidemia (Somm et al., 2009). Birth weight was neither consistently elevated nor decreased. Those authors argued that smoking cessation programs and legislation should be rapidly reinforced to limit fetal nicotine exposure contributing to development of metabolic syndrome.

Despite reports that 20-30% of female smokers continue to smoke during pregnancy, representing 10% of all pregnancies (Somm et al., 2008), few researchers have tackled the plausible relationship between prenatal exposure to nicotine and subsequent youth onset T2DM. Further studies directly examining those patients with youth onset T2DM and prenatal exposure to nicotine are needed. The writer suspects that the scarcity of research in this exact population is at least partly a reflection of the challenges in recruiting pregnant women who will admit to smoking during pregnancy – partly due to the stigma attached to smoking during pregnancy and partly due to the association between smoking during pregnancy and lower prenatal care. These challenges may be compounded by the overall small population with youth onset T2DM globally, and therefore human research in this area remains scarce.

Birth weight. Variations in birth weight have been examined to draw associations between risk of youth onset T2DM and the risk of childhood obesity. Children of women with pre-existent T2DM and GDM were larger for gestational age at birth and at every age beyond that these children were heavier than the offspring of pre-diabetic or women with diabetes (Dabelea, 2007; Pettitt et al., 1983). Birth weights of greater than 4000 grams have been positively associated with the future development of T2DM in adulthood (Whincup et al., 2008).

Though much of the literature focuses on the link between large birth weight and youth onset T2DM, or the link between large birth weight with both childhood and maternal obesity, studies noting a relationship between smaller birth weights and youth onset T2DM warrant discussion.

Since the 1980s, it has been acknowledged that intrauterine growth retardation (IUGR) predisposes to certain chronic illnesses, including T2DM and obesity in adulthood (Bartz & Freemark, 2012). In a systematic review conducted by Whincup et al. (2008), 31 reports were examined to explore any association between birth weight and risk of T2DM in adults. They concluded that, despite significant heterogeneity among populations studied, birth weight was inversely related to T2DM risk. This same inverse association of birth weight to risk of T2DM was first published in 1991, whereby the highest risks of T2DM occurred at the lowest levels of birth weight (Hales et al., 1991; Sommer et al., 2008). A meta-analysis of 14 studies reported a U-shaped relationship between birth weight and diabetes risk and further noted that the risks associated with high birth weight were equivalent to that of low birth weight (Harder et al., 2005).

One study explored the association between birth weight of diabetic pregnancies and subsequent childhood obesity and found that even with normal birth weights, childhood obesity was still more common in offspring of pregnancies impacted by diabetes than among the offspring of non-diabetic pregnancies (Pettitt, Knowler, Bennett, Aleck & Baird, 1987). It appears that both high and low birth weight have an association with subsequent development of T2DM, as well as having implications for obesity and other metabolic abnormalities.

Maternal nutrition. An increasing body of evidence garnered by epidemiological studies now suggests that early life exposures, including intrauterine exposures, such as poor maternal nutrition lead to large and long-term negative health consequences – including T2DM (Portrait, Teeuwiszen & Deeg, 2011; Roseboom, Painter, van Abeelen, Veenendaal & de Rooij, 2011). Over- and under-nutrition is associated with an adjustment of the intrauterine environment and scientists postulate that this adjustment thereby alters genome expression and subsequently

predisposes the individual to diseases such as T2DM in adult life (Gonzalez-Bulnes & Ovilo, 2012). Both rat and human studies have suggested maternal over-nutrition as a pathway to T2DM in the adult life for their offspring (Dabelea & Crume, 2011; Gniuli et al., 2008). Animal studies have shown that the offspring of rats fed a high-fat diet had increased beta-cell mass and neogenesis, leading to hyperglycemia and type 2 diabetes in the adult life (Gniuli et al.).

The Fetal Origins Hypothesis of diseases postulated by Barker in 1992 suggests that exposure to poor nutritional conditions in utero and/or during the first months of life leads to alterations in the development of vital organs, tissues and body systems (Barker, 1992). The Dutch Famine, during the winter of 1944-45, followed the end of World War II and has been used by researchers to investigate the effects of prenatal under nutrition in humans in this contained cohort that survived the Dutch Famine of that era. Researchers describe this population as a unique cohort as a) the famine was inflicted upon a population that was previously well-nourished, b) there was a sudden onset and sudden end to the famine, and c) despite the desperation that transpired during that time – medical personnel kept detailed obstetrical records that facilitate research today (Roseboom, Painter, van Abeelen, Veenendaal & Rooij, 2011). Studies conducted in different cohorts with varying research designs, demonstrated that those who were exposed to the Dutch Famine during the gestational stage were found to have raised glucose levels as adults (Lumey, Stein & Kahn, 2009). Conversely, Stanner et al. (1997) found no significant relationship between in utero under-nutrition and the prevalence of risk factors for diabetes in the adult years.

Early Feeding Patterns

Breastfeeding has been shown to reduce the risk of T2DM among Indigenous children and other various racial and ethnic groups in Canada, indicating that breastfeeding may be a potential intervention to control the disease (Crume et al., 2012). A case-control study conducted

by Young et al. (2002) examined 46 cases with T2DM and 92 controls without T2DM, all less than 18 years of age and matched for sex and age within 5 years. The strength of this study lay within its efforts to examine duration of breastfeeding, exclusivity of breast feeding and the age at which solids were introduced. The data was collected by interview, as opposed to questionnaire, though a weakness lies in self-reports. Breastfeeding longer than 12 months was found to be protective of the child developing T2DM and others suggested that breastfeeding should be promoted in effort to control the onset of this disease (Young et al.). The work of Young et al. supported earlier work by Pettitt, Former, Hanson, Knowler and Bennett (1997), in which a retrospective cohort study identified that not breastfeeding was a risk factor for T2DM.

Additional research examining the relationship between breastfeeding and the risk of childhood obesity was reviewed, as a factor related to youth onset T2DM. A 2005 meta-analysis, which included 17 studies, demonstrated that the duration of breastfeeding was associated with a reduced risk of obesity later in life (Harder, Bergmann, Kallischnigg & Plagemann, 2005). Bartz and Freemark (2012) state that the evidence suggests that breastfeeding does provide real, albeit limited, protection against childhood obesity; reducing childhood obesity may translate to protection from later development of diabetes. It has been hypothesized widely that as mothers breastfeed in response to infant cues of hunger instead of schedule (which may be the case in formula feeding) that this lends itself to the prevention of infant overfeeding (Fisher, Birchs, Smiciklas-Wright & Picciano, 2000).

A relationship has been clearly described between not breastfeeding and the development of youth onset T2DM. All studies that were reviewed describe breastfeeding efforts of six months or greater, however this study will review the method of infant feeding only in the time frame from birth to discharge from hospital. Due to the available secondary data that this study

will analyze, feeding practices –either early or long term – beyond the hospital will not be examined.

Theoretical Frameworks

Two theories were selected to provide the framework for the examination of a broad range of complex factors that may be associated with youth onset T2DM. Using two nursing theories has been applied in an effort to ground this study and to provide a broad lens as the associations between intrauterine life and youth onset T2DM were examined.

Theory of self-care. The first guiding theory is Orem’s Theory of Self-care. The Theory of Self-care is one of three constituent theories that together compose Orem’s general theory of nursing which is titled the “Self-care Deficit Theory of Nursing” (Orem, 2001; Taylor, 2006), and has also been described as “Orem’s Self-care Model” (Comley, 1994). Orem’s Theory of Self-care is a descriptive theory developed in attempt to clarify the aspects of care offered by nurses, as a well as an attempt to conceptualize the client (Smith, 1987).

The theory of self-care care describes what a person requires and what actions need to be taken to meet those requirements (Taylor, 2006). Orem (1985) defined *self-care* as “the practice of activities that individuals initiate and perform on their own behalf in maintaining life, health, and well-being” (p. 86). Orem (2001) specifies that self-care is not limited to a person providing care for him/herself, but also includes care offered by others on behalf of the person. Care may be offered by family members or non-family members until a person is able to perform self-care. Orem has continued to refine and extend the theory that appeared in that first edition, with revisions being published in 6 editions, ranging from the original in 1971 to the most current in 2001 (Orem). Taylor states that although empiric evidence has contributed to both revisions of

the theory and to development of the theory, basics of the original theory have remained unchanged (Taylor).

The theory of self-care is based on the fundamental idea that a relationship exists between deliberate self-care actions and the development and functioning of individuals and groups (Meleis, 1997). Taylor (2006) defines self-care as “a human regulatory function that individuals must, with deliberation, perform themselves or have performed for them to maintain life, health, development, and well-being” (p. 274).

The importance of this theory is evident in its widespread use among nursing practice in North America, and can be readily applied to care among those patients living with T2DM. If an individual is unable to meet essential self-care demands of T2DM in pregnancy (i.e. monitoring blood glucose levels and/or taking prescribed medications), complications related to hyperglycemia may occur for both the mother and the unborn fetus. The mother’s ability to meet the self-care demands of T2DM in pregnancy can also impact the short and long-term health outcomes for those offspring.

Social ecological theory. As there are significant external influences to one’s ability to employ self-care, and that it is necessary to address the context when attempting to promote health, a second theory has been chosen to guide this study - that theory is the Social Ecological Theory. The social ecological theory addresses the complexities and interdependencies between socioeconomic, cultural, political, environmental, organizational, psychological, and biological determinants of health (Stokols, 1996). This theory proposes that any individual behavior is supported and/or influenced by numerous other systems and groups (Wandersman et al., 1996). It is based upon the premise that lasting behavior change requires programs that target multiple levels of influence (Emmons, 2000).

