The Relationship Between High/Low Birth Weights

And Future Development Of Diabetes Mellitus

Among Aboriginal People:

A Case-Control Study Using Saskatchewan's Health Data Systems

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ABSTRACT

In recent decades, rates of type 2 diabetes mellitus (T2DM) and diabetic complications have reached epidemic proportions among Canadian Aboriginal people. Evidence in several populations suggests that abnormal birth weight, particularly low birth weight (LBW) and possibly high birth weight (HBW) may be linked to the development of T2DM. LBW often reflects poor maternal health/ nutritional status which may interfere with normal pancreatic development. HBW is a frequent complication of diabetic pregnancies which are associated with obesity and carbohydrate intolerance in adulthood. Since Saskatchewan Aboriginal newborns historically had higher rates of LBW, and more recently have experienced higher HBW rates, it follows that sub-optimal maternal/ fetal health may be important in the epidemic of T2DM in this population.

This thesis describes a case-control study that used Saskatchewan Health databases to determine the relationship between birth weight and T2DM. A sample of 846 adult diabetic Registered Indians (RI) were age and sex matched to three control groups: 1) non-diabetic RI, 2) diabetic general population (GP) subjects, and 3) non-diabetic GP subjects. RI subjects were identified as such by the provincial Health Insurance Registration File.

The results of this study show a significant association between HBW (> 4000 grams) and T2DM for RI people [odds ratio (OR) 1.63; 95% confidence interval (CI) 1.20, 2.24]. This association increased in strength from the middle to the latter part of this century and was found to be stronger for RI females than RI males. The comparison of birth weights within the four study groups revealed that diabetic RI (16.2%) were significantly more likely (p<0.05) than controls (10.7%, 10.0%, 7.5% respectively) to have HBW. An association between LBW and T2DM (< 2500 grams) was not evident within either RI or GP sample populations.

The findings of this study support the hypothesis that HBW and its causes may be risk factors for T2DM among RI people. Programs to prevent gestational diabetes, and to diagnose and optimally manage diabetes during pregnancy could help to reduce rates of diabetes in future generations of Aboriginal peoples.

ACKNOWLEDGEMENTS

To my parents, Frederik and Maria Klomp;
to Roland; and to the memory of Cleo.

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DISCLAIMER

This study is based in part on data provided by the Saskatchewan Department of Health. The interpretations and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

1. INTRODUCTION

Canadian Aboriginal people are experiencing an epidemic of type 2 diabetes mellitus (T2DM) and its complications[1-17]. The occurrence of T2DM within Aboriginal communities is a relatively recent phenomenon, increasing most dramatically since the mid 1900's. This event is believed to be the result of a combination of genetic and environmental factors which have been enabled by exposure to Euro-American influences and the subsequent erosion of traditional Native lifestyles. In particular, a hereditary predisposition towards carbohydrate intolerance and caloric conservation superimposed on changes in diet and activity could explain the high prevalence of obesity, a condition which exacerbates insulin resistance and increases the risk of developing T2DM.

Aboriginal women in North America have a greater risk of developing gestational diabetes (GDM) than women in the general population[18-23], this leads to increased rates of macrosomia (birth weight > 4000 grams) and perinatal complications. In Saskatchewan northern reserves, increased rates of GDM were found to occur in Aboriginal women even when the prevalence of T2DM was low in those same communities[24], suggesting that the epidemic of T2DM in Saskatchewan is at a relatively early stage and is probably still evolving. Long-term effects of GDM on the offspring include childhood obesity, and a propensity for these children to develop early age onset T2DM[25-28]. Women with GDM are also more likely to develop T2DM[21,29-32]. These long-term complications on both mother and child implicate an important contributory role of GDM in T2DM development among Aboriginal people.

A relationship between LBW and T2DM in later life has been observed in several different populations[33-41] including North American Indians[42] and has been interpreted as a reflection on poor maternal/fetal nutrition[43,44]. Specifically, it has been proposed that fetal undernutrition causes reduced pancreatic islet cell development leading to an increased risk for T2DM. Since Saskatchewan Aboriginal newborns have had higher rates of LBW in the past[45,46], this could also be a contributing factor in the current rising rates of T2DM among Aboriginal people.

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2. LITERATURE REVIEW

2.1   Identification of the Literature

MEDLINE was searched for relevant journal articles from the biomedical literature published in English from January, 1983 through October, 1997. The main medical subject heading and subheading combinations used were as follows: "Diabetes Mellitus, -Non Insulin Dependent"; "Diabetes Mellitus -Insulin Dependent"; "Diabetes, - Gestational"; "Indians, -North American"; "Ethnic Groups"; "Racial stocks"; "Birth Weight"; "Fetal Macrosomia"; and "Infant Low Birth Weight". As a result, 769 abstracts were reviewed and from these, 195 were determined as relevant to the subject of this paper; the majority of which were obtained as full articles and reviewed in more detail.   Pursuit of selected references indicated in these journal articles resulted in the review of an additional 50 or so papers. Critical evaluation of the literature was carried out according to the guidelines proposed by Greenberg[47].

2.2   Nomenclature

Throughout the literature review of this thesis, the I will use the same terminology related to North American Indigenous peoples as indicated in the corresponding source publication. To clarify the diverse nomenclature referent to this population, Young[48] outlines the following guidelines:

> The term *Native American* refers to the indigenous populations of North America that occupied the continent when members of various European nations first arrived. It encompasses North American Indians, Eskimos (Inuit) and Aleuts....*Native American* is widely accepted as the "correct" term In the United States, which is often expanded to the term *American Indian* in Government publications.
>
> ...In Canada, the term *Native* continues to be used by some Native organizations, although *Aboriginal* seems to be preferred. In constitutional negotiations over self government, three Aboriginal groups are recognized in Canada: Indians, Inuit and Métis. The term *Indian,* while still widely used by many Indians themselves, is slowly being replaced by *First Nation....*In

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Canada, a distinction is made between "status" ("Treaty", "registered"), and "nonstatus" Indians, which is defined legally by the Indian Act. Such status could be lost in the past through enfranchisement or, in the case of Indian women, through marriage to a non-Indian. (Alternately, such status could be gained by a non-Indian woman through marriage to an Indian man):-

...The term *Métis* is used only in Canada, and refers to a distinct cultural group that originated from mixed Indian-white marriages in the early settlement of the Canadian West. Although officially considered as Native, many Métis are not "status" Indians.

In the remaining chapters of this thesis, nomenclature that is both accurate and respectful of Canadian Indigenous peoples will be applied. *Aboriginal* will be used as an all encompassing term referring to all peoples of Indian, Inuit and Métis heritage, including nonstatus Indians. In keeping with current trends within the field of Native studies, I will use the upper case for the term *Aboriginal*. When the discussion pertains to only one group, such as Registered Indians, that fact will be indicated.

The term *non-Aboriginal* is used to refer to general population Canadians who are of "other than Aboriginal" heritage. In the data set used for this thesis, the sample population for non-Aboriginal people was taken from all Saskatchewan people other than registered Indians. Although this sample probably consists largely of non-Aboriginal Canadians, it will almost certainly contain some non-registered Indians and Métis. For practical purposes, I will use the term *general population* to refer to this comparison group which technically consists of "all Saskatchewan residents other than registered Indians, including non-registered Indians and Métis".

2.3 Epidemiology of T2DM and North American Indians

2.3.1 Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia and disturbances of carbohydrate, fat and protein metabolism associated with absolute or relative deficiency in the secretion and /or action of the hormone insulin.[49] The World Health Organization (WHO) classification of DM (Appendix I) considers the two major clinical types of diabetes as Type 1 DM (T1DM) or insulin-dependent diabetes mellitus (IDDM) and Type 2 DM (T2DM), or non-insulin-dependent diabetes (NIDDM). T1DM typically affects children and young adults whereas T2DM tends to appear in adults over age 40. T2DM is by far the most common form of diabetes, accounting for 85-90% of all cases[50].

Impaired glucose tolerance (IGT) is an intermediate category between diabetes and normal glucose tolerance and frequently represents a transient stage during the development of T2DM[50]. Individuals with IGT are at higher risk of developing T2DM and its complications than persons with normal glucose tolerance.

The pathogenesis of the two main clinical types of diabetes involves different underlying mechanisms. T1DM is recognized as an autoimmune disorder in which pancreatic beta-cell destruction occurs in a genetically susceptible host[50]. T2DM is believed to result from a complex admixture of genetic predisposition, increased resistance to insulin and, eventually, from a decrease in insulin production[51][52]. Obesity, particularly the abdominal/visceral type[53], and increasing age are contributing factors to insulin resistance; hypertension and lipid abnormalities may also play a role.

2.3.2 General History and Background

Diabetes was described more than 2000 years ago and has featured in the history of modern medicine for the past two centuries[50]. A recent summary of age-standardized global estimates of diabetes by King[54] showed striking world wide differences in prevalence rates of diabetes that ranged from the lowest in traditional communities of some developing countries (0 - <3%) to the highest in Micronesian

Nauruans (40%) and the Pima / Papagao Indians of Arizona (50%). The study identified high risk populations to include some Arab, migrant Asian Indian, Chinese and Hispanic Americans with prevalences of 14-20%. A trend in rising prevalence of diabetes with advancing age was found in all populations and the male:female ratio of diabetes prevalence varied markedly between populations with little discernible trend, although IGT was generally more common in women.

The most up-to-date studies in the Canadian and United States (US) general population estimate the age-adjusted prevalence of diabetes to be about 6%[54][55][56]. Incident studies of diabetes are scarce; however, available reports describe a relatively constant[57] or slowly rising[58][59] incidence of diabetes in North America. Temporal changes in the rates of diabetes are difficult to estimate because of different screening and diagnostic methodologies used in earlier epidemiological studies. However, international acceptance of standardized diagnostic criteria for DM and IGT, such as those proposed by WHO in 1980[60], has enabled more reliable between and within population comparisons of diabetes prevalence and incidence.

The wide range of sampling techniques used in studies has added to the difficulty of reviewing work in diabetes epidemiology. It has been reported that data based on physician diagnosed diabetes, such as registries and interview surveys, may grossly underestimate the frequency of diabetes by 50%[61]. The accumulation of diabetes prevalent cases has been partially attributed to longer survival of diabetics and natural aging of the population[58]. Other factors such as improved access to health care services, increased surveillance for and earlier recognition of the disease could also contribute to this phenomenon.

Diabetes has important public health implications because of its association with a number of acute, as well as chronic long-term complications. These conditions include coronary and peripheral vascular disease, retinopathy, nephropathy and peripheral neuropathy. This leads to premature morbidity and mortality[62] as well as contribute to increased health service utilization[63] and the rising economic burden of disease[64].

2.3.3 History and Background of T2DM in North American Indians

In North America, many Aboriginal populations are experiencing higher rates of diabetes than in the general population. This is a relatively recent phenomenon. Prior to 1940, diabetes was an almost unknown condition among North American Indians; however, since 1950 a dramatic rise in diabetes prevalence rates has marked this disease an epidemic in contemporary Aboriginal communities[1,2]. While the risk of T1DM is highest among Caucasian populations[65], the type of diabetes that occurs in Aboriginal peoples is almost exclusively T2DM[3]. Unless otherwise specified, all discussion on diabetes in this paper refers to T2DM.

The last two decades have witnessed a surge of epidemiological studies concerning diabetes among Canadian and American Indian tribes. In Canada, Young found that apart from remote northern areas, the prevalence of diabetes is 2-5 times higher among Native people than other Canadians and that the degree of this difference parallels the duration of exposure to European lifestyle influences along a north-south gradient of latitude[4]. In Saskatchewan, a 1937 report[5] stated no cases of diabetes were detected among 1500 Status Indians. In contrast, a 1990 study carried out on Saskatchewan reserves[6] showed that the age adjusted prevalence of diabetes among aboriginal adults older than 20 years was 9.7% compared to 6.1% for adults in the general population. The latter study also showed a female preponderance in the prevalence of diabetes among Saskatchewan Indians although Young has found that sex differences in diabetes prevalence are less apparent where the changes in Aboriginal life ways began in an earlier era[7]. In a remote northern Ontario community Native women were also found to have a higher prevalence of obesity, IGT and T2DM, all occurring at younger ages when compared to Native men[66].

Although intertribal differences have been found to exist, many studies regarding diabetes and North American Indians generally report a preponderance of female cases of T2DM and a younger mean age of disease onset, particularly in women, when compared to diabetics in the general population[16,17,67,68,69]. Among the Pima Indians of Arizona, incidence rates of diabetes are rising most visibly in the younger age groups[70,71]. In Manitoba, a trend toward earlier onset of T2DM for Natives during the young teen years has also been observed, with a prevalence of at

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least 0.53 per 1000 children 7-14 years of age[72][73]. This appears to be much higher than in the general population where T2DM is exceptionally rare among children.

Both Canadian and US national surveys have demonstrated an increased risk of mortality from diabetes among North American Indians. In a review of mortality on Canadian Indian reserves, the risk of death from diabetes was 2.2 and 4.1 times higher for Native men and women respectively than Canadian men and women in general[74]. An excess in diabetes associated mortality among Native Americans compared to the US all-races population has also been observed[75][76].