Historical, socioeconomic, political and environmental challenges present barriers to health have been well documented for Indigenous peoples in Canada, a population that is also challenged by high rates of T2DM (Adelson, 2005). Another example of the health challenges among Aboriginal peoples is the high rate of obesity. Willows, Hanley and Delormier (2012) suggest a socioecological model to address obesity in Aboriginal children, which would focus on multiple environment influences at different times in childhood that influence weight status, including prenatal, family, sociocultural, and community environments. A socioecological model offers a framework to account for the reciprocal interaction of individual behaviours and the environment in the development of obesity (Willows, Hanley & Delormier, 2012).

This above example of obesity parallels the complexities in the causal relationships in T2DM – causes linking genetic, physiologic, social, psychological and environmental factors as contributing to youth-onset T2DM. To gain a full understanding of the factors contributing to the high prevalence of diabetes in this Manitoba population, attention needs to be drawn to the fact that inequalities in the health of individuals and populations exist because of a complex interaction of various determinants (Adelson, 2005; Willows, Hanley & Delormier, 2012).

Figure 1 is based upon the work of Willows, Hanley and Delormier (2012). This model can be applied to examine the relationships that may be contributing to rising rates of youth onset T2DM. This figure illustrates the multiple levels that influence active living, the consumption of healthy foods, and health outcomes (weight status or T2DM) and recognizes that historical factors encompass and influence all ecological levels.

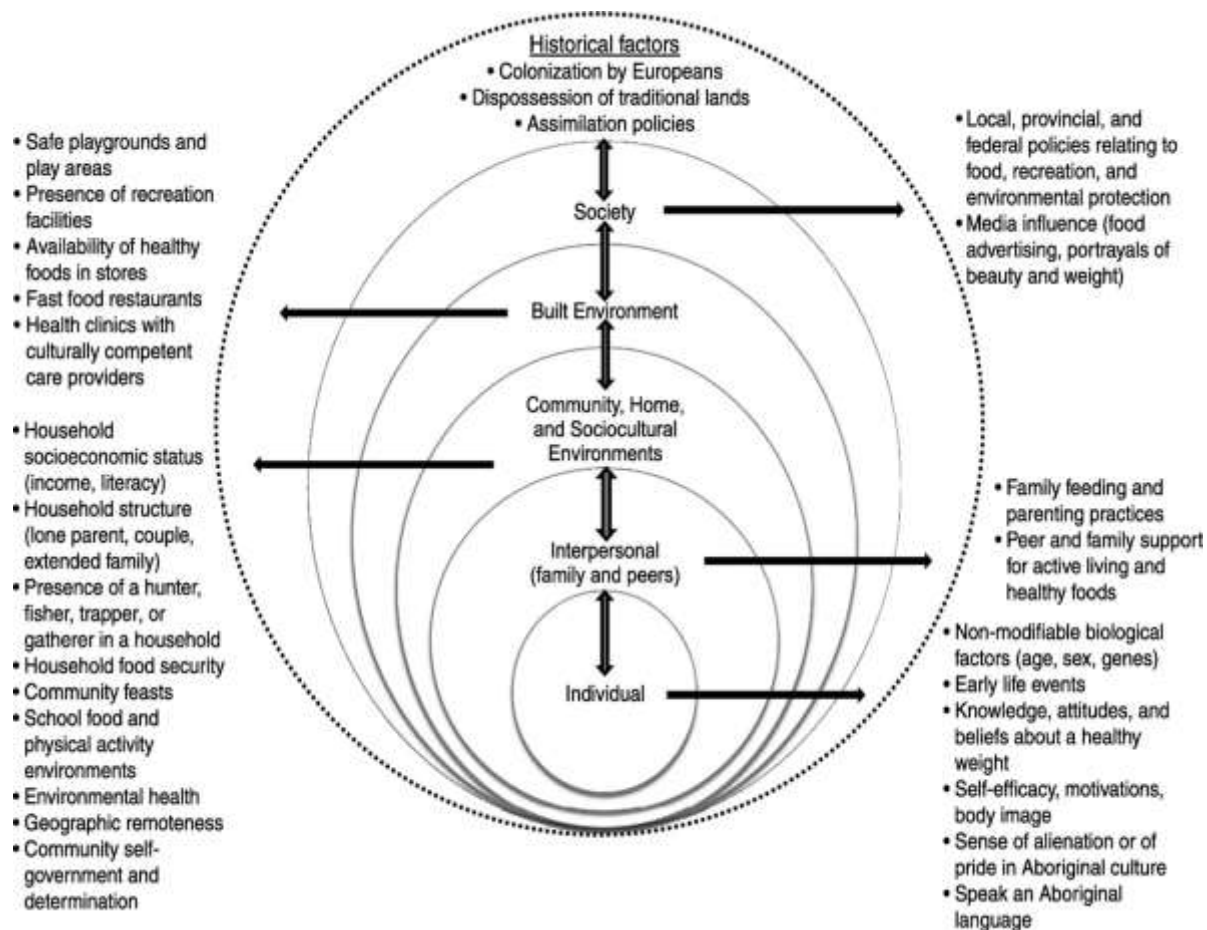


Figure 1 – Ecological model for understanding obesity and T2DM in children. Printed with permission (see Appendix 4)

No studies were located that used this model to directly support the exploration of relationships of the intrauterine environment to the development of youth onset T2DM. However, the social ecological theory was used to guide previous studies examining obesity and other health issues specific to Aboriginal populations – both factors associated with youth onset

T2DM. The social ecological theory supports the idea that efforts aimed at preventing youth onset T2DM should focus on promoting maternal health behaviours before and during pregnancy (including breastfeeding) and proper infant and child nutrition in the postpartum and early childhood development periods (Egger & Swinburn, 1997; Willows, Hanley & Delormier, 2012). The social ecological theory will be discussed further in the final chapter of this thesis.

Summary and Gaps in the Literature

Though an association has been noted between pre-pregnancy diabetes and the subsequent development of the onset of T2DM in those offspring, few studies have examined in detail the pregnancy and birth history in effort to further identify key factors associated with the growing incidence of youth onset T2DM. Two studies were located and reviewed that pointed to the significance of conducting this study among youth and their mothers in Manitoba. . Though numerous sources agree that the rates of youth onset are increasing around the world, overall incidence is still lower and many studies presented are of small sample size and/or underpowered. Additionally, while the body of knowledge pertaining to youth onset T2DM does indeed continue to grow, few research efforts exist that begin with a large cohort with youth onset T2DM and match those youth with youth without T2DM. Research that more closely explores the relationship between youth onset T2DM and maternal weight gain in pregnancy, rapidity of weight gain and BMI are needed. Certainly, the incidence of T2DM in Manitoba is climbing and the research base growing; however, a focused examination about the maternal health histories of youth with T2DM in this geographical setting has not been undertaken. This is the first Canadian study or that it attempted to match on ethnicity with geography as a surrogate. This chapter has presented relevant literature in effort to ground this study, enhance

understanding of the topic presented and its' associated issues, and ultimately to guide discussion in subsequent chapters.

Chapter 3: Methods

This study utilized a secondary analysis of select data housed at the Manitoba Centre for Health Policy (MCHP). Methodology and research design employed for this study, including a comprehensive description of the data bases from which data was retrieved will be presented. This chapter will also provide a detailed description of the sampling technique that was used, as well as an explanation of the matched sample that was assembled. The final section of this chapter will include a description of the quantitative methods that were used to analyze the data.

Research Design

A retrospective case control study was selected and undertaken as the design for this study. The non-experimental retrospective design begins with the manifestation of the dependent variable in the present (i.e. youth-onset T2DM), followed by the testing of hypothesized associations occurring in the past (i.e. exposure to maternal T2DM in utero). The marker of a retrospective case control design is that the researcher begins with the dependent variable and then examines whether it is correlated with one or more antecedent independent variables (Polit & Beck, 2008). While a prospective design may be more rigorous, this was not feasible or manageable due to the small numbers of patients being diagnosed with youth-onset T2DM and the lengthy time frame to diagnosis, within an urgent need to determine associated variables.

Within a case control design, a group of people who already have the outcome are matched with a group who do not, and the researcher determines the proportion in each who had previously been exposed to the suspected causal factor (Streiner, 2013). Case control studies, a type of cohort study, form a suitable design when attempting to assess associations between multiple factors and when randomization is not possible due to practical or ethical reasons (Euser, Zoccali, Jager, Dekker, 2009). The retrospective nature of this study is identified as a

strength in that it is a very time-efficient way of answering new questions with existing data (Euser et al.). Furthermore, the case control design, with an intentionally matched cohort allows even rare exposures to be studied, and allows the researcher to study multiple exposures in one cohort (Euser et al.; Polit & Beck, 2008). The known disadvantage of this design is that this study was unable to establish causal effects due to lack of randomization and possible selection bias (Polit & Beck). For these reasons, this design was selected to explore for correlations or relationships among the early-life factors and the outcome of youth onset T2DM.

A correlation is defined by Polit and Beck (2008) as “an interrelationship or association between two variables, that is, a tendency for variation in one variable to be related to variation in another” (p. 272). Correlational designs are useful when researchers study the effect of a potential cause (i.e. prevalent or pre-pregnancy T2DM) that they cannot manipulate. A strength of this approach is that the researcher does not control or alter in any way the independent variable, which may have already occurred, therefore lessening potential bias.

Data collection.

Approval process. Approval was obtained from the University of Manitoba’s Nursing Research Ethics Board. In order to gain access to the population data housed at the MCHP, approval was required from the Health Information Privacy Committee (HIPC) of Manitoba Health. The HIPC approval process required submission of forms detailing all co-investigators, as well as a concise description as to which data bases were to be accessed, for which years and the rationale stated for accessing those databases; those requirements were met and approval received. As a requirement for a request to access health data, individual approval from both the Winnipeg Regional Health Authority (WRHA) and Healthy Child Manitoba was obtained.

The researcher was required to submit proof of funding and/or demonstrate ability to pay for the estimated costs associated with use of the repository data prior to entering a researcher agreement with MCHP, which was achieved. The final step required to access the population health research data repository of MCHP was to enter into a signed Researcher Agreement for research being conducted by university researchers within the secure data environment of MCHP. With the signing of that final agreement, security access including electronic and a continuously changing passcode was obtained permitting access to both the locked computer stations at MCHP as well as access to the data bases themselves. Data for this project could only be accessed within the secure, locked environment of the MCHP Repository.

Retrieval of data. This retrospective case-control study gathered data housed in the population health research data repository at the Manitoba Centre for Health Policy (MCHP). The retrospective secondary data analysis included a review of the birth histories of Manitoba youth in an effort to evaluate the association of in-utero exposures to various clinical and social risk factors with the risk of youth onset T2DM. Utilizing SAS statistical software (Version 12.0) the chosen variables, as described later in this chapter, were retrieved.

Data sources. Data was collected from three linked databases, all of which are housed in the population health research data repository of the Manitoba Centre for Health Policy (MCHP). This section will describe the data collection setting of MCHP, as well as offer a description of all data bases from which data was retrieved. The data bases which were accessed include - a) Manitoba Health administrative databases b) social administrative databases –Healthy Child Manitoba, and c) the Diabetes Education Resource for Children and Adolescents (DER-CA) database, all housed at the MCHP.

The Setting: The Manitoba Centre for Health Policy. Data was accessed from MCHP, which is located within the Department of Community Health Sciences, within the Faculty of Medicine at the University of Manitoba. The population health research data repository (hereafter referred to as the Repository), is a comprehensive collection of population based administrative, registry, survey, social and other data relating to residents of Manitoba. The Repository, formally established in 1991, was developed to facilitate research that attempts to describe and explain health patterns and profiles, as well as facilitating cross-sector research in areas such as social services, health care, justice and education (Marchessault, 2011). The Repository provides an ideal resource for studying health and social outcomes from the prenatal period through to adolescence (Brownell, Kozyrskyj, Fuchs & Santos, 2011).

The Manitoba Health Services Insurance Plan (MHSIP) contains physician reimbursement claims, hospital discharge abstracts, registration files and records of all dispensed prescriptions. These data are de-identified and stored in the Repository within MCHP. Although data is de-identified, when approval is acquired from the provincial Health Information Privacy Committee (HIPC) and ethical approval is gained from the University of Manitoba Research Ethics Board, files can be linked at the person-level utilizing the Personal Health Identification Number (PHIN). Since 1984, every resident of Manitoba has been assigned a unique personal health identification number (PHIN) which can be used to link patient records across administrative health databases and create a longitudinal record for each patient. To protect patient confidentiality, the linkage in this study was performed, via scrambled PHINs, using anonymized versions of the Manitoba Health's administrative databases. Permission to access those records within this database was gained for records within the time frame of 1986-2011.

Healthy Child Manitoba. Another database that was accessed in this study includes that of the BabyFirst/Families First program, also housed in the repository at MCHP. Healthy Child Manitoba is responsible for the administration of this program, which was first introduced as the BabyFirst program in 1999, and renamed as Families First in 2002. This program is a targeted, multi-year home visiting program for families with newborns who are determined, via screening by public health nurses of all postpartum referrals, to be living under conditions of risk. Families are included in this database and then evaluated if they have accepted the home visiting program that is offered (Brownell et al., 2007). This database was accessed for all years available (2001-2011) in effort to study the maternal use of drugs and tobacco.

Drug Program Information Network. The Drug Program Information Network (DPIN) is an electronic system that records the prescription sales and activities of all Manitoba pharmacies, thereby capturing some information about the health practices of Manitoba residents (Doupe et al., 2006). This registry is maintained by the Government of Manitoba's Ministry of Health and access was gained for records within the time frame of 1995-2011. The DPIN registry began in 1995. Data from this registry was utilized to determine patients who have, or have not been prescribed known anti-diabetic medications as a marker for diabetes.

Pediatric diabetes database. All cases of pediatric T2DM identified between 1986 and 2011 and with a Manitoba Personal Health Information Number (PHIN) were identified from the database of the Diabetes Education Resource for Children and Adolescents (DER-CA) in Winnipeg, which is also housed at the Repository of the Manitoba Centre for Health Policy. The DER-CA is an integrated, inter-professional team of pediatric endocrinologists, nurse educators, dietitians, dental hygienists and mental health professionals. The DER-CA is part of Children's Hospital at the Health Sciences Centre in Winnipeg, a tertiary care centre with a large catchment

area serving children from all parts of Manitoba, south-eastern Saskatchewan, north-western Ontario, and Nunavut. Clinical care and on-going follow-up for youth with diabetes is provided by the DER-CA from diagnosis until the age of 18, at which time those youth are transitioned to adult care. Demographic and clinical data on all patients cared for in the DER-CA from 1986 onward have been prospectively entered in a computerized database (Dart et al., 2012). Within this database were clinical variables as well as the ability to differentiate between subtypes of DM. A recent study, demonstrated that the DER-CA clinical database has a minimum ascertainment of 86% for youth onset type 2 diabetes in Manitoba (Dart et al.).

Sampling Technique. All youth known to have youth onset T2DM as diagnosed and recorded within the Pediatric Diabetes Database from the years 1986-2011 were identified. Of that larger sample, inclusion criteria was: (a) those youth who were diagnosed with T2DM between ages 10 and 18 years, (b) found to have a valid Manitoba PHIN, and (c) had a Manitoba hospital birth record.

Upon retrieval of that sample, those youth were then matched to a control cohort identified from the population repository at the Manitoba Centre for Health Policy using a 1:5 case to control ratio. The matching criteria of age, sex and place of residence (with place of residence specified by postal code) at time of diagnosis were employed to create this matched sample. The index date for age matching was the age noted at date of diagnosis of T2DM. Geographical matching was achieved using the first 3 digits of the 6 digit Manitoba postal code.

Matching was employed to enhance the comparability and ultimately the rigor in this quantitative study. In addition to the aforementioned matching criteria, these two demographic variables (age and gender) were incorporated into the matching criteria as they are known to be confounding variables with a relationship to the onset of T2DM in youth. The third variable that

was selected as a matching criteria was that of geographical residence, as identified by Manitoba postal code. Geographical residence, marked by postal code, was chosen as a marker for both environmental influences and socioeconomic status, which have been described as similar in each postal code through studies of income levels. Individual RHAs were initially noted, and the 11 Manitoba RHAs were further categorized as: Urban (includes Winnipeg and Brandon), North (includes RHAs of Burntwood, Nor-Man and Churchill), and South (includes Assiniboine, Central, Interlake, North Eastman, Parkland and South Eastman). It has been well documented that T2DM has both environmental and social influences, which were controlled by matching geographic residence with the assumption that similar environments and income quintiles exist within the area of a particular postal code. Limitations of this matching strategy will be addressed in Chapter 5.

Once matching was complete and a control group of youth without T2DM retrieved, individual records were linked to their biological mother's health records by use of their Personal Health Information Number (PHIN) within the Manitoba Health Registry. Once the cohort was established, data retrieval then commenced from the above data bases utilizing SAS statistical analysis programming (Version 12.0).

Cohort definitions.

Youth onset T2DM: All incident cases of T2DM with valid Manitoba PHIN codes diagnosed at ages between 10 to 18 years of ages identified from the DER-CA registry housed at the MCHP.

Youth without T2DM: A control group, matched to the T2DM cohort on age, sex and geographical location, randomly selected from the MCHP Repository. Youth met the definition of 'no youth onset T2DM' if no ICD-9CM codes (as listed in the Appendix of this paper) or prescription use related to diabetes were located.

Independent Variables. The variables that were assessed in this study are summarized in Appendix A. This section will specify which data base each variable was retrieved from, and describe if necessary how the presence of, or measurement of a particular variable was assessed.

Maternal variables. In an effort to best examine factors of pregnancy that may or may not have a relationship to the development of youth onset T2DM, the following maternal variables were assessed – maternal age at time of index youth’s birth, obstetrical gravidity and parity, maternal income quintile at time of youth’s birth, presence of prevalent T2DM and presence of gestational diabetes mellitus (GDM). Data pertaining to the measurement of all of the aforementioned variables were retrieved from the Repository.

A list of Complications were assessed for all mothers in each of the case and control groups at the time of birth of the index youth, regardless of whether or not the mother was found to have prevalent or gestational diabetes, or found to have no diabetes (Table 4). The presence of these codes, as detailed in Appendix C was examined within a 730 day period (or 2 years) preceding the index birth. The complications that were examined include: presence of peripheral vascular disease, cardiovascular disease, cerebrovascular accident, renal, retinopathy, use of angiotensin-converting-enzyme inhibitor (ACE) inhibitor medications, presence of pre-eclampsia, as well as complications of a neurological or ophthalmologic nature.

The variable noted as “Maternal Substance Use” was calculated utilizing SAS code that captured both dependent and non-dependent use of alcohol and drugs at time of delivery. Maternal smoking status was assessed from the Healthy Child, Healthy Families database.

Youth variables. For all youth (cases and controls) the following variables were retrieved – sex, gestational age at birth, birth weight, mode of delivery (i.e. vaginal or caesarean), and infant feeding practice at time of discharge from hospital. Infant feeding was categorized as

exclusively breastfeeding, exclusively formula feeding, or a combination of the two feeding methods. All of the above mentioned variables were retrieved from the Administrative databases of Manitoba Health, held in the Repository, that include both hospital abstracts and physician billing data. For cases, age and body mass index at diagnosis were retrieved via linkage to the DER-CA.