Aboriginal communities are also suffering high rates of diabetic related complications. In Saskatchewan, end stage diabetic renal failure occurred in Aboriginal diabetics at seven times the rate seen among non-Aboriginal diabetics[8], which supports the trend found in other Canadian[9] and US[10][11] studies. Rates of diabetic retinopathy in Natives have been reported to be similar to or higher than in non-Native diabetics in Canada[12] and the US[13][14]. Lower extremity amputations were four times the rate in Pima Indians with T2DM than in US general population subjects with diabetes[15]. In Canada, high rates of other diabetic related complications, including ischemic heart disease, stroke and peripheral vascular disease have been documented in Aboriginal people with diabetes[16][17].

The history of diabetes in North American Indians parallels that of other 'New World' populations such as Pacific and Australian indigenous peoples, who have experienced rapid socioeconomic modernization during this century. To explain this phenomenon many look to the unproved but yet to be refuted "thrifty gene" hypothesis proposed by Neel[77]. The thrifty genotype is thought to have conferred a survival advantage to individuals in hunter-gatherer and early agricultural societies who were subject to periods of nutritional hardship, by favouring caloric conservation in the form of fat deposition during periods when food was abundant. However, the intense exposure to European influences has rendered the genotype disadvantageous in an environment of nutritional excess and decreased physical activity, favouring instead the development of obesity and T2DM.

2.3.4 Etiology and Risk Factors

T2DM is considered to be a disease of multifactorial etiology determined by a combination of genetic and environmental factors, although the complex interplay of these factors is poorly understood. To date, the chief potential risk factors for T2DM have been identified as heredity, obesity, physical inactivity, excessive dietary substances and certain metabolic factors. The relative importance of these determinants appear to vary among different population and ethnic groups[59]. For example, among the Pima and other American Indians, environmental factors are thought to have a major interactive effect on the expression of the diabetes-susceptibility genotype[78]. Despite many descriptive studies, relatively little is known about the risk factors for diabetes in Aboriginal peoples with the exception of the Pima Indians who have participated in a comprehensive longitudinal study of diabetes epidemiology since 1965[79].

T2DM shows strong family aggregation, however, a clear genetic pattern has not been defined and no single gene locus has been identified that significantly contributes to T2DM susceptibility. Data supporting the familial transmission of diabetes in the Pima suggest that susceptibility to diabetes with an early age onset is inherited by the offspring. In studies involving parent-offspring pairs among the Pima the risk of T2DM was found to be 2.3 times higher for offspring with one diabetic parent and 3.9 times higher for offspring with two diabetic parents, compared to those with neither parent diabetic and adjusting for age and obesity[80]. In offspring <25 years, T2DM occurred only with at least one diabetic parent and was more frequent if that parent had diabetes of early onset (<45 yrs)[81]. It should be noted that a genetic explanation of familial aggregation by itself can be questioned by considering that common exposure to (familial) environmental factors could have been responsible.

Further support for a genetic role in diabetes etiology is derived from studies involving twins, and populations with different genetic admixture such as that between Aboriginal and Caucasian people. Several US studies have shown that diabetes prevalence correlates in a dose-response relationship with the degree of Indian ancestry as estimated by skin colour measurements[82], self report of Indian inheritance[68 83] or as determined by genetic evaluation[84]. These findings support the

contention that a North American Indian background is an important risk factor for diabetes.

Obesity is considered the strongest potential environmental risk factor for T2DM, although many unanswered questions surround the complexity of this relationship. The duration and degree of obesity are thought to be more important to the risk of diabetes than current obesity[85]. *Central* or *truncal* obesity appears to be predictive of T2DM and is believed to play a critical role in the etiology of diabetes either in addition to, or instead of, overall obesity[86][87].

Widespread obesity has been observed among many modern day groups of North American Indians[88][89][90]. A high prevalence of obesity has also been documented in children and adolescents of the Pima[91], Cherokee[92] and Navajo[93] Indian tribes. As recently as the 1940s, surveys in northern Manitoba[94] and Ontario[95] reported Canadian Bush Indians to have "a considerable degree of underweight" suggestive of malnutrition, with underweight most prevalent (> 50%) in adolescent girls and women during child bearing years. Three decades later, a Nutrition Canada survey[96] showed that 60% of Native women between 20 and 40 years were at moderate to high risk for obesity compared to the Canadian national rate of 43%. Confirmation of this trend was provided by a 1987 survey of northern Canadian Indians in which the prevalence of obesity in Natives exceeded that of the Canadian general population in all age-sex groups. The study identified the predominant pattern of obesity as the central type and the overall level of obesity in Native women was higher than in Native men[97].

In many different populations, cross-sectional surveys have demonstrated a strong and consistent positive association between prevalence of T2DM and mean body weight of that population. However, these studies can be confusing because weight loss can actually be a manifestation of diabetes. In the 1992 analysis of Canadian Heart Health surveys, Reeder et al[55] found a parallel increase in prevalence of diabetes and obesity, especially abdominal obesity, with age, among Canadian adults. In a recent Saskatchewan study, Dyck and Tan[24] showed that rates of obesity and self-reported diabetes in three remote Aboriginal communities increased with increasing geographic accessibility to urban centres. In all three communities, Aboriginal women had higher rates of obesity and diabetes, but sex differences were less apparent in the most accessible village where, presumably,

non-traditional lifestyles had been adopted earlier. According to Dyck and Tan, these findings emphasize the importance of environmental determinants of diabetes and suggest that Aboriginal females were the first to be consistently affected by lifestyle changes during early stages of acculturation.

In a longitudinal study of the Pima, Knowler et al[80] showed that a continuous increase in diabetes incidence was strongly related to increasing measures of preceding obesity, as estimated by body mass index (BMI: weight/height^2). Current obesity and a history of parental diabetes were found to increase incidence rates synergistically; the highest rates were seen in obese subjects with at least one parent who had early onset diabetes (<45 yrs). The authors concluded that obesity magnifies the risk of T2DM in the genetically susceptible and suggested their findings, together with the increasing incidence of diabetes in the Pima, further supported the interaction of environmental and genetic etiologic factors related to T2DM in this population.

The independent effects that diet and physical activity have on the emergence of diabetes are not yet clearly defined and are especially difficult to determine since these factors may be diabetogenic through enhancing the risk of obesity. An increased risk of T2DM has been associated with the consumption of specific nutrients such as carbohydrates, sucrose, fat and lack of fiber as well as total caloric intake[59 98 99]. Cross-sectional studies have correlated the prevalence of diabetes with non-traditional dietary patterns in many Native populations[48]. Several prospective studies have provided evidence to suggest that exercise has a protective effect against the development of T2DM, especially in people who are at greatest risk for the disease [100 101 102]. An investigation comparing two geographically distinct populations of Pima ancestry showed that a traditional lifestyle (characterized by diet including less animal fat and more complex carbohydrates and greater energy expenditure in physical labour) may protect against obesity and T2DM, despite a similar potential genetic inclination to these conditions[103].

The role of socio-economic status as a risk factor for T2DM is variable in studies done to date. Historically, diabetes was considered to be a disease of the rich and ruling-class[59]. This pattern appears to be changing in contemporary societies and seems to correspond to the degree of that society's "affluence" and modernization. Low socio-economic status has been linked to higher frequency of

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T2DM in the US[104] and England[105] but in Central America, diabetes prevalence was reported to be four times greater among the upper classes than in the poor[106].

Other potential risk factors for T2DM include certain metabolic factors, particularly those associated with the event of pregnancy. Evidence to support the diabetogenic role of pregnancy and the intra-uterine environment will be discussed in sections 2.4 and 2.5 of this chapter.

2.3.5 Summary

In summary, it is clear that North American Aboriginal peoples are experiencing an epidemic of diabetes and its complications. The occurrence of T2DM within Native communities is a relatively recent event, increasing most dramatically since the mid 1900's. This phenomenon is believed to be the result of a combination of genetic and environmental factors which have been enabled by exposure to Euro-American influences and the subsequent erosion of traditional Native lifestyles. In particular, a hereditary predisposition towards carbohydrate intolerance and caloric conservation superimposed on changes in diet and activity could explain the high prevalence of obesity, a condition which exacerbates insulin resistance and increases the risk of developing T2DM.

2.4   Gestational Diabetes, High Birth Weight and T2DM

2.4.1   Introduction

The effects of the intrauterine environment on childhood growth and the development of T2DM in adult life have been the subject of a growing body of epidemiological literature. This section will discuss the contributory role of gestational diabetes in relation to T2DM development. Section 2.5 will discuss the evidence that implicates nutritional deprivation in utero in the etiology of T2DM.

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy[107]. The definition applies regardless of whether insulin is used for treatment or the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated the pregnancy. Interest in the diagnosis and treatment of GDM has grown because of its association with increased perinatal and maternal risks, many of which are related to large sized or macrosomic infants. GDM also has long-term implications for the health of both mother and child.

The pathophysiology of GDM is believed to arise from a number of factors that act to alter the blood glucose concentration during pregnancy[108]. By mechanisms poorly understood, it appears that an insulin-resistant state similar to T2DM may be characteristic of normal pregnancy[109]. This, combined with the tendency of certain hormones to increase maternal blood glucose, sets off a demand for increasing insulin production that progresses throughout pregnancy. In a small proportion of women, the insulin resistance phenomenon exceeds the capacity for insulin secretion. This results in glucose intolerance and/or the development of GDM, usually late in the second trimester.

Medically, GDM represents an area of ongoing unresolved controversy[110]. To date, there is no international consensus with regard to screening and diagnostic criteria for GDM, its treatment, and definitions of outcome measures such as macrosomia[107]. This impedes the comparability of GDM rates, risk factors and adverse perinatal/maternal outcomes in different populations. Also, the current definition of GDM encompasses a heterogeneous spectrum of glucose intolerance, so that significant degrees of unrecognized pregestational DM are possibly being

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diluted with milder forms of pregnancy induced glucose intolerance[111]. These "subsets" of GDM, may each have a different impact on pregnancy outcome, which further complicates the evaluation of epidemiological data.

2.4.2 GDM: Epidemiology and Risk factors

In North America, it is estimated that 3-4% of pregnant women are affected by GDM[112 113]. Several studies have provided evidence to support an independent effect of race on the prevalence of GDM; consistently higher rates have been reported in Oriental, Hispanic, Indian Subcontinental, Middle Eastern and African American women[114 115 116]. North American Aboriginal women also have an excess risk of GDM although data documenting the extent of the problem is scarce. Compared to national rates, higher rates of diabetes in pregnancy have been reported among Navajo (6.1%)[18 19], Yup'ik Eskimo (6.7%)[20], Pima (9.7%)[21] and Zuni (15.3%)[22] women.

In a 1988 Canadian national breast feeding survey[23], 6.1% of Inuit and Indian women indicated they had diabetes during pregnancy with rates as high as 16% in some regions of the country. On northern Saskatchewan reserves, Dyck and Tan[24] found that up to 16% of women over the age of 18 gave a history of GDM; high rates of GDM paradoxically occurred even in communities where the prevalence of T2DM was low. To interpret this phenomenon, the authors proposed that the diabetes epidemic among Saskatchewan Indians is at a relatively early stage and is probably still evolving. The authors also suggested that GDM may be one of the initial manifestations of carbohydrate intolerance in this population.

The most common risk factors identified for GDM include advanced maternal age, obesity, family history of T2DM, previous delivery of a macrosomic, stillborn or anomalous infant, previous pregnancy with GDM, abnormal glucose tolerance, and a history of certain obstetrical problems[109 111 117]. Twin pregnancy[118] and multiparity[111] have also been associated with a higher prevalence of GDM. For selective screening purposes, there is substantial evidence to suggest that the sole reliance on common risk factors fails to identify a high proportion of GDM[119 120]; many experts in the field therefore argue in favour of universal screening for GDM[107 121].

Recent analysis of about 15,000 pregravid women in The Nurses' Health Study cohort[122] (women without previous GDM or other known diabetes who reported

a singleton pregnancy) found that certain risk factors associated with T2DM also proved to be statistically significant independent predictors for GDM. These included advanced maternal age, first degree relative with T2DM, higher pre-pregnancy BMI, weight gain in early adulthood and non-white ethnicity. Mothers aged ≥ 40 had a twofold greater relative risk of GDM versus women aged 25-29, with risk increasing 4% for every year over age 25. The relative risk for GDM was 1.68 among women having a first degree relative with T2DM which increased further (1.9) when that relative was the mother. However, the risk for GDM was greatest (2.87) when diabetes was reported in both parents. Smoking at least 5 -14 cigarettes per day before pregnancy was also found to be an independent risk factor for GDM.

2.4.4 Maternal and Fetal Risks in GDM

Maternal risks from a gestational diabetic pregnancy are greater than from non-diabetic pregnancies; delivery by cesarean section is more frequent as are other complications such as toxemia and hypertension[109]. Women with GDM are likely to have it again in a subsequent pregnancy and are at greater risk of developing T2DM in the future. In North America, the reported rates of GDM recurrence have been slightly above 50%[123 124 125] and one Australian study found a recurrence rate as high as 84%[126]. These studies as well as others found that fetal macrosomia, maternal obesity, older maternal age, higher parity and previous use of insulin in the index pregnancy were most commonly predictive of GDM recurrence[127 128 129].

Several studies in Aboriginal and non-Aboriginal populations have used cumulative life table analysis to determine the excess risk of diabetes for women with previous GDM compared to controls who had non-diabetic pregnancies. The results can be summarized as follows: Pima women had a 28% excess risk within 4-8 years[21]; Australian women had a 30% excess risk by 17 years[29]; and women in Boston had a 62% excess risk after 24 years of follow-up[30]. All of these studies reported that recurrence of GDM, obesity and a greater degree of glucose intolerance in pregnancy were important predictors for diabetes later in life. In another study, a life table analysis predicted that Navajo women with previous GDM had a 53% likelihood of having T2DM within 11 years[31].