The variable of birth weight was combined with the variable of gestational age in effort to quantify the youth's size for gestational age at delivery. The values for "Size for Gestational Age (GA)" were assembled within the following seven categories:

1. Preterm-Acceptable for GA,
2. Preterm –Small for GA
3. Preterm – Large for GA
4. Term – Acceptable for GA
5. Term – Small for GA
6. Term – Large for GA
7. Post-term – Acceptable for GA

Data Analysis Procedure

Initial descriptive statistics were obtained using student *t* tests and chi squared tests. The initial analysis did not include any post hoc analysis and therefore reports of statistical significance are reflective of whether the whole factor is significant for overall group effect. All variables, as retrieved and acknowledged, then underwent a univariate analysis in a conditional logistic regression model to determine the predictive nature of each variable. Following the univariate analysis, all statistically significant findings were then analysed using a multiple

regression model to identify factors of pregnancy commonly related to the development of T2DM in their children as compared to those a control group of children without diabetes.

After this first analysis using a multiple regression model, a second multiple regression model was created which included only those variables that remained significant in the first and larger multiple regression model that was first analyzed. Multiple regression analysis is a statistical procedure that is ideal for understanding the effects of two or more independent (predictor) variables (i.e. income quintile and maternal diabetes status) on a dependent variable (i.e. youth onset diabetes). Conditional logistic regression analysis was used to generate odds ratios and 95% confidence intervals for the association of in-utero exposures and the identified outcomes of pregnancy with the outcome of youth onset T2DM (Hailpern & Visintainer, 2003). Conditional regression logistic models are an extension of simple regression models and employed in effort to account for matching. Calculation of these odds ratios provide additional information about an outcome in an exposed group to the odds of that outcome in the group that was not exposed to a particular variable. The results of the statistical analysis will be described in Chapter 4.

Chapter Summary

This chapter described in detail the research design and methodology utilized for this study. Rationale for choosing a case control study to answer the research objective was provided. Steps for accessing the population health repository of MCHP were detailed in this chapter, as were the specific databases that were accessed in effort to clearly define variables. Following univariate analysis of the data, a series of conditional logistic regression models were conducted and odds ratios were calculated. Chapter 4 will present the findings that were determined as a result of the research design and methodology.

Chapter IV: Results

This chapter will present the results obtained following the research methodology and data analysis that was accomplished as detailed in Chapter 3. Firstly, a description of the sample will be provided, with details pertaining to both the youth and the mothers in this study cohort. Additionally, results obtained via both univariate and multivariate analysis will be presented.

Description of Sample

A total of 387 adolescents with youth onset T2DM were identified from the DER-CA database. Of these 387, 270 were found to have a Manitoba PHIN, a Manitoba record of birth and were within the age group of 10-17 years at the time of their diagnosis of T2DM. These youth were then matched to a control cohort on a 5:1 ratio utilizing the matching criteria of age, sex and geographical region of residence. Inclusion criteria for youth in this matched sample included the availability of a Manitoba hospital birth record. The final sample was comprised of 270 youth with T2DM and 1341 youth without T2DM, for a total of 1611 youth.

Demographics of youth. The mean age of youth with T2DM at time of diagnosis was 13.12 years (SD 1.82). The median age was found to be 13 years, with a range defined by the inclusion criteria of age 10 to 17 years. Demographics for youth in this sample are illustrated in Table 1. Data was available on the sex of all 1611 study youth participants, and it was determined that of the case group, 38.15% were male and 61.85% were female.

The mean birth weight of youth with T2DM was 3449.68 grams (SD 692.30, range of 1790 to 5600 grams), while the mean birth weight of control group youth was 3416.05 grams (SD 627.04, range of 1460 to 4760 grams). Gestational Age (GA) was available on 1608 of the examined records, and did not differ between those with T2DM and controls (38.26 vs. 38.98 weeks, $p>0.05$).

The largest number of youth with T2DM resided in the North RHAs (41.1%), with approximately equal number in the South (30.0%) and Urban RHAs (28.9%). The majority (71.1%) of youth with T2DM resided in rural areas at time of diagnosis, while only 28.9% resided in the urban centres (Brandon or Winnipeg).

The majority of youth in both the control and case groups were in the category of “Term Acceptable for GA” – at 51.48% and 69.22% respectively. See Table 2 for full description of size for gestational age.

Table 1 – Description of youth with and without T2DM

Variable	N	Youth with T2DM (n=270)	Control Group (n=1341)	P value
Age (at diagnosis)*	270	Mean= 13.122 Median & Mode= 13 Std Dev: 1.822 Range: 10-17 years	—	—
Sex *	1611	Male: 103 (38.15%) Female: 167 (61.85%)	Male=517 (38.55%) Female= 824 (61.45%)	—
RHA (of youth at time of diagnosis)*	1611	North: 111 (41.11%) South: 81 (30.0%) Urban: 78 (28.89%)	North: 548 (40.87%) South: 403(30.05%) Urban: 390 (29.08%)	0.9968
BMI (at diagnosis)	270	Mean= 31.7565kg/m2 Std dev: 7.3959 Range: 16.38 –57.43 Mean BMI z score: 2.01	--	—
Gestational Age weeks	1611	Mean= 38.26 Median=39.0 Mode= 40.0 Std Dev=3.861	Mean= 38.98 Median=40 Mode=40 Std Dev=3.370	0.1032
Mode of Delivery	1607	Vag: 200 (74.35%) C/Sec: 69 (25.65%)	1136 (84.90%) 202 (15.10%)	<0.0001
Newborn Feeding	1510	0=other: 4 (1.58%) 1=fully BF: 105 (41.50%) 2=formula: 118 (46.64%) 3=partially BF: 26 (10.28%)	0= 26 (2.07%) 1= 707 (56.25%) 2= 397 (31.58%) 3= 127 (10.10%)	<0.0001
Birth weight grams	1611	Mean=3449.68 Median=3500.00 Mode=3000.00 Std Dev= 692.206	Mean=3416.05 Median=3449.00 Mode=3260.00 Std Dev=627.038	0.1229

*denotes matching criterion.

Table 2 - Size for Gestational Age

Category	Cases (n=270)	Match (n=1341)	P value
Missing or invalid combination	2 (0.74%)	11 (0.82%)	<0.0001
Preterm-Acceptable for GA	12(4.44%)	73 (5.44%)	
Preterm-Small for GA	3 (1.11%)	8 (0.60%)	
Preterm-Large for GA	22 (8.15%)	5 (0.37%)	
Term-Acceptable for GA	139 (51.48%)	937 (69.87%)	
Term-Small for GA	24 (8.89%)	113 (7.01%)	
Term-Large for GA	56 (20.74%)	149 (8.43%)	
PostTerm-Acceptable for GA	11 (4.07%)	33 (2.46%)	
PostTerm-Small for GA	1 (0.37%)	5 (0.37%)	
PostTerm-Large for GA	0	7 (0.52%)	

Size is defined as birth weight in grams, while Gestational Age is measured in weeks.

Data describing mode of delivery as either vaginal or caesarean section, was available for 1607 youth. For the youth with T2DM, it was established that 74.4% were delivered vaginally, and 25.7% were born by caesarean section. For the control group, 88.90% of youth were delivered vaginally, while 15.1% were delivered by caesarean section.

At time of discharge from hospital post-delivery, 41.5% of youth with T2DM were exclusively breastfed, 46.64% were exclusively formula fed, and 10.28% of infants were be partially breastfed (combination of formula and breastfeeding). Of the control group, 56.25% were exclusively breastfed, 31.58% were exclusively formula fed, and 10.10% were partially breastfed.

Data on Body Mass Index, or BMI, at time of diagnosis of T2DM was available on 270 youth. The mean BMI of those youth with T2DM was 31.8 kg/m² (SD: 7.40). Data pertaining to BMI of the control group was unavailable.

Demographics of mothers

Table 3 - Demographics of Biological Mothers – at time of delivery

Variable	N		Cases n=270	Control n=1341	P value
Age in years at time of delivery <i>Years</i>	1610		Mean: 24.25 Std Dev: 5.80 Range: 14-41	Mean: 24.05 Std Dev: 5.82 Range: 14-43	0.9007
Age at time of youth's dx of T2 <i>Years</i>	270		Mean: 37.4794 Std Dev: 6.32 Range: 26-57	N/A	–
Prevalent Diabetes Number of cases and percentage (%)	1611		No: 216 (80.0%) Yes: 54 (20.0%)	No: 1317 (93.44%) Yes: 24 (1.79%)	< 0.0001
Gestational Diabetes Number of cases and percentage (%)	1611		No: 191 (70.74%) Yes: 79 (29.26%)	No: 1253 (81.75%) Yes: 88 (6.56%)	< 0.0001
OB Gravida (number of pregnancies including current pregnancy & abortions) <i>And percentage (%)</i>	1607 4* missing	00		31 (2.32%)	0.5806
		01	82 (30.48%)	340 (25.41%)	
		02	47 (17.47%)	345 (25.78%)	
		03	57 (21.19%)	239 (17.86%)	
		04	28 (10.41%)	151 (11.29%)	
		05	20 (7.43%)	96 (7.17%)	
		06	14 (5.20%)	55 (4.11%)	
		07	9 (3.35%)	40 (2.99%)	
		08	7 (2.60%)	11 (0.822%)	
		09	6 (2.20%)	20 (1.50%)	
		10		90 (0.67%)	
OB Para (number of previous deliveries resulting in live birth or stillborn) <i>N (%)</i>	1611	00	96 (35.69%)	440 (32.88%)	0.8381
		01	63 (23.42%)	367 (27.43%)	
		02	54 (20.07%)	245 (18.31%)	
		03	28 (10.41%)	128 (9.57%)	
		04	14 (5.20%)	76 (5.68%)	
		05	8 (2.97%)	34 (2.54%)	
		06	3 (1.11%)	21(1.49%)	
		07	4 (1.48%)	10 (0.75%)	
		08		11 (0.82%)	
Maternal Substance Use <i>N (%)</i>	1607		No: 254 (94.42%) Yes: 15 (5.58%)	No: 1257 (93.9% ⁵) Yes: 81 (6.05%)	0.7630
Maternal Income Quintile <i>N (%)</i>	1611	1	136 (50.37%)	506 (37.73%)	< 0.0001
		2	64 (23.70%)	283 (21.10%)	
		3	24 (8.89%)	149 (11.11%)	
		4	23 (8.52%)	146 (10.89%)	
		5	18 (6.67%)	212 (15.81%)	

Pre-pregnancy diabetes was present in 20% of the mothers of youth with T2DM compared with only 1.79% of the mothers of the controls (<0.0001). Gestational diabetes was found in 29.26% of cases, and found in 6.56% of mothers in the control group (<0.0001). Cases and controls do not differ significantly with regards to gravidity and parity.

“Maternal substance use” was noted in 5.58% of cases and similarly for 6.05% of controls and was not found to be significantly different. Attempts were made to examine rates of smoking in the sample group, however were unsuccessful in doing so, having secured only 40 records – each of which was incomplete in its attempts to assess rate of maternal smoking.

Maternal complications of diabetes. The presence of maternal complications as related to diabetes, were assessed utilizing ICD-9CM Procedure and Diagnostic codes that are known descriptors of each complication. Complications are presented in Table 4. Rates of complications were very low in both groups. Both pre-eclampsia ($p=0.0021$) and retinopathy ($p=0.0010$) were found to be associated with youth onset T2DM as these associations were statistically significant.

Table 4 - Maternal complications of diabetes at time of delivery

Complication	Cases (n=270)	Controls (n=1341)	P value
Peripheral Vascular Disease Yes/No (%)	4 (1.48%) 266 (98.52%)	35 (2.61%) 1306 (97.39%)	0.2710
Cardiovascular Disease Yes/No (%)	0 270 (100%)	6 (0.45%) 1335 (99.55%)	0.2708
CVA Yes/No (%)	0 270 (100%)	0 1341 (100%)	0.4366
Neurologic Yes/No (%)	11 (4.07%) 259 (95.93%)	37 (2.76%) 1304 (97.24%)	0.2463
Renal Yes/No (%)	1 (0.37%) 269 (99.63%)	1 (0.07%) 1340 (99.93%)	0.5253
Ophthalmologic Yes/No (%)	4 (1.48%) 266 (98.52%)	4 (0.30%) 1337 (99.70%)	0.0616
ACE therapy Yes/No (%)	0 270 (100%)	1 (0.07%) 1340 (99.93%)	0.6535
Retinopathy Yes/No (%)	4 (1.48%) 266 (98.52%)	2 (0.15%) 1339 (99.85%)	0.0010
Pre-eclampsia Yes/No (%)	3 (1.11%) 266 (98.5%)	5 (0.37%) 1336 (99.63%)	0.0021

Maternal income. Table 3 reveals that the majority of mothers in the case group (50.37%) were found to be in Quintile 1 (lowest income quintile), which was also true for the majority of control mothers with 37.73% found to be in Quintile 1. The least common quintile for the case group mothers was Quintile 5 with 6.67% of mothers noted, while the least common income quintile for the control group was found to be Quintile 4 with 10.09% falling within that grouping.

Univariate Analysis

All variables as retrieved and acknowledged in the previous descriptive tables underwent a univariate analysis in a conditional logistic regression model to determine the predictive nature of each variable. Only those findings of that univariate analysis that were statistically significant (with a *p* value less than 0.05) are detailed in Table 5.

Table 5 – Univariate Analysis Results of Perinatal Risk Factors for the Development of Youth Onset T2DM

Predictor	Odds Ratio	95% Confidence Interval	p-value
Cesarean Section	1.970	1.434 – 2.707	<0.0001
Gestational Age	0.893	0.842 – 0.947	0.0002
Prevalent diabetes	12.796	7.644 – 21.419	<0.0001
Gestational diabetes	6.512	4.512 – 9.399	<0.0001
Income Quintile			
Quintile 1 vs 5	6.777	3.047 – 15.074	<0.0001
Quintile 2 vs 5	5.331	2.363 – 12.028	<0.0001
Quintile 3 vs 5	3.807	1.587 – 9.134	0.0028
Quintile 4 vs 5	1.744	0.756 – 4.022	0.1924
Infant feeding – breastfeeding vs. formula	0.4740	0.3509 – 0.6404	<0.0001
Size for Gestational Age	0.893	0.842 - 0.947	0.0002

All results produced from conditional logistic regression models. Though non-significant contrasts were performed on all variables in effort to determine univariate predictor potential, only those that were statistically significant with p value less than 0.05 are shown in Table 5.

Multivariate Analysis

Having determined those variables which were significant following univariate analysis, a multivariate model was then created. Those results that were not found to be statistically significant predictors in the univariate analysis were excluded from the multivariable conditional regression logistic model and these results are detailed in Table 6.

Table 6 - Multivariate Analysis of Variables Predictive of Youth Onset T2DM

Predictor	Odds Ratio	95% Confidence Interval	p-value
Cesarean Section	1.348	0.870 – 2.090 –	0.1810
Gestational Age	0.978	0.903 – 1.058	0.5794
Prevalent diabetes	5.827	2.981 – 11.389	<0.0001
Gestational diabetes	4.329	2.753 – 6.806	<0.0001
Income Quintile			
Quintile 1 vs. 5	6.669	3.008 – 14.787	<0.0001
Quintile 2 vs. 5	5.442	2.412 – 12.277	<0.0001
Quintile 3 vs. 5	3.584	1.494 – 8.600	0.0042
Quintile 4 vs. 5	1.788	0.773 – 4.140	0.1746
Linear Trend Test		Linear Trend Test: P = <0.0001	
Infant feeding –formula			
Breast vs. Formula	0.5175	0.3641 – 0.7354	0.0002
Breast vs. Combination	0.965	0.517 – 1.801	0.9119
Formula vs. Combination	1.866	0.999 – 3.489	0.503
Size for Gestational Age	See Table 7		

All results produced from a multivariate conditional logistic regression model.

Following a multivariate analysis of the above variables and with numerous confounding variables now excluded, delivery by caesarean section ($p=0.1810$) and gestational age ($p=0.5794$) were no longer found to be predictors of youth onset T2DM. However, as noted in Table 6, most variables included within the multivariate model remained significant once adjustment for confounding variables had been made.

In a multivariate model, prevalent diabetes in the mother remained a statistically significant risk factor for youth onset T2DM (OR 5.83 with 2.981-11.389CI). Similarly, maternal gestational diabetes remained a significant risk factor for youth onset T2DM with an OR of 4.33 (2.753-6.806 CI).

A lower income quintile at time of birth was found to be more significantly associated with the development of youth onset T2DM than increasingly higher income quintiles ($p < 0.0001$). The inverse effect of maternal income quintile on the offspring's risk of developing youth onset T2DM was consistent across a comparison of all income quintiles, and remained highly significant in a linear trend test ($p < 0.0001$). Infant feeding was categorized as Breast, Formula or Combination and a comparison of each of those categories with each other was performed in this model. When compared with formula feeding, breastfeeding was found to be protective (OR=0.5175, 95% CI 0.3641-0.7354, $p=0.0002$). Size for gestational age was determined and clustered into categories as described earlier in this chapter. In the multivariate model, each category was contrasted with each of the other 6 categories to determine specific associations. The effect of size for gestational age was determined to have a significant association on the development of youth onset T2DM ($p=0.0037$). These results are shown in Table 7.

Table 7 – Size for Gestational Age (GA) as a Predictor of Youth Onset T2DM in a Multivariate Analysis

Predictor Comparisons	Odds Ratio	95% Confidence Interval	p-value
1 vs. 3	0.1430	0.0325 – 0.6049	0.0084
1 vs. 4	0.7511	0.3372 – 1.6730	0.4836
1 vs. 5	0.4492	0.1773 – 1.1381	0.0916
1 vs. 6	0.4102	0.1740 – 0.9667	0.0416
1 vs. 7	0.325	0.105 -1.009	0.0519
3 vs. 4	5.3551	1.4675 – 19.5412	0.0111
3 vs. 5	3.2028	0.7865 – 10.8732	0.1092
3 vs. 6	2.9244	0.7017 – 10.2883	0.1491
3 vs. 7	2.319	0.510 – 10.546	0.1763
4 vs. 5	0.5981	0.3439 – 1.0401	0.0687
4 vs. 6	0.5461	0.3517 – 0.8480	0.0071
4 vs. 7	0.433	0.183 – 1.024	0.0565
5 vs. 6	0.9131	0.4817 – 1.7306	0.7804
5 vs. 7	0.724	0.282 – 1.860	0.5023
6 vs. 7	0.793	0.317 – 1.985	0.6204

Categories for classifying “size (weight) for Gestational Age (GA) listed as: 1 - Preterm–Acceptable for GA, 2 - Preterm-Small for GA, 3 - Preterm-Large for GA, 4 - Term-Acceptable for GA, 5 - Term-Small for GA, 6 - Term-Large for GA, 7 - Post-term-Acceptable for GA. Category 2 was excluded from this analysis due to sample size in that category.

Chapter Summary

This chapter provided a description of the sample that was utilized for this case control study, as well as the results that were obtained. Univariate and multivariate analyses were performed and the findings of these statistical tests were presented.