In an Australian study, Yue et al[32] observed differences in the average time between the onset of GDM and later development of T2DM for women of six different ethnic origins. They found that Aboriginal women had the narrowest "GDM-T2DM age gap" of all groups, and a five fold greater risk for susceptibility to T2DM compared to anglo-celtic women, after adjustment for BMI and maternal age.

Peters et al[130] investigated the long-term diabetogenic effect of a single pregnancy complicated by GDM in women who recovered normalglycemic status post-partum. Findings of the study revealed that a single additional pregnancy more than tripled the rate ratio of T2DM compared with women who did not have another pregnancy (adjusted for antepartum and postpartum glucose tolerance, postpartum BMI and weight change, breast feeding and months of contraceptive use). The independent effect of parity on the subsequent risk for diabetes remains controversial in the current literature. In studies that have controlled for obesity and age, some have reported that parity is associated with an increased risk for T2DM[131 132] whereas others have failed to demonstrate this association[133 134].

Adverse fetal outcomes associated with a GDM pregnancy include perinatal death, fetal macrosomia with its attendant risks, congenital malformations and certain metabolic disturbances such as hypoglycemia. Delivery of a macrosomic infant contributes to perinatal / maternal morbidity and mortality because it can result in birth trauma, fetal asphyxia and the need for cesarean section. Studies in the 1960's and 1970's[135 136] described excess perinatal mortality among women with GDM compared with non-diabetic pregnancies, but this is less likely with modern obstetrical care. The reported increase in congenital anomalies in diabetic pregnancies is seemingly related to poorly controlled hyperglycemia in early pregnancy and is largely restricted to offspring of women with preexisting diabetes[137].

2.4.4 Macrosomia: Epidemiology and Risk Factors

It has been estimated that of all women with "diabetes in pregnancy", about 90% have GDM and 10% have "overt diabetes" prior to pregnancy. This is usually T1DM[138]. Macrosomia is the most frequent complication independently associated with the diabetic pregnancy and is commonly defined as birth weight > 4000 g or birth weight above the 90th percentile for gestational age[139]. Macrosomia occurs in

approximately 20% of GDM pregnancies[109] with prevalence rates ranging from 10% to 32% in Caucasian populations[140]. Women with T1DM have twice the risk of delivering a HBW child than women with GDM[141].

In North America, infants weighing > 4000 g account for 8-10% of all deliveries in the general population; 1-2% of all infants weigh > 4500 grams (g)[142]. While GDM is commonly associated with HBW, several independent risk factors in the non-diabetic pregnancy have also been found to be associated with macrosomia. These include maternal obesity, gestational age >42 weeks, male sex[143] and multiparity (beginning at parity >2)[144]. Although advanced maternal age is often linked with high birth weight, it does not appear to an independent risk factor for macrosomia after multivariate analysis[145], even if the pregnancy is complicated by GDM[119 146].

According to Pederson[147], the pathogenesis of macrosomia related to GDM is a result of maternal hyperglycemia; this stimulates fetal hyperinsulinemia, which in turn mediates accelerated fuel utilization, adipose tissue accumulation and excessive growth. Pederson's hypothesis was the first to suggest a potential link between maternal metabolic control and fetal growth. Freinkel[148] further proposed the "fuel-mediated teratogenesis" hypothesis which suggests that exposure of the developing fetus to maternal hyperglycemia and other nutrient abnormalities during mid to late gestation might cause permanent metabolic and anthropometric changes. Factors associated with the diabetic intrauterine environment may directly affect the fetus by altering fetal pancreatic islet cells, fat stores and muscle cells, all of which could contribute to the development of insulin resistance many years later.

There is evidence to suggest that macrosomia is also independently associated with milder forms of gestational impaired glucose tolerance (IGT). Investigators with The Toronto Tri-hospital GDM project have recently conducted a prospective cohort study that followed about 4300 nondiabetic pregnant women, aged ≥ 24 years, receiving prenatal care[149]. The group studied the impact of carbohydrate intolerance on pregnancy outcomes in women who did not meet the standard diagnostic criteria for GDM. Multivariate analysis showed that increasing maternal carbohydrate intolerance was associated with a graded increase in macrosomia (birth weight >4000 g) and independently predicted HBW. Furthermore the untreated "borderline GDM" group had a 29% rate of macrosomia compared with

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14% in normoglycemic controls (p<.001) [150]. These findings supported several earlier studies reviewed by Hod[140] in which rates of macrosomia ranged from 12-28% among offspring of women with some degree of gestational IGT. The Toronto investigators[113] and others[151] have suggested that 10-16% of pregnancies could be complicated by either GDM or milder forms of gestational IGT combined. This would indicate that in fact a much greater proportion of women are at risk for pregnancy related carbohydrate intolerance induced complications than is usually considered in only the 3-4% women who meet the standard diagnostic criteria for GDM.

The relative contribution of GDM to macrosomia is difficult to estimate because of the interrelated nature of other potential risk factors. In a study of 574 infants weighing >4500 g, Spellacy et al[152] found that GDM contributed to about 5% of the macrosomic group, whereas maternal obesity and postmaturity were associated with 45% and 11% of the macrosomic group respectively. In the same study, T1DM contributed to almost 3% of infants with birth weight > 4500 g.

There is evidence that ethnic origin could influence birth weight patterns. Of interest to the topic of this paper, Aboriginal ancestry is a risk factor for HBW. Among the Pima, rates of fetal macrosomia as high as 80% have been found in women with GDM compared to 94% in those with gestational IGT, 43% in those with diabetes and 23% in women who were nondiabetic[21]. In Canada, reports from northwestern Ontario[153] and British Columbia[154] showed increased rates of macrosomia among Native newborns compared to those in the general population. The latter study observed less frequent HBW in remote areas than in non-remote areas among Natives in B.C. Excess heavy birth weight appears to be a new phenomenon affecting Native Canadian infants; in 1962, only 12% were > 4000 g while 22% were reported to be so in a 1983 Indian and Inuit breast feeding survey[155].

In a Saskatchewan population-based survey from 1975 to 1988, Dyck and Tan[156] compared rates of birth weight > 4000 g between northern (mainly Aboriginal) and southern (mainly Caucasian) residents. The overall HBW rate was greater in northern (16.3%) than in southern (12.4%) Saskatchewan; during the 14 year study time-frame, this rate increased from 12.6% to 19.2% in the north, but from only 10.2% to 12.8% in the south. The authors concluded that their observations were consistent with higher rates of obesity and/or GDM among Aboriginal women.

Based on the data by Dyck and Tan and reasonable inferences from the literature, one can estimate the attributable risk (AR) for macrosomia by GDM in the Aboriginal and non-Aboriginal populations of pregnant women in Saskatchewan. Because these calculations require that some assumptions be made, a possible range of AR for both populations is estimated, as summarized in Table 2.1 (see Appendix II for calculations).

Table 2.1. Attributable risk (AR) for birth weight (bwt) >4000 g by GDM in Aboriginal and non-Aboriginal populations of pregnant women in Saskatchewan

	Incidence of GDM	Rate of bwt >4000g in GDM	Overall rate of bwt >4000g	Risk Ratio	AR per 100 pregnancies
Non-Aboriginal women	3%	20%	12%	1.7	8.2
	4%	"	"	1.7	8.3
Aboriginal women	10%	30%	16%	2.1	15.6
	15%	"	"	2.2	16.5
	10%	40%	"	3.0	26.7
	15%	"	"	3.4	28.2

Assuming the rates indicated in Table 2.1, the risk for birth weight > 4000 g attributable to GDM would be around 8% for pregnancies among non-Aboriginal women and would range from about 15% to almost 30% for pregnancies in Aboriginal women.

2.4.5 Long Term Effects of GDM on Offspring

The long term effects of the diabetic pregnancy on the offspring have been extensively investigated among the Pima Indians by Pettitt et al[25]. The offspring were followed for up to 25 years and were divided into three groups according to their mother's diabetic status during and after pregnancy: 1) nondiabetic; 2) prediabetic (normal glucose tolerance during pregnancy but developed DM later); and 3) diabetic (preexisting DM or GDM). The study design allowed for a separation of effects thought to be attributable to the intrauterine environment and those thought to be attributable to heredity.

Multivariate analysis revealed that maternal diabetes was an independent predictor of subsequent diabetes and obesity in the offspring, even after controlling

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for paternal diabetes, the age of diabetes onset in the parents and degree of obesity in the offspring. In each age group and whether or not they had fetal macrosomia, the offspring of diabetic women had a higher prevalence of obesity than offspring in each of the other two groups, after adjustment for maternal obesity[26]. Earlier evidence of fasting hyperinsulinemia and higher rates of abnormal carbohydrate tolerance also occurred in offspring of diabetic women[27]. Furthermore, 45% of these children developed T2DM by age 20-24 compared to 1.4% of children born to nondiabetic women and 8.6% of children born to prediabetics[28]. The authors concluded that, in addition to genetic factors, the effect of the diabetic intrauterine environment was an important determinant for the development of obesity and earlier age onset of T2DM in the offspring.

Pettitt and his colleagues commented on how the long-term effects of diabetic pregnancies on offspring may contribute to the transmission of risk for the same problems developing in the next generation, resulting in a vicious cyclic transference of diabetogenic effects[28]. The early appearance of T2DM in female offspring would in turn be expected to lead to an increase in the proportion of diabetic pregnancies and an even earlier appearance and higher frequency of T2DM and obesity in the subsequent generation. The authors suggested that the same cyclic phenomenon associated with diabetic pregnancies in the Pima may occur in other Native populations who have high rates of obesity and diabetes.

Of interest in the observations by Pettitt et al is that birth weight was not found to be predictive of childhood / early adult obesity in this group, although infants of diabetic women were on average heavier at birth. Also, a significant relationship between maternal obesity and offspring obesity was found only for nondiabetic and prediabetic groups, but not for the diabetic group. To explain this phenomenon, the authors concluded that the effect of exposure to a diabetic environment during gestation on the development of obesity in offspring was likely so strong that the effects of birth weight and maternal obesity were obscured[28]. Upon review of the data, a relatively small number of subjects in the diabetic group could have also reduced the statistical power of these analyses. Silverman et al[157] provided further support for these findings in a prospective evaluation of adolescent offspring of mothers with GDM or pre-GDM. The study showed that many offspring of diabetic mothers with fetal hyperinsulinemia were not overweight by usual standards and

many offspring with later obesity and glucose intolerance were not macrosomic at birth.

2.4.6   Other Relevant Studies

The hypothesis that T2DM is preferentially transmitted through the maternal line is the subject of recent debate. Some family surveys conducted in different populations have found that individuals with T2DM are more likely to report a history of diabetes in the mother than in the father[158][159] yet other studies have not shown an excess in maternal transmission of T2DM[160]. While a stronger maternal transmission may have a genetic basis, these findings could also be interpreted to support the long-term effect of exposure to the diabetic intrauterine environment in the offspring.

In the literature search for this thesis, only one study by Kaufmann et al[161] was found to have examined the relationship between macrosomia and later development of T2DM among offspring of GDM mothers. Using an animal model, Kaufmann and colleagues showed that mice pups who became diabetic as adults were significantly larger at birth compared to those who did not become diabetic ($p = 0.0001$). The authors concluded that in the GDM complicated pregnancies, macrosomia may in part be determined by the genetic susceptibility to develop T2DM in the future.

Numerous studies have investigated the association between increased birth size and the development of T1DM in childhood or adolescence. Although the link between HBW and childhood obesity in this group seems probable[162], the link between HBW and T1DM remains unclear. Several studies show no evidence of an association between macrosomia and T1DM[163][164][165], and others have found either lower[166] or higher birth weight[167] to be associated with the development of the disease. In a population based case-control study in Sweden, Dahlquist et al[168] reported a clear trend in the adjusted odds ratio for juvenile onset diabetes according to birth weight; small for gestational age decreased the risk (OR = 0.81; 95% CI 0.65, 0.99) and large for gestational age increased the risk (OR = 1.20; 95% CI 1.02, 1.42). Although maternal diabetes was controlled for, the authors acknowledged that underreporting of maternal GDM could have influenced the study results. Also,

the authors did not specify the diagnostic criteria used for T1DM, leading the reader to wonder if misdiagnosis of childhood T2DM could have affected the results.

2.4.7 Summary

In summary, Aboriginal women are experiencing higher rates of GDM than women in the general population; this contributes to increased rates of macrosomia and perinatal complications. Offspring exposed to the diabetic intrauterine milieu suffer long-term complications including a higher frequency of insulin resistance, childhood obesity and T2DM, with the onset of diabetes appearing at a very early age. Subsequent development of diabetes is also a long-term complication for women with GDM, a risk that is greater and occurs at younger ages in First Nations women. The adverse consequences of GDM for both the Aboriginal mother and child implicate GDM as contributing to the epidemic of T2DM evidenced by First Nations people today.