De-identified health records were examined from a sample comprised of 270 youth (aged 10 – 17 years at the time of diagnosis) with T2DM and 1341 youth without T2DM, for a total number of cases of 1611 along with their de-identified biological mothers’ health records. The mean age at time of diagnosis was 13.1 years and over 61% were females. The majority (71.1%) of youth with T2DM resided in rural areas at time of diagnosis.

Univariate descriptions of associations were obtained and multiple conditional regression analysis was performed to identify key factors associated with T2DM in youth. This study found

a 14-fold increase in the risk of youth onset T2DM when the mother had prevalent diabetes, and 6.5-fold increase in that risk if the offspring's mother had GDM. A lower income quintile at time of birth was significantly associated with the development of youth onset T2DM than increasingly higher income quintiles ($p = <0.0001$). Breastfeeding was found to be protective when compared with formula feeding, (OR=0.5175, 95% CI 0.3641-0.7354, $p=0.0002$). The effect of size for gestational age had a significant association on the development of youth onset T2DM ($p=0.0037$), with the largest association found in youth who were born in the “preterm-large for GA” category. These findings will serve as the basis for the discussion that follows in the next chapter.

Chapter 5: Discussion & Summary

This chapter is divided into four sections. Within the first section, findings will be discussed relative to the literature and the research objective. The next two sections will focus on the implications of the study findings and their influence on clinical practice and future research. The link of the chosen theoretical frameworks to findings of this study will be presented in relation to clinical care and the broader determinants of health. The final section of this chapter will provide an overview of the non-significant findings, as well as both the strengths and limitations of this study.

Discussion

The overall purpose of this research was to explore demographic and perinatal factors that may be associated with the development of youth onset T2DM. Both univariate and multivariate analysis revealed several significant findings which will be discussed in this section. Attention will also be spent discussing those findings which were not found to be significant and related to current literature.

The mean age of 13.1 years noted in our cohort is consistent with other studies from DER-CA in both this Manitoba population and broader Canadian data (Amed et al., 2010; Pettitt et al., 2008; Sellers, Wicklow & Dean, 2012). Sellers, Wicklow and Dean discuss the global hypothesis that the physiologic state of insulin resistance of adolescence related to hormonal changes, compounded by a setting ripe for rapid rise in rates of obesity, result in the ‘perfect storm’ for precipitating beta cell fatigue and youth onset T2DM. However, while the majority of cases of T2DM are noted in the age group above 10 years of age, this disease is not isolated to adolescents. At the DER-CA in Manitoba, Canada, 9.7% of youth diagnosed with T2DM were

less than 10 years of age (Sellers, Wicklow & Dean), while the Canadian Pediatric Surveillance Program reported that 8% of youth diagnosed with T2DM were younger than 10 years of age (Amed et al.).

Maternal diabetes. Not surprising was the finding that the presence of diabetes in the mother, either prevalent T2DM (pre-dating the pregnancy) or GDM was strongly associated with youth onset T2DM in the offspring. This study identified a 14-fold increase in the risk of youth onset T2DM when the mother had prevalent diabetes, and 6.5-fold increase in that risk if she had GDM. However, it is likely that the effect of maternal diabetes is not a variable of isolated influence or effect. When other confounding variables were eliminated in the multivariate analysis, the predictive nature of both prevalent and gestational diabetes – though still significant, decreased to 5.827 OR (95%CI 2.981-11.389, $p<0.0001$) and 4.329 OR (95% CI 2.753-6.806, $p<0.0001$). These findings supported other studies of smaller sample sizes, including the SEARCH for Diabetes Study (Dabelea et al., 2008) and a study conducted on a Manitoba cohort by Mendelson et al. (2011) which found 43% of offspring born to mothers with youth onset T2DM did develop T2DM within the 10-19 years age group.

Size for gestational age. The most significant association between size for gestational age and youth onset diabetes was found to be within the category of “*preterm – large for gestational age*”, which consistently revealed an increased OR when, compared with all other categories of size for gestational age. An infant born preterm and large for gestational age appears to have a 2-5 fold increased risk of developing youth onset T2DM with a range of 2.319 OR (0.510-10.456 CI) to 5.355 OR (1.468-19.541 CI) as previously described. Not that long ago, numerous sources reported the largest concern for the infants of mothers with diabetes as being within “*term-large for gestational age*” category (Aljohani et al., 2008b), and in effort to lessen

perinatal morbidity, common obstetrical practice grew to encourage delivery of these maternal-child pairs on or around 36 weeks – just prior to term. It may be possible that the decision to deliver the infant of a mother with diabetes prior to term may be in fact a reflection of worsening health, deteriorating glucose control or the development of complications (either obstetrical or diabetes-related) and therefore the learned association is related to a deteriorated state of health, as opposed simply to size in relation to gestational age.

The findings of this study and the significant relationship of the infant's size for gestational age to the risk of youth-onset diabetes warrants discussion among obstetrical care providers. Is more harm being done by delivering these infants of mothers with diabetes prior to term? While this early delivery may have perinatal and obstetrical benefit (i.e. reduced rate of shoulder dystocia), is the long-term health of the child and subsequent adult jeopardized by this practice? The answer to this question will require Pediatric and Adult Endocrinologists to work together with Obstetrical care providers on research efforts in this area.

Socio-economic status. Socioeconomic determinants of health, such as low employment, poverty and low parental education, influence the burden of illness in general, and more specifically the development of obesity and T2DM (Adelson, 2005; Dean & Sellers, 2007; Raphael, 2000;). No studies were found that attempted to correlate maternal income or socioeconomic status with the occurrence of youth onset T2DM. However, studies were found that reported an inverse relationship between parental socioeconomic status and childhood obesity (Crawford, Story, Wang, Richie & Sabry, 2001; Reinehr, 2013).

As a marker of socio-economic status, income quintiles were reviewed for all mothers within our sample. Low socio-economic status was found to be significantly associated with the

development of youth onset T2DM with an odds ratio of 7.651 (95% CI) when “income quintile 1” was compared with all other “income quintiles”, (see Table 6 – Chapter 4). This inverse relationship of income to risk of youth onset T2DM was not only evident when comparing the lowest income quintile to the highest, but additionally when a linear trend test was completed, the results remained statistically significant emphasizing that the risk of youth onset T2DM increases as maternal income decreases.

Acknowledgement of this trending and predictive aspect of maternal income, also described as an SES gradient, to the development of youth onset T2DM demands the attention of policy makers and health care providers. One can debate whether this effect is due solely to poverty or compounded by concomitant factors such as lack of education, poor nutrition or increased rates of depression— these are only a few factors that are knowingly associated with low income; likely the relationship is multifactorial (Black, Raine & Willows, 2008). Intervention studies and health care initiatives, grounded within a multifactorial socio-ecological model and directed at narrowing the economic disparities amongst these vulnerable populations are urgently needed. The Social Planning Council of Winnipeg (2014) recommended:

Governments must focus on improving equality through social programs that supplement income and more progressive income taxes and transfers that redistribute wealth and move people out of poverty. Currently, before taxes and transfers, the 20 % of the population with the lowest income has just four percent of all income in the province. After taxes and transfers, this doubles to eight percent. Other jurisdictions have a greater redistribution of income through taxes and transfer programs. It becomes obvious, when looking at where growth in income has gone in the past 21 years, why levels of poverty

have not decreased. To seriously address child poverty, improvements in income equality are needed (p. 6).

Breastfeeding. The statistical significance noted of the protective effective of breastfeeding against the development of youth onset T2DM in this cohort demands attention. Certainly other studies have described this protective effect of breastfeeding and/or breast milk associated with a decreased risk of youth onset T2DM, in that regard this finding is certainly not new (Mayer-Davis et al., 2007; Osgood, Dyck & Grassman, 2011). The SEARCH for Diabetes study advocated that any amount of breastfeeding was protective especially for the first two months of life (Mayer-Davis et al.). However, the majority of located studies explored long-term feeding patterns, garnering data via self-report of the mothers about feeding practices from birth to one year of age. In these studies, indeed breastfeeding was reported as offering health benefits to offspring – one of which health benefit is a decreased risk of youth onset T2DM.

What is interesting is that the method of infant nutrition in this cohort was assessed solely as the reported method of feeding at the time of discharge from hospital, likely only one to four days after birth. Realizing that many women who initiate breastfeeding in hospital may neither continue to breastfeed once home nor choose to breastfeed beyond 3 months, it is highly probable that rates of breastfeeding did not increase beyond our study, and may in fact have been much lower a short while after this assessed time frame of infant nutrition. This study focused on the identified approach to infant nutrition within a brief period following birth. Interestingly, both breastfeeding alone and a combination of breastfeeding and formula feeding were found to associated with lower rates of youth onset T2DM, when compared in a multivariate model with formula feeding.

The strong relationship noted in this period of early infant feeding, that may or may not be reflective of feeding practices either shortly after discharge or by one year of age, may be suggestive of the power of colostrum, or a mother's first milk, and its' protective nature. While highly speculative, it is intriguing to think that breast milk – even if offered for only a few days and/or in combination with formula within those first few days, may offer substantial protection from youth onset T2DM for the offspring of mothers with diabetes. Based on the findings of this study, it is suggested that women whose pregnancy is impacted by diabetes –either prevalent or GDM, be educated from early in the prenatal period as to the proposed benefits of breastfeeding for their offspring. These same women require formal and informal support in breastfeeding initiation and continuation from delivery onward – recognizing that the early breast milk may offer significant protection from youth onset T2DM.

Implications for Clinical Practice

Maternal diabetes. The predictive relationship of maternal diabetes to development of youth-onset T2DM in offspring remains alarming. This study echoes and draws attention to the importance of the intrauterine environment and its implications for long term morbidity. Recognition of the role of developmental origins of health and the effects of maternal diabetes – whether prevalent or gestational, necessitates that care providers enhance efforts aimed at recognition, intervention and treatment of varying degrees of maternal glycemia. Government support and funding for early screening and detection of T2DM such as the Diabetes Integration Project in Manitoba is paramount.