2.5 Fetal Undernutrition, Low Birth Weight and T2DM

2.5.1 Introduction

In the last decade, a growing body of evidence has implicated intrauterine growth retardation in the development of diabetes and other adult chronic diseases. Initial hypotheses proposing that chronic disease in adults have their origins in fetal and infant life first appeared in 1934[169]. Forty years later, Forsdahl[170] rekindled interest in the subject by demonstrating an ecological association between then current mortality rates from arteriosclerotic heart disease and past adverse living conditions as reflected by infant mortality rates. Forsdahl concluded that both infant and adult mortality were related to poor maternal and infant nutrition. More recent studies have used cross-sectional techniques to compare indices of poor fetal and infant growth such as birth weight, birth length, ponderal index (weight/length^3), placental weight, placental/birth weight ratios, head circumference, and weight at age 1 year with the occurrence of chronic disease and related risk factors in later life.

2.5.2 Review of Epidemiological Studies

The bulk of recent epidemiological work in this area originates from England and includes studies that have shown statistical associations between indices of poor early fetal and childhood growth and subsequent glucose intolerance and T2DM in later life. The discovery that adult Cambridgeshire residents with IGT were significantly shorter than controls led to a study by Hales, Barker et al[33] which showed that LBW or low weight at age year 1 was strongly related to glucose intolerance in men whose average age was 64 years. In this study, the prevalence of either IGT or newly diagnosed T2DM fell progressively from 40% in those with birth weight <2500 g to 14% in those with birth weight ≥ 4.310 g (9.5 pounds). In the same population similar but less strong relationships were observed in women[34]. These trends were independent of social class and adult BMI.

In a separate English community, where more detailed birth size measurements were available for 50 year old residents, Phipps et al[35] showed that abnormal thinness at birth, as indicated by a low ponderal index, had a stronger

association with IGT or T2DM than LBW. Direct testing of these same subjects by Phillips et al[36] revealed that thinness at birth predicted insulin resistance which led the investigators to suggest that the association between reduced fetal growth and increased risk of T2DM is mediated through insulin resistance rather than insulin deficiency.

Further analysis of the above studies revealed the strongest relationships were found between birth weight and the cluster of features known as the "insulin resistance syndrome" (syndrome X) as defined by the loss of glucose tolerance, hypertension and a raised plasma triglyceride concentration[37]. A male infant of bwt <2500g was 18 times more likely to show these features than one of bwt ≥ 4310 g. The relationship between birth weight and subsequent glucose intolerance, and that between thinness at birth and subsequent insulin resistance were both found to interact with adult obesity; the combined effect of poor early growth and subsequent adult obesity led to the greatest adverse changes in later life.

In a recent review, Hales[38] indicated that the effects of poor early growth on glucose tolerance were also detected in much younger populations of 7 year old children and men aged 18-25 years. However, the nature and strength of these relationships were less consistent than in studies involving older subjects.

2.5.3   Thrifty Phenotype Hypothesis

The collective findings from the above studies have been interpreted as showing that the long-term effects of environmental factors (probably nutritional) from early life, predispose to the later development of T2DM. This is the basis of the "thrifty phenotype hypothesis" put forth by Hales and Barker[43] which challenges traditional arguments supporting the genetic basis of T2DM and suggests a key role for early environmental factors in the etiology of T2DM. The authors favor evidence that supports low maternal dietary protein as one important contributor to this process.

The "thrifty phenotype" hypothesis states that IGT and T2DM are mainly the result of complex systemic adaptations to undernutrition in the early fetal and possibly infant environment. In adapting, the fetus and infant have to be nutritionally "thrifty", thereby increasing fuel availability. If poor nutrition continues throughout life, these

adaptations are not detrimental. However, if adult nutrition is improved, the ability of the pancreas to maintain carbohydrate homeostasis is exceeded with resulting diabetes. Interaction with later life influences such as obesity, aging and physical inactivity, likely play a role in determining when and how much the capacity is exceeded; this determines the timing and severity of the disease.

Regarding the etiology of T2DM, the concept underlying the thrifty phenotype hypothesis is that poor fetal and infant growth have long-term consequences for carbohydrate metabolism. In a recent review, Barker[44] describes this process as follows: Undernutrition during "critical periods" of fetal development may result in poor development of the pancreatic islets of Langerhans, Beta cells and other tissues in order to diminish detrimental consequences to certain organs such as the brain. Through mechanisms poorly understood, the necessary adaptations the fetus makes to sustain its development permanently change the organism's physiology and metabolism. These "programmed" changes and "memories" of early undernutrition may later translate into pathogenetic mechanisms that lead to T2DM.

Several classic studies support the strong influence of environmental factors on the growing fetus. Studies correlating the birth weights of relatives[171], and evidence from cross breeding experiments of animals[172], have led to the conclusion that the diversity of birth size of babies born after normal pregnancies is essentially determined by the intrauterine environment rather than the fetal genotype[173]. Furthermore, animal studies have shown that the supply of nutrients and oxygen is the aspect of the intrauterine environment that usually limits fetal growth[174].

2.5.4   Surviving Small Baby Genotype Hypothesis

The link between LBW / reduced fetal growth and subsequent IGT or T2DM has been confirmed in a variety of different populations including Mexican Americans[39], Swedish men[40] and US men[41]. Of interest to the subject of this paper is a longitudinal study by McCance et al[42] involving Pima Indians aged 20-39 years. Contrary to the findings of Hales and Barker, McCance et al found that the association of birth weight and T2DM had a U-shaped distribution, with the highest prevalence of diabetes occurring in those with both high and low birth weights. In this study, the age adjusted prevalences of T2DM were 30%, 17% and 32% among those

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with birth weights < 2500 g, 2500-4500 g and ≥ 4500 g respectively. When data was controlled for age, sex, BMI and maternal diabetes during pregnancy, individuals with birth weights < 2500 g had a higher rate of T2DM than those in the 2500 - 4500 g range (OR 3.81, p = 0.001). Although the authors did not comment upon it, their data shows that diabetics diagnosed at a younger age were less likely to have been low birth weight infants than those diagnosed at an older age. This may reflect improving maternal / fetal nutrition in the latter part of the century.

McCance and colleagues concluded that the risk for subsequent T2DM among HBW infants was largely explained by maternal diabetes during pregnancy because, after adjusting for this factor, the association between HBW and T2DM was no longer significant; however, the strong significant relation between LBW and diabetes in later life remained. Despite the higher rates of diabetes associated with extremes of the birth weight distribution, birth weight < 2500 g and ≥ 4500 g contributed only 6% and 5% respectively to the overall prevalence of diabetes in this population. Thus, most Pima who developed diabetes had birth weights that fell within the intermediate range. To explain why the U - shaped curve findings appeared among the Pima and not in the British studies, the authors suggested that a lower prevalence of diabetes during pregnancy among British women likely accounted for the absence of a HBW / T2DM association in this population. Other researchers in the field have agreed with this interpretation[175].

To explain the association of diabetes with LBW, McCance et al have proposed a more genetically based alternative to the thrifty phenotype hypothesis, namely the "surviving small baby genotype" hypothesis that takes into account the high mortality of LBW infants. This hypothesis states that small infants with an apparent genetic predisposition to insulin resistance and T2DM are more likely to survive than those without such a genotype. Furthermore, the selective survival advantage of this genotype through generations contributes to high prevalences of T2DM and other expressions of insulin resistance in contemporary populations.

2.5.5   Critique of the Literature

Numerous reviews have discussed the limitations inherent in cross-sectional studies that imply a causal link between early life experience and adult chronic

disease[176]. The main criticisms are directed at the many potential biases in these studies such as selection bias, loss to follow-up from death, migration, untraceability, and refusal to participate. Failure to define, measure and adequately control for the confounding health consequences of social/economic disadvantage and other possible factors related to either exposure or outcome may also be important. Joseph and Kramer[177] pointed out that the lack of an association between social class at birth and LBW in the British studies was a good indication of bias because such an association has been consistently documented in the literature across decades. The use of birth weight as a proxy for fetal nutritional status is also questioned, given the multifactorial determinants of birth weight and the inability to quantify their individual effects in retrospective studies. Despite the limitations mentioned above, some critics believe there is reasonable biologic plausibility to the hypothesis that intrauterine and infant malnutrition may predispose to glucose intolerance and T2DM in later life[178]; however, the metabolic link between the intrauterine insult and adult insulin resistance remains elusive[179].

2.5.6   Risk Factors for LBW

In addition to poor intrauterine growth resulting in an infant smaller than expected for his or her gestational age, LBW can also be the outcome of shortened gestation (preterm delivery), or a combination of both these conditions. The W.H.O. defines LBW as a weight of 2500 g or less at birth and prematurity as born before 37 weeks gestation[180]. In Canada, approximately 5.7% of all infants born annually since 1980 weighed ≤ 2500 g[180]. The importance to differentiate between LBW for gestational age and prematurity is recognized; however, the literature has used LBW as a crude marker for adverse perinatal outcome because it is the dominant factor determining infant mortality, despite the relative effects of gestational age[181]. During the neonatal period, infants weighing ≤ 2500 g are 40 times more likely to die than infants of normal birth weight[181].

In addition to preterm delivery, a multitude of potential risk factors associated with LBW have been identified. These have been reviewed by Behrman[181] and can be summarized accordingly. Demographic risks include maternal age younger than 18 and older than 35 years, African-American race, low socioeconomic status and

being unmarried. Medical risks include parity of 1 or ≥ 4, multiple pregnancy, low maternal prepregnancy BMI, poor gestational weight gain, some diseases such as T1DM and hypertension, certain infectious diseases, and a poor obstetrical history such as previous LBW infant or multiple spontaneous abortions. Behavioral and environmental risks during pregnancy include smoking, malnutrition and alcohol / substance abuse. Other risks include absent or inadequate prenatal care, short interpregnancy interval and short maternal stature.

Behrman indicates that although many interdependent relationships are likely to exist with these risk factors, the independent effect of each on LBW is gradually being defined through carefully conducted epidemiological studies. For example, in a recent cross-sectional study of young, white, married mothers who had the characteristics of most middle-class Americans, mothers aged < 20 years had a significantly higher risk of delivering an infant < 2500 g than those aged 20 -24 years[182]. The highest risk was for young teenage mothers in the 13 -17 year age group (OR =1.7 ; 95% CI 1.5, 2.0).

2.5.7   LBW in Saskatchewan Aboriginal People

Two studies have examined epidemiological aspects of LBW in Aboriginal people of Saskatchewan. Edouard et al [45] looked at differences in pregnancy outcomes among registered Indians and the provincial population using vital statistics data from 1980 through 1986. During the study period, the rates of neonatal death, infant death and stillbirth were higher among Indians compared to provincial rates. The overall incidence of birth weight ≤ 2500 g was 6.5% among Indians compared to the provincial rate of 5.2%. In the provincial population, LBW was most frequent among the youngest (<20 yrs) and oldest (≥ 35 yrs) mothers, which followed the commonly found J-shaped distribution. In the Indian population, however, a different pattern was observed; LBW was less frequent among teenaged mothers (4.7%) than in mid-aged mothers (8.5%) and those ≥ 35 yrs (8.1%). The authors hypothesized that this unusual distribution could have been due to adverse lifestyle conditions of the mid to older aged Indian mothers.

Tan, Irvine et al[46] showed that the rate of LBW infants in northern Saskatchewan (mainly Aboriginal residents) decreased from 7.2% to 5% between

1975 and 1988 when it dropped to levels observed in southern Saskatchewan (mainly Caucasian residents). During the same time period LBW rates dropped from 6% to 5% in the south. The authors suggested that LBW rates were probably even higher among Saskatchewan Indians in earlier years when poor maternal / fetal nutrition was more likely and health care was less accessible.

2.5.8 Summary

In summary, an association between LBW and the development of T2DM in later life has been shown in several different populations including North American Indians. Some have interpreted these findings as a reflection of fetal adaptation to undernutrition in utero during critical periods of gestation, suggesting that early environmental factors play a major etiologic role in T2DM. Others favor a more genetically based interpretation of fetal adaptation, in keeping with the principles of evolution and selective survival. The link between LBW and diabetes has reshaped the nature versus nurture debate regarding the mechanisms which predispose to T2DM; in particular, the relative effects of intrauterine environmental exposures on the development of T2DM are being carefully examined.

3.   RATIONALE

As described in the above literature review, GDM may play a pivotal role in the increasing occurrence of T2DM among Saskatchewan Aboriginal people. Since GDM is frequently complicated by macrosomia, HBW could be used as a proxy measure of maternal GDM. Based on limited data available in Saskatchewan and reasonable inferences from the literature, the attributable risk for birth weight > 4000 grams by GDM among Saskatchewan pregnant women is estimated to be about 8% for non-Aboriginal women and to range from 15% to 30% for Aboriginal women.

LBW has been shown to predict T2DM in several different populations including North American Indians and has been interpreted as a reflection on nutritional deprivation in utero. In the data used for this study, an observed association between HBW and diabetes would provide strong circumstantial evidence of prenatal exposure to GDM, while an association between LBW and diabetes would suggest that poor maternal/fetal nutrition may contribute to the later development of T2DM.

This study will add to the existing body of knowledge by using a different study population, namely a sample of the Saskatchewan Aboriginal population in which the epidemic of T2DM appears to be at a relatively early stage and is probably still evolving. The use of Saskatchewan's Health Data Systems will be the first Canadian study to examine the relationship between birth weights and T2DM and will provide a unique opportunity to explore new angles of this relationship on a large scale. In doing so, it will be possible to investigate gaps in the existing body of knowledge such as if the relative importance of high versus low birth weights and if their relationship to T2DM has changed from the middle to the later part of this century and what the impact of Aboriginal ancestry is on the relationship between abnormal birth weight and the development of diabetes in later life. This knowledge could be instrumental in supporting appropriate primary prevention initiatives against factors related to the epidemic of T2DM in Aboriginal people.

This study also represents the first time a record linkage between Health Care Utilization Data files and Vital Statistics was ever performed in Saskatchewan.

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4.   OBJECTIVE AND RESEARCH QUESTIONS

<u>Study Objective:</u>

The primary objective of this study is to examine the relationship between HBW and/or LBW and the existence of T2DM among Aboriginal people in Saskatchewan. In this study, Aboriginal people are represented by a sample of Saskatchewan registered Indians (RI). Non-Aboriginal people are represented by a sample of all Saskatchewan residents other than RI and will be referred to as general population (GP) subjects. The specific research questions are as follows:

<u>Primary Research Question:</u>

1.   Among Saskatchewan RI people, is there an association between HBW or LBW and T2DM?

    1.1   Has the strength of this association changed from the middle to the latter part of this century?

    1.2   Is the strength of this association the same between males and females?

<u>Secondary Research Questions:</u>

2.   Is there a similar association between HBW or LBW and T2DM among GP people in Saskatchewan?

    2.1   Is there a difference in the degree of these associations between RI and GP people in Saskatchewan?

3.   Among those with T2DM, is there a difference in the rates of HBW or LBW between RI and GP people in Saskatchewan?

4.   Among non-diabetics, is there a difference in the rates of HBW or LBW between RI and GP people in Saskatchewan?

5.   Is there a difference in the rates of HBW or LBW between RI people with T2DM and GP people without diabetes?

5.   METHODS

5.1   Description of Research Design

This is a 1:3 matched case-control study in which <u>cases</u> are Saskatchewan RI people with diabetes and the three age and sex matched control groups are:

1) Saskatchewan RI people without diabetes;

2) Saskatchewan GP subjects with diabetes; and

3) Saskatchewan GP subjects without diabetes.

This study was supported by a Saskatchewan Health Services Utilization and Research (HSURC) grant awarded to Drs. R.F. Dyck and L.K. Tan in March, 1995[183]. It provided the opportunity to use Saskatchewan Health's medical record linkage of the Physicians Services database (DRSV), the Health Insurance Registration file (HIRF) and the Unique Identifier file (UID) for the selection of study subjects. Information on study subjects would then be linked with vital statistics data sources. The original study design proposed that 200 subjects in each group of cases and matched controls would be identified from five 10 year age groups ranging from ages 20 to over 60 years. This would have yielded a total of 1000 (5 x 200) 1:3 matched quartets, or 4000 individual study subjects. The original study proposal excluded individuals below 20 years of age to minimize the likelihood of capturing subjects with juvenile onset diabetes. Diabetic subjects would be identified according to the presence of a diabetic service code on the DRSV database for the two year time period of January 1, 1993 through December 31, 1994. (ICD9 codes 250 or 362 indicate the clinical encounter of diabetes and diabetic complication respectively.) Non-diabetic controls would be selected from the HIRF-UID file. Specific details regarding the case-control selection process is discussed in part 5.4 of this chapter.

5.2   Sample Size Calculations

The sample size for this study was calculated using a conventional alpha level of 0.05 (two tailed) and a beta level of 0.20. The calculations were based on the finding that about 12-15% of live births in northern Saskatchewan between 1975-88 weighed more than 4000 grams[156] and that 5% weighed less than 2500 grams[46]. Assuming that an odds ratio (OR) of 2.0 for high birth weight rates would constitute a clinically relevant difference, approximately 200 subjects in any given group of cases and controls would be necessary to demonstrate a statistically significant difference. This is also a sufficient number to demonstrate an OR of 3.0 for low birth weight rates between cases and controls.

5.3   Data Search Problems Encountered and Subsequent Revisions

Several unanticipated problems were encountered during the data search and matching process which resulted in necessary revisions to the original study proposal. At the time of data collection, it was discovered that birth weights were recorded inconsistently prior to 1952 and 1957 among GP and RI populations respectively, which reduced the original target sample size. For this reason, subjects born before 1950 were not included in the study. Furthermore, the minimum age criterion for study subjects was lowered from 20 to 10 years of age. In addition, to fulfill sample size requirements for comparisons of age groups, the time period used to capture a diabetic / diabetic complication event was extended back by two years, therefore being newly defined as the four year time period of January 1, 1991 through December 31, 1994.

After completion of the DRSV-HIRF-UID file search and case-control matching, it was discovered that ICD9 code 362 could not be used alone to determine the diabetic population because non-diabetic conditions were also classified under the 362 code (see APPENDIX III). This resulted in a plan to identify, exclude and replace subjects in the diabetic population (using DRSV file) so that *362-only* diabetics would be replaced with a 250; however, if the diabetic had both 362 and 250, the original 362 would not be replaced. Diabetics classified as *362-only* corresponded to 95 cases and 248 controls. For the 95 362-*only* cases, no

additional cases with a 250 code were available to allow replacement. To fulfill sample size requirements, it was decided that these 365-*only* cases would not be excluded. For the 248 *362-only* diabetic controls, 224 were excluded and replaced, but the other 24 remained in the study because they were matched to *362-only* diabetic cases.

5.4   Identification of Cases and Controls and Matching Process

To produce the information for this study, it was required that administrative data sets were linked by Saskatchewan Health Research Services, as illustrated in Figure 5.1. A more detailed outline of this process is available in APPENDICES V,VI and VII. All subjects for this study were identified using the linkage of DRSV, HIRF and UID records. The sorting, subgrouping and matching of subjects was done with the UID file. The UID record is cross referenced to all identification and demographic changes on the HIRF to ensure that residents with more than one provincial health benefit number over a lifetime only have one UID number (see Rawson et al[184] for specific details regarding the UID file). In this study, only those subjects born on or between January 1, 1950 and December 31, 1984 were included. To enhance the possibility of birth registration data linkage, study subjects more likely to be born in the province or more likely to have provincial health coverage since its inception were selected.

The selection of cases and controls proceeded in the following manner: first, the diabetic population was determined from the DRSV database according to the first ICD9 250 or 362 event between January 1, 1991 and December 31, 1994 (inclusive). The DRSV file was then linked to the UID-HIRF files so that selected diabetics were "flagged" on the UID file by UID number. Subjects on the UID file without an existing DRSV diabetes record were considered to be potential candidates for the non-diabetic sample population. At this point, subjects on the UID file were essentially classified as diabetic or non-diabetic. Registered Indians were then identified according to the presence of an "R" indicator with their provincial health Registered beneficiary number (RegBen number or RBN), which is documented on HIRF and cross referenced to the UID record. (It was not possible to distinguish any other group than RI so that other Aboriginal groups were incorporated into the GP

sample).   Subsequently, four subgroups were created with the UID file: 1366 RI diabetic "cases" and three potential control groups consisting of RI non-diabetics, GP diabetics and GP non-diabetics.

The selection of cases and controls as described above imposed certain limitations on the study. These are discussed in detail in Chapter 7.

In preparation for matching, each group was sorted according to gender and ascending year and month of birth on the UID file. No other systematic ordering of subjects was done. In three separate computer runs, the 1366 RI diabetic cases were matched one on one to each of the three potential control groups. Cases were matched to the first potential control recognized as being suitable according to gender and birth date (year and month) of the RI diabetic case. Essentially, Saskatchewan Health's research consultants considered this to be a random process. At this stage, when the ICD9 code *362-only* problem was realized (discussed in above section) the same process was used to match the 224 replaced diabetic controls. The factor determining the total number of subjects in this study subject file (4 x 1366 = 5464) was evidently the number of RI diabetic cases.
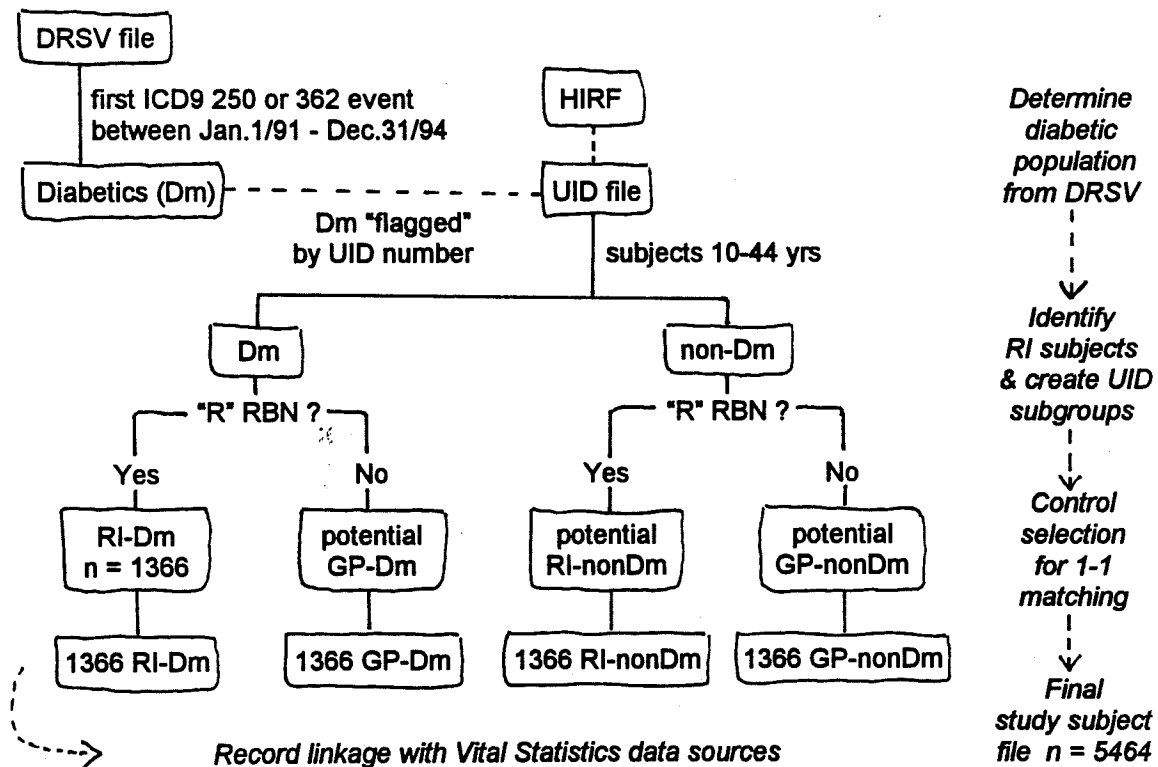
Figure 5.1   Process of case/control selection by Sask. Health Research Services

5.5   Linkage Of Case/Control Subject File With Vital Statistics Data Sources

Once matching of cases and controls was complete, birth certificates for these same subjects were obtained to access the following information: birth weight, gestational age, number of babies born alive (including current birth), type of birth (single or twin), previous stillborn, maternal age and paternal age.   Using Saskatchewan's Vital Statistics data sources, a search for birth registration was done for all 5464 study subjects identified above. Due to the fact that health services numbers (HSN) were not recorded on birth registrations, it was necessary to do a deterministic[185] match of the information on UID study subjects with identifiers recorded on the birth registration (see APPENDIX VIII). The matching process used to identify and obtain information required from the birth registrations involved many manual searches and a large quantity of data transcription from birth registration forms. Therefore, to validate accurate transcription of data, a random sample of 118 birth registrations (personal identifiers removed) was copied and forwarded to the researchers.

The two data files designed and forwarded by Sask. Health Research Services for this study are summarized below:

a) The **"Study Subject file"** consists of 5464 subjects identified from the linked DRSV, HIRF and UID files. These subjects make up 1366 complete quartets containing three age and sex matched controls for each case ranging from 10 to 44 years of age.

b) The **"Birth Registration File"** consists of 4833 subjects derived from merging the "Study Subject File" with Vital Statistics data sources. Birth registration data was available for only 4833 of the initial 5464 subjects thereby leaving a number of case-control quartets incomplete. In addition, birth weight was available for only 3992 of the 4833 subjects, resulting in a further reduction of complete case-control quartets.

In summary, the "final" study sample used for this thesis is the one with birth weight information; this corresponds to an overall n = 3992 and is comprised of unequally sized case and control groups. The loss of birth weight information

reduced the 1366 complete 1:3 case-control quartets in the original sample to only 561 complete quartets. Therefore, to minimize the loss of potentially useable data and retain matching, the analyses were carried out according to 1:1 matched case-control pairs instead of 1:3 matched case-control quartets. Figure 5.2 provides a overview of how the final study sample was derived.