Findings of this study highlight the clinical importance of identifying and adequately treating GDM not only for the short-term health benefit of mother and baby, but also potentially

for the longer-term prevention of obesity and its comorbidities including T2DM in the offspring (Lawlor, 2011). There is sound evidence from diabetes prevention programs that T2DM can be either prevented or delayed after GDM when affected by a change in maternal lifestyle or by use of medications (Metzger et al., 2010). While the effect of GDM on an offspring's risk of youth-onset T2DM is well documented, what is lacking are intervention studies in that population. While some efforts have been initiated, the samples of intervention studies aimed at decreasing youth-onset T2DM remain small and therefore limit generalizability.

As rates of youth onset T2DM continue to rise, so too will the rates of prevalent diabetes in pregnancy. For this reason, there needs to be a heightened emphasis on pre-conception planning as well as pregnancy care for those mothers affected by T2DM in order to effectively decrease rates of youth onset T2DM –if it can be shown that better glucose control in pregnancy would have this effect. Based on this study's findings and the current evidence, it is reasonable to suggest that an important aspect of pre-conceptual counselling and perinatal care for women with either prevalent diabetes or at risk for GDM, would be to address and suggest appropriate weight gain on the lower end of the recommended weight gain for pregnancy. Addressing weight and tackling the weight gain issue in pregnancy, an often sensitive topic, will require courage and sensitivity from prenatal and obstetrical care providers as they strive to promote the potential health benefits for both offspring and mothers.

Pre-conception and perinatal care for women with diabetes. This study also draws attention to both the rates of youth onset T2DM in Manitoba, as well as the factors of pregnancy that are associated with this disease. As rates of youth onset T2DM continue to rise, it is time for Aboriginal organizations, policy makers and health care administrators in all regions of Manitoba to creatively and actively design programs that can engage and support women with

diabetes. Care for women known to have T2DM who may be considering a pregnancy should have readily available pre-conception care and counselling available to them in all geographical locations.

The prevention of GDM is one of the key potential approaches for the prevention of T2DM (Aljohani et al., 2008a). Clinical care for women with either a history of or risk for GDM, should effectively and creatively offer both medical attention and additional resources for education of appropriate nutrition and encouragement of increased physical activity (Aljohani et al.). Women whose pregnancy is impacted by either T2DM or GDM should also be offered care that includes diabetes management and youth onset T2DM prevention strategies targeted during pregnancy. Due to the known interplay of social, environmental and behavioral risk factors that occurs in addition to effects of genetics and genetic susceptibility (Reinehr, 2013) all interventions and clinical care requires creative thought to developing primary care programs and spaces that respect cultural safety for this population (Sellers, Wicklow & Dean, 2012).

Role of nursing. Firstly, nurses are leaders in the support of breastfeeding – both at home and in hospital. Their role will be a large one in efforts aimed at both creating awareness of the importance of breastfeeding for reasons associated with diabetes, and in supporting mothers to breastfeed their infants. Nurses will be advocates for these mothers and their families, to create environments that support breastfeeding, such as educational offerings and home support for women needing on-going support. This study's results suggest that even a few days of breast milk may significantly decrease the rates of youth onset T2DM then nursing care and leadership within the hospital setting must work together to further increase rates of breastfeeding in hospital. Efforts directed at increasing breastfeeding support in the hospital may have staffing implications and require nursing management to support this endeavour.

Nurses, trained with both clinical skills and the ability to communicate with compassion and sensitivity will be poised to work in interdisciplinary teams that attempt to manage diabetes in pregnancy. Addressing issues such as obesity, weight gain in pregnancy and nutrition are areas that nursing can be involved in. Additionally, nurses possess the skills to effectively assist mothers in managing both T2DM and GDM during pregnancy with tasks such as glucose monitoring, and supporting adherence to medication regimes including insulin administration. Nurses will need to be resourceful while supporting women and their families in their attempts to strive for health while managing poverty and lifestyle challenges.

Care of women who either have diabetes in pregnancy, or are at risk for diabetes in pregnancy, should be cared for by an interdisciplinary team composed of nurses, physicians, dietitians, social workers, lactation consultants and exercise physiologists and with access to lab and fetal assessment support. Ongoing support for mothers and families would be necessary to support healthy lifestyle changes, and care should begin for these women in the pre-conception period and continue through early post-partum. Ideally, the establishment of such a clinical program focusing on diabetes in pregnancy would have a built in research and/or quality component, lending itself to contribute to the scant research areas that have been identified.

Implications for Future Research

Maternal BMI and weight. Working within the constraints of the data available, this study was unfortunately unable to assess maternal BMI and weight in the stages of pre-pregnancy, pregnancy itself and post-pregnancy. Therefore, there was an inability to explore the relationship of these weight factors and address questions relating to rapidity of perinatal weight gain, range of weight gain and pre and post-pregnancy body mass index and their relationship to

youth onset T2DM. The effect of pre-pregnancy overweight and obesity has been documented as contributing to large for gestational age (LGA) infants (Black, Sacks, Xiang & Lawrence, 2013; Lawlor et al., 2011; Salsberry & Reagan, 2005). With this study having confirmed a significant relationship between LGA infants and youth onset T2DM as previously described, it would be ideal to document these attributes in the health record. Furthermore, future studies in this same population are recommended to focus on maternal weight, body mass index and maternal weight gain throughout pregnancy and determine the association with youth onset T2DM.

Maternal smoking. It is unfortunate that rates of maternal smoking during pregnancy could not be captured in this study. With an association already reported linking maternal smoking to T2DM in adults, it is necessary for further studies within the pediatric population to be conducted that would examine that relationship that has been reported by authors such as Somm et al. (2008). While a retrospective chart review could potentially gather the information needed, a limitation of assessing smoking in pregnancy as reported by the mother, will be the mother's willingness to self-report a behavior that has known stigma and negative social connotations.

Maternal diabetes. It remains essential that health researchers determine whether identification and treatment of GDM can interrupt the current cycle of diabetes leading to more diabetes (Metzger et al., 2008). Future research is needed to determine whether better glucose control can be achieved throughout pregnancy that would prevent diabetes in the offspring of diabetic mothers (Dabelea, 2007). Randomized controlled trials and systematic reviews are needed to determine whether improved glucose control and weight gain patterns can be achieved throughout pregnancy that would prevent consequences for the offspring (Dabelea & Crume, 2011).

Non-significant Findings

The discussion thus far has emphasized those findings which conveyed statistical significance, however equally as important are those findings that were not significant. Complications of diabetes were neither common nor found to be significant in their association with youth onset T2DM. We chose to examine rates of maternal diabetes complications expecting their presence to be a surrogate for worsening diabetes, or declining glycemic control; however diabetes complications in the childbearing age are not common. ACE inhibitor medications, often used for their renal protective effect in diabetes and said to be a surrogate measurement of diabetes complications, was rare when examined in the mothers of this study. Though the use of ACE inhibitors may indeed reflect presence of complications in diabetes, their contraindicated use in pregnancy lends itself to results that were expected.

Theoretical Frameworks: Applicability to Further Research and Clinical Care

The theory of self-care. The theory of self-care is based on the fundamental idea that a relationship exists between deliberate self-care actions and the development and functioning of individuals and groups (Meleis, 1997). With a demonstrated association between maternal diabetes and the development of youth onset T2DM, it is essential that the self-care of childbearing women aimed at lessening the effects of diabetes, be supported. Self-care including exercise, healthy eating and availability of quality prenatal care needs to be encouraged and supported. With self-care defined as “the practice of activities that individuals perform on their own behalf in maintaining life, health and well-being” (Orem, 1985, p. 86), it seems that all tasks related to prevention or management of maternal T2DM do encompass a requirement of self-care and thus support the use of this theory in this study.

Self-care is not limited simply to a person providing care for him/herself, but also includes care offered on behalf of the person (Orem, 2001). Strategies aimed at promotion of breastfeeding as a means of lessening T2DM will require a component of self-care, in effort to support women and families to both initiate and continue breastfeeding their newborn. All clinical interventions within the pre-conception, prenatal and postpartum periods will demand self-care as offered by the individual as well as the families and systems that support these women. Interventions designed too, with a self-care theory in mind could strengthen feelings of self-efficacy and motivation – traits that could possibly be assistive in creating a healthier lifestyle, higher education levels and thereby lessening poverty and the effects of poverty within a family unit. With a known relationship between lower maternal income and youth onset T2DM, it is important to acknowledge the challenge to effecting self-care on a limited income; policy makers will need to be aware of this association as supportive funding and programs are urgently needed.

The social ecological theory. The social ecological theory supports the idea that efforts aimed at preventing youth onset T2DM should focus on promoting maternal health behaviours before and during pregnancy and on breastfeeding and proper infant and child nutrition in the postpartum and early childhood development periods (Egger & Swinburn, 1997; Willows, Hanley & Delormier, 2012). Due to the multifactorial nature of youth onset T2DM, it makes sense that both prevention and treatment strategies be multifactorial as well; the socio-ecological theory can effectively guide the design of such strategies.

One such prevention strategy speaks to three elements of prevention in this population, and is proposed by McIntyre, Thomae, Wong, Idris and Callaway (2009). The concept of a triple prevention strategy aimed at 1. Prevention of diabetes, 2. Prevention of pregnancies in women

with poorly controlled T2DM, and 3. Prevention of further complications when a pregnancy is complicated by T2DM may be a potential place to start. Arguments for costs associated with such a prevention program need to explain that while costly, any investment in preventive programs, rapid diagnosis, and aggressive treatment among women either already impacted or at high-risk for diabetes, may offer high returns in improved health not only throughout the mother's life but also for many generations to come (Osgood, Dyck & Grassman, 2011).