RI-Dm = registered Indian diabetic, RI-nonDm = registered Indian non-diabetic,
GP-Dm = general population diabetic, GP-nonDm = general population non-diabetic
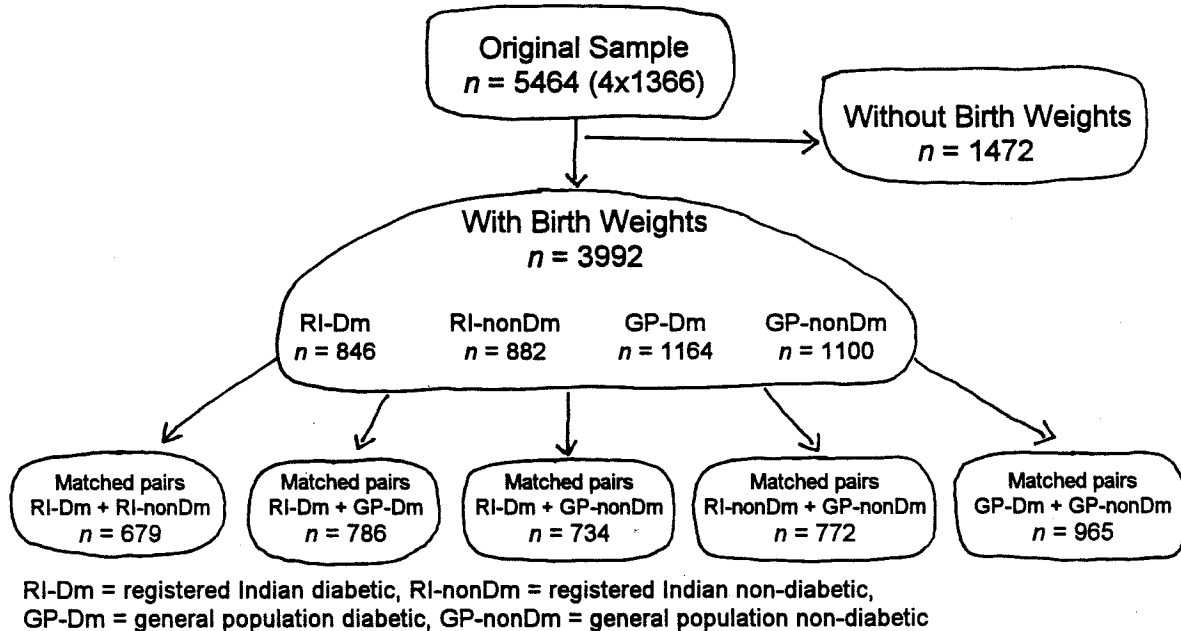
Figure 5.2   Overview of the derivation of the final study sample

5.6   Description of Data Sources

All data for this study was collected in the Spring of 1996 by Saskatchewan Health Research Services. The data from linked DRSV-HIRF-UID files (see "Study Subject File", APPENDIX IV) was forwarded in ASCII format. This information, merged with Vital Statistics data was forwarded in both ASCII and EXCEL spreadsheet format ("Birth Registration File", APPENDIX IV).

5.7   Ethics Approval and Confidentiality

The original study proposal was approved by the University of Saskatchewan Advisory Committee on Ethics and Human Experimentation. The data files forwarded by Saskatchewan Health identified all study subjects by only their Study ID number. As well, all personal identifiers on the 118 randomly selected birth registrations were removed and replaced by the subject's study ID number.

5.8   Description of Analytic Strategy

In preparation for data analysis, the data was sorted and variables were transformed or recoded into a format conducive for analysis. A list of the "template" variables used in the data analysis and a description of any necessary transformation of variables is given in APPENDIX IX. There are four main parts to the analysis of data which correspond to the objective and research questions of this thesis.

5.8.1   Unavailability of Data and Subsequent Loss of Study Subjects

Due to incomplete birth registration data on the original target sample identified from the linked DRSV-HIRF-UID files, the "final" study sample used throughout the data analysis required examination for potential selection bias and generalizability. This began with a comparison of available data at three stages, namely, study subjects initially identified (n = 5464), subjects with available Birth Registration (n = 4833) and subjects with recorded birth weight (n =3992), to assess the proportion of withdrawal of subjects within each of the case and three control groups. Missing birth weights were assessed according to year of birth and group. For subjects with birth weight, missing birth registration data was also examined.

Next, descriptive statistics and assessment of outliers in the Study Subject & Birth Registration files was carried out. In one case, a discrepancy in date of birth existed between the Birth Registration ASCII and EXCEL formatted files. After confirmation with Research Services, the date of birth value in the EXCEL file was corrected. Three extreme values in the variable "Gestational Age" were followed-up

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with the Vital Statistics staff. All three outliers were verified to have been transcribed correctly by reference to original records. As result, no records were censored.

An examination for differences due to withdrawal of subjects and incomplete birth registration records was carried out by a comparison of subjects with and without birth weight in each of the Study Subject and Birth Registration files. In the Study Subject File the variables age and sex were examined for differences, and in the Birth Registration File all remaining variables other than birth weight were examined. For the categorical variables sex, type of birth, previous stillborn and parity, a percent comparison was carried out and a Yates' corrected X^2 was calculated. For the continuous variables age, gestational age, maternal age and paternal age, a t-test for independent sample means was used and confirmed with the non-parametric equivalent Mann-Whitney U test. A value of $p \leq 0.05$ (two tailed) was considered to be statistically significant for differences due to withdrawal of subjects. In this thesis, both singleton and twin births were included throughout the analyses.

5.8.2   Analyses Of Association Between Birth Weight And Diabetes

The analyses in this section answers research questions #1 and #2. Although the questions are directed primarily at within sample group differences [pairs (i) and (v) below], the differences between sample groups [pairs (ii), (iii) and (iv) below] were also compared for a more complete examination of results. This section consists of three main steps and uses the 3992 subjects with birth weight in the five age and sex case-control matched pairs defined as follows:

pair (i)   RI diabetics + RI non-diabetics   .... } within RI sample group
pair (ii)   RI diabetics + GP diabetics
pair (iii)   RI diabetics + GP non-diabetics   .... } between sample groups
pair (iv)   RI non-diabetics + GP non-diabetics
pair (v)   GP diabetics + GP non-diabetics   .... } within GP sample group

First, a comparability analysis of case and control groups was done to identify potential confounders among the variables used in this study. Second, a crude odds

ratio (OR) for the association between HBW and/or LBW and T2DM was estimated for each of the five case-control matched pairs. Third, a multivariate analysis, using the conditional logistic regression technique, estimated the adjusted ORs of these matched pairs. Finally, a predictive model for birth weight and T2DM within the RI sample population was developed.

5.8.2.1   *Comparability Of Cases And Controls*

For the five matched pairs defined above, cases and controls were examined for comparability on each of the following potential confounding variables: age, sex, gestational age, parity, previous stillborn, type of birth, maternal age and paternal age. The pair-wise comparisons were analyzed using appropriate parametric and non-parametric statistical tests which retains the pairing of cases and controls. McNemar's Chi square (X^2) was used for the binomial variables sex, previous stillbirth and type of birth. The non-parametric paired signed ranks test was used for the categorical variable parity. Paired t-tests were used for the continuous variables age, gestational age, maternal age and paternal age and were confirmed with the non-parametric equivalent paired signed ranks test. The comparisons of age and sex were expected to be confirmatory since study subjects were matched on these two variables. Any variable that revealed a detectable significant difference at the level $p \leq 0.05$ in the comparability analysis was treated as a potential confounder in the multivariate analysis.

To address the issue of LBW rates known to be higher among infants of teenaged mothers, pair wise case-control analysis according to maternal age less than 20 years was carried out using McNemar's X^2.

5.8.2.2   *Estimation Of Crude ORs*

Three key potential risk factors (independent variables) were examined in this study: HBW (>4000 g), LBW (<2500 g) and high or low birth weight (HorLBW). Each of these potential risk factors was analyzed separately in the five age and sex matched pairs described above using McNemar's statistical tests[186]. For dichotomous variables, McNemar proposed that inference regarding the difference in proportions

derived from matched pairs be made solely on the basis of discordant pairs. Figure 5.3 shows the data layout for matched analysis with one control per case. Denoting the presence or absence of exposure by + or − respectively, the four possible outcomes for each pair (case, control) are: (++), (+−), (−+) and (− −). McNemar's maximum likelihood estimate of the OR, conditional on the number of discordant pairs B and C is given by $\hat{\psi}$ = B / C. The estimate of the OR that ignores matching is biased toward unity.

Controls

		+	−	Total
Cases	+	+ + A	+− B	A + B
	−	−+ C	− − D	C + D
	Total	A + C	B + D	N pairs

* exposed (+) , non-exposed (-)

Figure 5.3. Frequency of exposure* among case-control pairs[186]

McNemar's test enables a X^2 analysis to assess the significance of the difference between compared proportions and calculates a point and 95% CI estimation of the crude OR. The birth weight analyses were carried out initially by using "all other birth weights" as the denominator and then using "normal birth weights" as the denominator. The results were compared.

Since the greatest concentration of unrecorded birth weights occurred prior to 1957 for RI subjects, analyses of the crude ORs for HBW and LBW was repeated with the exclusion of subjects born prior to 1957. Results of the ORs with and without subjects born before 1957 were compared.

5.8.2.3   *Estimation of Adjusted ORs and Predictive Model*

To account for potential confounders identified in the matched pair analyses (Section 5.8.2.1), a multivariate analysis using conditional logistic regression (LR) was used to estimate adjusted ORs and their corresponding 95% CIs. To explain why conditional LR is suitable in a study such as this, Kleinbaum[187] states:

Conditional LR is the appropriate technique for a matched pairs study design analysis because it controls for the matching by using dummy variables to reflect the different matching strata, each of which involves a different matched pair. ...In so doing, this approach yields an unbiased OR.∗ ...In contrast, inappropriate use of the unconditional LR approach in a matched pairs study can give biased results, in particular, overestimate the ORs of interest.

In carrying out the conditional LR for this study, I respected the general goals of any multivariate analysis; namely, to develop a model which, given the set of variables, is the most biologically reasonable, the best fit and the most parsimonious[188]. To achieve this, the following steps were taken for each of the five within and between sample population paired data sets:

1. With birth weight only in the model (separate runs for each of the three dichotomized independent birth weight variables), the crude ORs and 95% CIs derived by McNemar's test were confirmed by comparing them with the exponential Beta coefficient values and CIs of the LR output.

2. With other than birth weight variables singularly in the model (gestational age, parity, previous stillbirth, type of birth, mother's age and father's age), those variables identified as being potential confounders in Section 5.8.2.1 were confirmed by an indication of statistical significance at $p \leq 0.05$ in the LR output.

3. With birth weight in the model and identified potential confounders as optional variables to the model, a forward stepwise LR technique determined which covariates among the identified potential confounders, should remain in the final model. Only those covariates that were statistically significant at $p \leq 0.05$ in the presence of the remaining variables were accepted.

4. With birth weight and only those covariates deemed to be significant by stepwise LR in the model, the final adjusted ORs and corresponding CIs were determined. In so doing, a final predictive model for birth weight and T2DM was developed for each of the five within and between sample population paired data sets.

5.9.3   Analyses For Differences In Strength Of Association

The analyses in this section answers research questions #1.1, #1.2 and #2.1.
Although the questions are directed primarily at <u>within</u> sample group differences, the
differences <u>between</u> sample groups were also compared for a more complete
examination of results. For each of the five age and sex matched pairs, an analysis
for differences in strength of association over time and according to gender was
carried out. One could also view this to be the analysis of interaction with age and
sex in the relationship between birth weight and diabetes in the different group
comparisons.

The analyses for interaction with age was done to investigate if the strength of
association, between HBW or LBW and T2DM, has changed from the middle to the
latter part of this century. Using age tertiles to produce a balanced distribution, the
data was stratified into three birth "cohorts" that ranged from a relatively older group
(i.e. from an earlier birth cohort), to a younger group of subjects (i.e. from a more
recent birth cohort). Compared to all other birth weights, a X^2 analysis for linear trend
in each HBW and LBW rates over time was carried out in the four study groups.
Using the same birth cohort strata defined above, birth weight comparisons over time
was done for matched case-control pairs within and between sample populations.
For each pair-wise comparison, a point and 95% CI estimation of the OR for three
birth cohorts was calculated and compared.

The analyses for interaction with sex investigated if the strength of association
between HBW or LBW and T2DM is the same between males and females. Sex-
specific ORs with corresponding 95% CIs were calculated and compared.

5.8.4   Differences in Rates of High or Low Birth Weights

This section answers research questions #3, #4 and #5, and relies on the
matched pair data analyses already discussed in section 5.8.2. The questions are
directed primarily at the differences between sample groups which correspond to
matched pairs (ii), (iii) and (iv) described in section 5.8.2. A comparison of HBW and
LBW rates was carried out for the cases and three control groups. The differences
were tested for statistical significance by McNemar's X^2 using "all other birth weights"

as the denominator. Although not required for research questions #3, #4 and #5, an estimation of the crude and adjusted ORs with corresponding 95% CIs was calculated for a more complete examination of results.

5.8.5   Software

The majority of data analyses for this thesis was performed using SPSS for windows, version 6.0. The initial sorting of data and transformation of some variables was performed using Microsoft Excel for windows, version 5.0. The matched pair analyses (McNemar's X^2 and ORs with corresponding 95% CIs) was performed using Epi -Info, version 6.02 and SPSS. Multivariate analysis using the conditional LR technique was performed largely by the Biomedical Data Processing Program (BMDP) available through the University of Saskatchewan SKYFOX VAX computer, in addition to SPSS.

6.   RESULTS

This chapter will follow the same basic outline as in the analytic strategy of section 5.8.2. However, in view of the overlapping nature of the data analyses, relevant descriptive data are grouped and presented with corresponding matched pair analyses. Hopefully this will facilitate the reading of this section.

6.1   Unavailability of Data and Subsequent Loss of Study Subjects

Due to incomplete birth registration data on the original target sample, the "final" study sample used for analyses was examined for generalizability. As I will show, the unavailability of birth weight data tended to make the final study sample younger (Table 6.4) with relatively more females (Table 6.5); mothers of these subjects tended to have lower parity and relatively more previous stillbirths (Table 6.6). Overall, the final study sample was slightly older in gestational age and had younger parents (Table 6.7). Loss of birth weight data was greatest for older RI subjects (Table 6.2), particularly RI diabetics, and RI males (Table 6.5). The effects of this potential selection bias will be considered in the interpretation of results.

Birth registration information was available for 88% of the 5464 target sample initially identified from DRSV and UID-HIRF files; birth weight was recorded for 73% of these 5464 subjects (Table 6.1). This represents an overall 27% withdrawal of subjects from the study with the highest proportion of withdrawal in the RI diabetic (38%) and RI non-diabetic (35%) groups. A further loss of subjects occurred during the analyses of matched pairs. Consequently, paired analyses within the RI sample population was based on 50% of the initial target sample data and paired analyses within the GP sample used 71% of the target sample data.

Birth weight was not consistently available for all study subjects until 1957 (Table 6.2). In the years 1950-56, the greatest proportion of missing birth weights occurred among RI people, particularly RI diabetics, for whom 27-97% birth weights were missing in a given year compared to 1-60% for GP subjects. By 1952, at least 82% of birth weights were available for GP subjects and increased dramatically there

after. However, it was not until 1957 that a comparable number of birth weights (87%) was available for RI people.

Table 6.1. Examination of available data at four stages.

Group	Initial File n	Birth Reg. File n	Birth Reg. File % of 1366	Subjects with Bwt n	Subjects with Bwt % of 1366	Pair wise comparisons		Pair wise comparisons n pairs	Pair wise comparisons % of 1366
RI-Dm	1366	1242	90%	846	62%	RI-Dm + RI-nonDm		679	50%
RI-nonDm	1366	1191	88%	882	65%	RI-Dm + GP-Dm		786	58%
GP-Dm	1366	1239	91%	1164	85%	RI-Dm + GP-nonDm		734	54%
GP-nonDm	1366	1161	85%	1100	81%	RI-nonDm + GP-nonDm		772	57%
TOTAL	5464	4833	88%	3992	73%	GP-Dm + GP-nonDm		965	71%

Table 6.2. Count and percent of recorded birth weight (Bwt) on birth registration according to group and year of birth (YOB).

YOB	Count & % of recorded Bwt in a given year RI-Dm		RI-nonDm		GP-Dm		GP-nonDM		Overall %
1950	$^2/_{70}$	3%	$^7/_{67}$	10%	$^{29}/_{73}$	40%	$^{24}/_{59}$	41%	23%
1951	$^{10}/_{69}$	15%	$^{18}/_{57}$	32%	$^{42}/_{62}$	68%	$^{44}/_{53}$	83%	47%
1952	$^{16}/_{69}$	23%	$^{16}/_{68}$	24%	$^{65}/_{67}$	97%	$^{45}/_{55}$	82%	55%
1953	$^{13}/_{65}$	20%	$^{17}/_{60}$	28%	$^{52}/_{55}$	95%	$^{57}/_{59}$	97%	58%
1954	$^{16}/_{75}$	21%	$^{22}/_{66}$	33%	$^{62}/_{65}$	95%	$^{65}/_{66}$	99%	61%
1955	$^{12}/_{59}$	20%	$^{29}/_{58}$	50%	$^{55}/_{55}$	100%	$^{52}/_{54}$	96%	66%
1956	$^{46}/_{63}$	73%	$^{47}/_{67}$	70%	$^{65}/_{65}$	100%	$^{51}/_{52}$	98%	85%
1957- 62	:	87-90%	:	87-96%	:	98-100%	:	98-100%	94-97%
1963- 70	:	96-100%	:	100%	:	100%	:	100%	99-100%
1971- 84	:	100%	:	100%	:	100%	:	100%	100%
TOTAL	$^{846}/_{1242}$	68%	$^{882}/_{1191}$	74%	$^{1164}/_{1239}$	94%	$^{1100}/_{1161}$	95%	83% $^{3992}/_{4833}$

For subjects with available birth weight, information on birth registration forms is 99.3 -100% recorded for all study variables except gestational age and father's age (Table 6.3). Missing gestational age data varies from 10-15% in a relatively even way across all four study groups. However, a greater proportion of father's age data is missing for RI people (31-34%) compared to GP subjects (5-6%).

A comparison of subjects with and without birth weight for the variables age and sex in the initial dataset is summarized in Tables 6.4 and 6.5 respectively. Subjects are grouped into the "birth cohort" categories that were used to answer

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research questions #1.1 and #2.1. For age, a progressively greater loss of birth weight information occurs as age increases, and is the greatest in the oldest age group (also referred to as the earliest birth cohort) in which a 43% difference is found between those with and without birth weight. For comparisons according to gender, the greatest loss of birth weight information occurs for RI males and is found to be significant (p = 0.04) among RI diabetics.

Table 6.3. Percent data available from birth registration for subjects with Bwt.

| Group | n at 100% | % of n | | | | | |
		Gest. Age	Mother's Age	Father's Age	Maternal Parity	Previous Stillborn	Type of Birth
RI-Dm	846	90	99.9	66	99.5	99.3	100
RI-nonDm	882	85	100	69	100	100	100
GP-Dm	1164	87	100	94	99.9	99.9	100
GP-nonDm	1100	88	100	95	100	100	100
OVERALL	*3992*	*88*	*99.9*	*80*	*99.9*	*99.8*	*100*

Table 6.4. Comparison of study subjects with and without Bwt for age according to age categories, using initial dataset (n 5464).

| Age group (yrs) | % of n Distribution | | Mean values | | Independent mean t-test p value* | Mann-Whitney p value* |
	with Bwt n 3992	no Bwt n 1472	with Bwt	no Bwt		
10 - 24	21%	4%	19.7	20.8	0.03	0.04
25 - 34	38%	12%	30.6	31.5	< 0.001	< 0.001
35 - 44	41%	84%	39.2	41.5	< 0.001	< 0.001
OVERALL	*100%*	*100%*	*31.8*	*39.4*	*<0.001*	*< 0.001*

* statistically significant at p ≤ 0.05

Table 6.5. Percent comparison of subjects with and without Bwt for gender according to group, using initial dataset.

| Group | with Bwt n 3992 | | without Bwt n 1472 | | Difference (%) | p value* (X^2) |
	M (% of n)	F	M (% of n)	F		
RI-Dm	34.5	65.5	40.2	59.8	5.7	0.04
RI-nonDm	35.3	64.7	39.3	60.7	4.0	NS
GP-Dm	36.7	63.3	36.6	63.4	0.1	NS
GP-nonDm	36.8	63.2	36.1	63.9	0.7	NS
OVERALL	*35.9*	*64.1*	*38.7*	*61.3*	*2.8*	*NS*

* statistically significant at p ≤ 0.05

A comparison of subjects with and without birth weight in the birth registration file for all remaining variables other than birth weight is summarized in Tables 6.6 and 6.6. Subjects are found to be no different for type of birth but differ significantly for maternal parity and previous stillbirths (Table 6.7). Subjects in the final study sample have mothers with lower parity ($p \leq 0.001$) and relatively more previous stillbirths ($p \leq 0.01$). Overall significant differences are detected between withdrawals and birth weight subjects for gestational age, maternal age and paternal age (Table 6.7). Overall, compared to withdrawals, subjects in the final study are 1 week older in gestational age ($p<0.01$), have mothers who are 10.8 months younger ($p<0.01$) and have fathers who are 15.3 months younger ($p<0.01$).

Table 6.6. Percent comparison of study subjects with and without Bwt for categorical variables, using birth registration dataset.

Variable	with Bwt (% of n)	without Bwt (% of n)	Difference (%)	p value* (X²)
Maternal parity	**n 3987**	**n 837**		
1	24.6	14.6	10	<0.001
2	19.5	15.4	4.1	<0.01
3	14.2	14.0	0.2	NS
4+	41.7	56.0	14.3	<0.001
OVERALL	100%	100%		<0.001
Previous stillbirths	**n 3895**	**n 832**		
None	93.2	95.9	2.7	<0.01
1 +	6.8	4.1	2.7	<0.01
OVERALL	100%	100%		<0.01
Type of birth	**n 3992**	**n 835**		
Singleton	98.1	98.9	0.8	NS
twin	1.9	1.1	0.8	NS
OVERALL	100%	100%		NS

* statistically significant at $p \le 0.05$

♣

Table 6.7. Comparison of study subjects with and without Bwt for continuous variables, using birth registration dataset.

Variable	Distribution % of n		Mean values		Independent mean t-test p value*	Mann-Whitney p value*
	with Bwt	no Bwt	with Bwt	no Bwt		
Gest. Age (wks)	**n 3525**	**n 49**				
< 38	14%	31%	35.4	35.0	NS	NS
38 - 41	81%	69%	39.8	39.7	NS	NS
≥ 42	5%	0%	42.5	none	unable	unable
OVERALL	100%	100%	39.3	38.3	<0.01	<0.001
Mother's Age (yrs)	**n 3991**	**n 836**				
< 20	19%	14%	17.6	17.9	<0.05	NS (0.06)
20 - 29	51%	54%	24.2	24.3	NS	NS
30 - 39	26%	28%	33.7	33.7	NS	NS
≥ 40	4%	4%	42.1	42.2	NS	NS
OVERALL	100%	100%	26.0	26.9	< 0.01	<0.001
Father's Age (yrs)	**n 3182**	**n 676**				
< 20	4%	1%	18.3	18.9	<0.01	NS (0.1)
20 - 29	42%	38%	24.9	25.1	NS	NS
30 - 39	36%	40%	34.0	34.1	NS	NS
≥ 40	18%	21%	46.1	46.3	NS	NS
OVERALL	100%	100%	31.7	33.0	<0.001	<0.001

* statistically significant at $p \le 0.05$

6.2 Analyses of Association Between Birth Weight and Diabetes

The analyses in this section answer research questions #1 and #2 and use only subjects with birth weight. The analyses consist of three main steps: first, identification of potential confounders among the variables in this study; second, estimation of the crude ORs for the association between HBW and/or LBW and T2DM and; third, estimation of the adjusted ORs. Since the matched pair data analyses were done for all five pairs identified in section 5.8.2, this section also answers an extension of research questions #3, #4 and #5. The reader is therefore simultaneously viewing differences within and between sample population groups.

6.2.1 Descriptive Statistics and Matched Pair Analyses

In this first phase, each potential confounding variable was examined separately. Any descriptive data relevant to the variable being examined is presented with the corresponding matched pair analyses. McNemar's statistical tests for matched pairs is derived on the basis of discordant pairs. As I will show, pair wise analyses confirmed accurate matching on the variables age and sex (Tables 6.9, 6.10) and identified potential confounders in this study to be mother's age, father's age, parity and previous stillbirth, (Tables 6.14, 6.17, 6.19, 6.20). Also, within both sample populations, non-diabetic controls tended to have younger mothers than diabetics. No differences were found between pairs on gestational age and birth type.

Age & Sex

A descriptive analyses of age and sex is summarized in Table 6.8. For age, subjects are grouped into the "birth cohort" categories that were used to answer research questions #1.1 and #2.1. In the final study sample, the age of subjects ranges from 10.5 to 44.9 years. Within the RI sample population, the mean age is noticeably lower (30.5 and 30.8 for cases and controls respectively) and the male to female ratios indicate 3-5% fewer males compared to GP subjects. Tables 6.9 and 6.10 outline the matched pair analyses according to age and sex, the variables study subjects were matched on. Results confirm 100% accurate matching on gender; however, a statistically significant difference is found for age in two of the five pair

wise comparisons. Upon further examination, these age differences amount to 9.8 and 13.5 days, which for this study, is not considered to be clinically significant.

Table 6.8. Descriptive analyses of Age and Sex for subjects with Bwt.

Group	n	Age (yrs) Mean (SD)	Distribution in Age group (% of n)			Male:Female Ratio
			10 - 24yrs	25 -34yrs	35 - 44yrs	
RI-Dm	846	30.5 (7.3)	23%	44%	33%	53 : 100
RI-nonDm	882	30.8 (7.6)	23%	42%	35%	55 : 100
GP-Dm	1164	32.8 (8)	19%	35%	46%	58 : 100
GP-nonDm	1100	32.6 (8.1)	19%	35%	46%	58 : 100
OVERALL	3992	31.8 (7.9)	21%	38%	41%	56 : 100

Table 6.9. Matched pair analyses of study groups according to Age.

Pair-wise comparison	n pairs	Mean Age (years)				mean of paired differences	paired t-test p value*	paired signed ranks test p value*
		RI-Dm	RI-nonDm	GP-Dm	GP-nonDm			
RI-Dm + RI-nonDm	679	29.33	29.33	-	-	- .001	NS	NS
RI-Dm + GP-Dm	786	30.18	-	30.22	-	- .037	<.001	<.001
RI-Dm + GP-nonDm	734	29.78	-	-	29.78	- .006	NS	NS
RI-nonDm + GP-nonDm	772	-	30.21	-	30.21	- .005	NS	NS
GP-Dm + GP-nonDm	965	-	-	31.82	31.79	+ .027	<.001	<.001

* statistically significant at p ≤ 0.05

Table 6.10. Matched pair analyses of study groups according to Sex.