A multifactorial study by Black, Raine and Willows (2008) details how multiple, interconnected influences on weight gain in pregnancy were observed and supports the suggested use of the socio-ecological theory in designing weight interventions in the prenatal period; interventions would require a multilevel, multi-sectorial approach to population based diabetes prevention. Weight related care and intervention should begin in the pre-conception period and early prenatal period, whereby interventions that would effectively help women lose weight and/or control weight gain during the pregnancy would be employed (Black et al., 2013).

This same theory proposes that any individual behavior is supported and/or influenced by numerous other systems and groups (Wandersman et al., 1996); furthermore, lasting behavior change requires programs that target multiple levels of influence (Emmons, 2000). An example of the need to cultivate a multifactorial and socio-ecological approach can be found when discussing the association between lower maternal income and youth onset T2DM. A socio-ecological systems approach to lessening both low income effects in child-bearing women and those at risk of T2DM, will require the effort and support of government agencies, community systems and clinical care providers. Understanding barriers to breastfeeding in the population most at-risk of both T2DM and youth-onset T2DM necessitates a socio-ecological approach that

supports health behavior change in the mother that is associated with positive health benefits to the child.

A look back at Figure 1 (in Chapter 2), illustrates the interplay among levels that affect health – in that example the model is used to understand childhood obesity (Willows, Hanley & Delormier, 2012). Numerous parallels between childhood obesity and youth onset T2DM can be drawn, and therefore this theory was a useful guide in this study. Searches were conducted in effort to locate studies which used a social ecological model and then were able to discern which of the levels were most responsible and/or most easily intervened within – in the example of childhood obesity. It is plausible that if interventions were designed using a social ecological model and then targeted at levels within that model (i.e. examining interventions within the “community and home environment” instead of the “built environment” if that is most likely the level which success would be met) then perhaps a gain towards lessening rates of youth onset T2DM would be achieved. Several Indigenous scholars argued that the distal determinants impacted intermediate determinants, which in turn affected the proximal determinants of health (Adelson, 2005). Therefore, health care providers may need to refocus their attention on the distal determinants of health and lobby for more equitable health and social policies to prevent T2DM.

Using two theories to ground this study provided a broad lens and facilitated a strengths-based approach to the prevention, early detection, and management of youth onset T2DM. . As described earlier in this chapter, nurses will play a key role within the clinical care of this population and within intervention studies related to decreasing rates of youth onset T2DM. Nurses are leaders in promoting self-care of the individual and in supporting self-care behaviours of care-givers; nurses also have the ability to effect change and offer support at all levels within a

social ecological model. As efforts move forward in conquering issues surrounding and related to diabetes in pregnancy, nursing will be called upon to be leaders within interdisciplinary teams and federal, provincial, and regional government agencies.

Study Strengths

The most significant strength of this study is the size of the cohort of youth with T2DM that comprised the study's sample. The majority of researchers who have explored relationships between the intrauterine environment and the occurrence of youth onset T2DM have focused primarily on the recruitment of the biological mothers as their case and control groups. The uniqueness of this population-based study, is that it accessed and analyzed all de-identified health records of youth born in a Manitoba hospital who were diagnosed with T2DM between the years 1986-2011. While the overall numbers may initially be regarded as "small," the unusually high precedence of youth onset T2DM in Manitoba makes this a representative and adequate sample size. Though some of the reported findings are neither novel nor unique, findings gained following review of this large cohort will be helpful in furthering our understanding of this newer face of diabetes – youth onset T2DM.

Efforts to match on sex, age and geographical region on a 5:1 ratio of controls to cases, is a major strength of this study. Matching enhances the overall comparability of our two cohorts and contributes to the scientific merits of the study. For example, the study's results are generalizable to the overall population. Analysis of findings within a multivariate conditional regression model, versus only univariate or unconditional regression modelling, strengthens the validity of findings.

Few studies have formed their sample by initially recruiting youth and then retrospectively analyzing the pregnancies that led to those offspring, as was done in this study. Instead, the vast majority of population based studies have established cohorts of women and then retrospectively examined factors of their pregnancies that may have influenced the intrauterine environment and the relationship of those factors associated with increased rates of youth onset T2DM. Having first established our sample with youth in a designated age group, and controlling for confounding variables such as geographical location and sex, this cohort lends itself to a thorough multivariate analysis that affords confidence in its findings. Numerous variables pertaining to the intrauterine environment were examined with; several newly identified key factors. The ability to closely examine the variable of *size for gestational age* was one such variable that has received limited examination when associated with youth with T2DM.

Study Limitations

Several limitations need to be acknowledged. One limitation is the lack of data on maternal smoking, which limited the ability to examine associations between this health risk factor and the development of youth onset T2DM. The available records that could capture maternal smoking in this population included only those records of the Baby First program. Within those records, only 40 records were located – each of which were incomplete. The Baby First program is an initiative of the Province of Manitoba and as such is not administered on federal land, including Indian Reserve lands. With increased rates of both adult and youth-onset T2DM documented in First Nations people in Manitoba, it is likely that a large number of our sample is of First Nations heritage, though we were unable to gather First Nations status within this study. The unavailability of The Baby First program within the First Nations communities,

and therefore not having this program's results and/or information for at least some of our cohort, is a limitation of this dataset.

The use of secondary datasets, such as those records housed at The Manitoba Centre for Health Policy, though convenient and readily accessible do have some limitations. Warranting discussion is the fact that several outcomes in this study were based largely on the review of diagnostic codes assigned in outpatient physician billing records. Physicians are only able to assign one diagnostic code for each patient encounter and therefore it is possible that some diagnoses may have not been captured, especially if multiple diagnoses could have been assigned.

Conclusion

Certainly the pandemic of T2DM in adults is upon us; however, it is especially alarming to observe the rapidly rising rates of T2DM in the youth around the world (Pettitt et al., 2014). The high rates of youth onset T2DM that have been documented in Manitoba garner special attention (Amed et al., 2010). Efforts aimed at detecting, treating and documenting the natural history of this disease has begun, but health care professionals' work is far from over. A continued and coordinated multidisciplinary approach is required, one that involves public health providers, clinicians, educators, scientist, policy makers and the people at risk (Nolan, Damm & Prentki, 2011). The findings of this study argue that efforts aimed at preventing a pandemic of T2DM in the youth of our country must begin in the pre-conception period and continue throughout pregnancy and early life of the offspring, if we are to re-route the current path of increasing rates of youth onset T2DM in youth around the globe.

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Appendix 1.0

Youth Variables

- Sex
- Gestational age at delivery
- Birth weight
- Mode of delivery (vaginal vs. caesarean)
- Mode of infant feeding at time of discharge from hospital
- Youth onset T2DM cohort-
 - Age at diagnosis of T2DM
 - RHA at time of diagnosis of T2DM
 - BMI at time of diagnosis of T2DM

Maternal Variables

- Age at time of index youth's birth
- Maternal income quintile at time of youth's birth
- Presence of prevalent T2DM
 - If yes,
 - Age at diagnosis of T2DM
- Presence of gestational diabetes
- Maternal complications of diabetes
 - Peripheral Vascular Disease
 - Cardiovascular Disease
 - Cardiovascular Accident
 - Neurological
 - Opthomalogical
 - Renal
 - Retinopathy
 - ACE therapy use
 - Pre-eclampsia
- Gravidity and Parity
- Maternal substance use – alcohol, drugs and smoking

Appendix 2.0 - ICD-9CM Procedure and Diagnostic codes

Healthcare utilization codes used to identify complications in mothers of youth cohorts at time of delivery.

Type of Complication	*ICD-9CM	Type of Complication	*ICD-9CM
Renal	Procedure Codes: 581 (Nephrotic Syndrome) 583 (Nephritis & Nephropathy) 585 (Chronic Kidney Disease) V56 (Encounter for Dialysis & dialysis catheter care) V45.1 (Real dialysis status) 791 (Proteinuria) 91 (Early syphilis) 791 (proteinuria) Diagnostic Codes: 39 (Hemodialysis) 55 (Kidney transplant)	Cardiovascular	Diagnostic Codes: 410 (Acute MI) 411 (Increased Blood Pressure) 412 (Previous MI) 413 (Angina Pectoris) 414 (Ischemic Heart Disease) 36 (Meningococcal Meningitis)
Ophthalmologic	Procedure Codes: 14 (Laser Therapy) Diagnostic Codes: 362 (Diabetic Retinopathy) 365 (Glaucoma) 366 (Cataract) 369 (Blindness & low vision)	Peripheral Vascular Disease	39 (Actinomyotic infections) 84 (Malaria) 440 (Atherosclerosis) 441 (Aortic aneurysm) 442 (Other aneurysm) 443 (Other peripheral vascular disease) 445 (Atherosclerosis) 785 (Symptoms involving CV system)
Neurological	Diagnostic Codes: 337 (Autonomic neuropathy) 354 (Mononeuropathy) 355 (Mononeuritis) 356 (Hereditary & peripheral neuropathy) 357 (Inflammatory & toxic neuropathy) 358 (Myoneural disorders) 536 (Gastroparesis) 713 (Arthropathy & GI disorders)	Cerebrovascular Accident	430 (Subarachnoid hemorrhage) 431 (Intracerebral hemorrhage) 432 (Other unspecified intracranial hemorrhage) 433 (Occlusion & stenosis of cerebral arteries) 434 (Occlusion of cerebral arteries) 435 (Transient cerebral ischemia) 436 (Acute but ill-defined CVD) 437 (Other & ill-defined CVD) 438 (Late effects of CVD)

*International Classification of Disease 9th Revision, Clinical Modification