Pair-wise comparison	n pairs	Number of discordant pairs for Sex				McNemar's X^2 p value*
		RI-Dm	RI-nonDm	GP-Dm	GP-nonDm	
RI-Dm + RI-nonDm	679	0	0	-	-	unable
RI-Dm + GP-Dm	786	0	-	0	-	unable
RI-Dm + GP-nonDm	734	0	-	-	0	unable
RI-nonDm + GP-nonDm	772	-	0	-	0	unable
GP-Dm + GP-nonDm	965	-	-	0	0	unable

* statistically significant at p ≤ 0.05

Gestational Age

The overall mean gestational age is 39.3 weeks with 81% of subjects between 38-41 weeks, 14% less than 38 weeks and 5% more than 41 weeks gestation (Table 6.11). The case and control groups appear to be similar with respect to mean values and percent distribution of gestational age. Pair wise comparability analyses (Table 6.12) indicate no significant differences in gestational age between study groups.

Table 6.11. Descriptive analyses of Gestational Age for subjects with Bwt.

Group	n	Gest. Age (wks) Mean (SD)	% of n in each Gest. Age category		
			< 38 wks	38-41 wks	≥ 42 wks
RI-Dm	759	39.3 (2)	15	80	5
RI-nonDm	784	39.1 (2)	16	80	4
GP-Dm	1015	39.3 (2)	13	82	5
GP-nonDm	967	39.4 (1.9)	14	80	6
OVERALL	3525	39.3 (2)	14	81	5

Table 6.12. Matched pair analyses of study groups according to Gestational Age.

Pair-wise comparison	n pairs	Mean Gestational Age (weeks)				mean of paired differences	paired t-test p value*	paired signed ranks test p value*
		RI-Dm	RI-nonDm	GP-Dm	GP-nonDm			
RI-Dm + RI-nonDm	601	39.3	39.3	-	-	+ .008	NS	NS
RI-Dm + GP-Dm	692	39.29	-	39.37	-	- .083	NS	NS
RI-Dm + GP-nonDm	660	39.3	-	-	39.4	- .09	NS	NS
RI-nonDm + GP-nonDm	673	-	39.27	-	39.46	- .19	NS	NS
GP-Dm + GP-nonDm	832	-	-	39.38	39.41	- .037	NS	NS

* statistically significant at p ≤ 0.05

Mother's Age

The overall mean Mother's age for subjects with birth weight is 26 years with 19% less than age 20 and 4% aged ≥ 40 years (Table 6.13). The individual group mean values indicate that mothers of both diabetic groups are older than mothers of both non-diabetic groups. This finding is apparent again in the age category percent distribution where the highest proportions of mothers < 20 years are found in the non-diabetic groups and the highest proportions of mothers aged ≥ 30 years are found in the diabetic groups. Matched pair analyses (Table 6.14) indicate statistical significant

differences in Mother's age between all study groups except between RI and GP diabetics. These differences are probably clinically significant because older maternal age is a known risk factor for GDM.

There are significant differences between study groups according to mothers aged < 20 years (Table 6.15). Specifically, more non-diabetic subjects have mothers under age 20 than diabetic subjects. However, between the two diabetic groups, RI diabetics have a significantly greater proportion of mothers < 20 years than GP diabetics. Further analyses (not shown) indicate that only RI diabetics have a significantly greater proportion of mothers aged $\geq$ 40 years (p <.001) when compared to RI non-diabetics. No other group comparisons were significantly different.

Table 6.13. Descriptive analyses of Mother's Age for subjects with Bwt.

Group	n	Mother's Age (yrs) Mean (SD)	% of n in each Age Category			
			< 20 yrs	20-29 yrs	30-39 yrs	$\geq$ 40 yrs
RI-Dm	845	26.9 (7.2)	18	48	29	5
RI-nonDm	882	24.1 (6.4)	29	51	18	2
GP-Dm	1164	27.4 (6.6)	11	54	30	5
GP-nonDm	1100	25.5 (6.8)	22	51	23	4
OVERALL	3991	26 (6.7)	19	51	26	4

Table 6.14. Matched pair analyses of study groups according to Mother's Age.

Pair-wise comparison	n pairs	Mean Age of Mother (years)				mean of paired differences	paired t-test p value*	paired signed ranks test p value*
		RI-Dm	RI nonDm	GP-Dm	GP nonDm			
RI-Dm + RI-nonDm	678	26.9	23.8	-	-	+ 3.1	<.001	<.001
RI-Dm + GP-Dm	785	26.9	-	27.2	-	- .3	NS	NS
RI-Dm + GP-nonDm	733	26.8	-	-	24.9	+ 1.9	<.001	<.001
RI-nonDm + GP-nonDm	772	-	24.0	-	25.0	- 1	.002	.004
GP-Dm + GP-nonDm	965	-	-	27.2	25.3	+ 1.9	<.001	<.001

* statistically significant at p $\leq$ 0.05

Table 6.15. Matched pair analyses of study groups according to Maternal Age <20.

Pair-wise comparison	n pairs	Number of discordant pairs for Maternal Age <20 years				McNemar's X^2 p value*
		RI-Dm	RI-nonDm	GP-Dm	GP-nonDm	
RI-Dm + RI-nonDm	678	85	170	-	-	<.001
RI-Dm + GP-Dm	785	120	-	76	-	.002
RI-Dm + GP-nonDm	733	92	-	-	148	<.001
RI-nonDm + GP-nonDm	772	-	151	-	125	NS
GP-Dm + GP-nonDm	965	-	-	81	188	<.001

* statistically significant at p $\leq$ 0.05

Father's Age

The overall mean Father's age for subjects with birth weight is 31.7 years with 4% less than age 20 and 18% aged ≥ 40 years (Table 6.16). On average, as with Mother's age, fathers of both diabetic groups are older than fathers of both non-diabetic groups. The highest proportions of fathers < 20 years are found in the non-diabetic groups and the highest proportions of fathers aged ≥ 30 years are found in the diabetic groups. Matched pair analyses (Table 6.17) indicate a similar pattern of statistical significant differences in Father's age as in the analyses for Mother's age (see Table 6.14). These differences in Father's age are not likely to be considered clinically significant because they probably reflect a proximity in age of the mother.

Table 6.16. Descriptive analyses of Father's Age for subjects with Bwt.

Group	n	Father's Age (yrs) Mean (SD)	% of n each Age Category			
			< 20 yrs	20-29 yrs	30-39 yrs	≥ 40 yrs
RI-Dm	611	32 (8.8)	3	42	35	20
RI-nonDm	530	30.2 (8.9)	7	46	36	11
GP-Dm	1084	32.5 (7.6)	1	38	43	18
GP-nonDm	957	31.3 (10)	6	45	30	19
OVERALL	*3182*	*31.7 (8.9)*	*4*	*42*	*36*	*18*

Table 6.17. Matched pair analyses of study groups according to Father's Age.

Pair-wise comparison	n pairs	Mean Age of Father (years)				mean of paired differences	paired t-test p value*	paired signed ranks test p value*
		RI Dm	RI nonDm	GP Dm	GP nonDm			
RI-Dm + RI-nonDm	284	32.4	30.0	-	-	+ 2.4	.002	<.001
RI-Dm + GP-Dm	521	32.3	-	32.0	-	+ .3	NS	NS
RI-Dm + GP-nonDm	452	31.8	-	-	30.6	+ 1.2	NS	.02
RI-nonDm + GP-nonDm	404	-	30.1	-	31.8	- 1.7	.01	.04
GP-Dm + GP-nonDm	776	-	-	32.5	31.1	+ 1.4	<.001	<.001

* statistically significant at p ≤ 0.05

Maternal Parity, Previous Stillbirth, Type of Birth

Table 6.18 summarizes the descriptive analyses of maternal parity, maternal history of at least one previous stillbirth and type of birth. The overall proportion of maternal parity ≥ 4 is 42% and previous stillbirth ≥ 1 is 7%. The highest rate of parity ≥ 4 is found in the RI diabetic group (56%) followed by RI non-diabetics (44%). As

well, the highest rates of previous stillbirth ≥ 1 are in the RI diabetic (10%) and non-diabetic (7%) groups. Matched pair analyses (Table 6.19) indicate statistical significant differences in maternal parity between all study groups except within the GP sample population. These differences are probably clinically significant because higher parity is a known risk factor for GDM. Statistical significant differences in previous stillbirth between cases and each of the GP control groups were observed (Table 6.20). Again, because previous stillbirth is a known risk factor for GDM, these differences are probably clinically significant.

Table 6.18. Descriptive analyses of categorical variables for subjects with Bwt.

Group	Maternal Parity (% of n)					Previous Stillborn (% of n)			Type of Birth (% of n)		
	n	1	2	3	≥ 4	n	0	≥ 1	n	single	twin
RI-Dm	842	17	16	11	56	840	90	10	846	98.8	1.2
RI-nonDm	882	26	18	12	44	882	93	7	882	99	1
GP-Dm	1163	26	22	18	34	1163	95	5	1164	97.6	2.4
GP-nonDm	1100	28	21	14	37	1100	94	6	1100	97.5	2.5
OVERALL	*3987*	*25*	*19*	*14*	*42*	*3985*	*93*	*7*	*3992*	*98.1*	*1.9*

Table 6.19. Matched pair analyses of study groups according to Maternal Parity.

Pair-wise comparison	n pairs	Number of cases ranked for higher Parity				paired signed-ranks test
		RI-Dm	RI-nonDm	GP-Dm	GP-nonDm	p value*
RI-Dm + RI-nonDm	675	301	192	-	-	<.001
RI-Dm + GP-Dm	782	383	-	187	-	<.001
RI-Dm + GP-nonDm	732	378	-	-	186	<.001
RI-nonDm + GP-nonDm	772	-	308	-	239	<.01
GP-Dm + GP-nonDm	964	-	-	359	355	NS

* statistically significant at p $\leq$ 0.05

Table 6.20. Matched pair analyses of study groups according to Previous Stillbirth.

Pair-wise comparison	n pairs	Number of discordant pairs for stillbirth ≥ 1				McNemar's X^2
		RI-Dm	RI-nonDm	GP-Dm	GP-nonDm	p value*
RI-Dm + RI-nonDm	674	64	44	-	-	NS (.07)
RI-Dm + GP-Dm	780	73	-	34	-	<.001
RI-Dm + GP-nonDm	730	65	-	-	36	<.01
RI-nonDm + GP-nonDm	772	-	49	-	38	NS
GP-Dm + GP-nonDm	964	-	-	45	56	NS

* statistically significant at p $\leq$ 0.05

Overall, 98.1% of subjects with birth weight are singleton births. There were no multiple births other than twins reported in this study. The highest rates of twin birth subjects are in the GP groups (2.4% and 2.5%). Matched pair analyses (Table 6.21) indicate no significant differences in type of birth between study groups.

Table 6.21. Matched pair analyses of study groups according to Twin Birth.

| Pair-wise comparison | n pairs | Number of discordant pairs for Twin Birth | | | | McNemar's X^2 |
		RI-Dm	RI-nonDm	GP-Dm	GP-nonDm	p value*
RI-Dm + RI-nonDm	679	7	6	-	-	NS
RI-Dm + GP-Dm	786	10	-	14	-	NS
RI-Dm + GP-nonDm	734	9	-	-	11	NS
RI-nonDm + GP-nonDm	772	-	8	-	16	NS
GP-Dm + GP-nonDm	965	-	-	21	23	NS

* statistically significant at p ≤ 0.05

Birth Weight

In doing the descriptive and matched pair analyses of the variable birth weight, research questions #3, #4 and #5 were answered. These questions are concerned with the differences in the rates of HBW and LBW between RI and GP sample populations. In view of the logical sequence of analyses in this section, the information on birth weight seems to fit at this point and is therefore presented here.

As indicated in Table 6.22, RI diabetics have the highest mean birth weight (3462 g), followed by RI non-diabetics (3371 g), GP diabetics (3304 g) and last, GP non-diabetics (3268 g). In the same pattern, the highest proportion of HBW (>4000g) is among RI diabetics (16.2%) followed by the three control groups (10.7 %, 10% and 7.5% respectively). Of note is that both diabetic groups have higher birth weight means and HBW rates than their non-diabetic counterparts. The highest proportions of LBW (<2500 g) is found in the two GP groups (8.6% and 8.2%). Both RI groups have the same, but lower, LBW rates (4.8%).

The differences in HBW are statistically significant only for RI cases compared to all three control groups (Table 6.23). For LBW (Table 6.24), no significant differences are found within either of the RI or GP groups. However, all three between sample population comparisons found the higher LBW rates among GP subjects to be significantly different.

Table 6.22. Descriptive analyses of Bwt.

| Group | n | Bwt (g) Mean (SD) | distribution low, normal & high Bwt (% of n) | | |
			< 2500 g	2500-4000 g	> 4000 g
RI-Dm	846	3462 (623)	4.8	79	16.2
RI-nonDm	882	3371 (544)	4.8	84.6	10.7
GP-Dm	1164	3304 (586)	8.6	81.4	10
GP-nonDm	1100	3268 (540)	8.2	84.4	7.5
OVERALL	3992	3342 (577)	6.8	82.4	10.7

Table 6.23. Matched pair analyses of study groups according to HBW with all other Bwts as denominator.

| Pair-wise comparison | n pairs | Number of discordant pairs for Bwt >4000 g | | | | McNemar's X^2 p value* |
		RI-Dm	RI-nonDm	GP-Dm	GP-nonDm	
RI-Dm + RI-nonDm	679	103	63	-	-	0.003
RI-Dm + GP-Dm	786	116	-	63	-	< 0.001
RI-Dm + GP-nonDm	734	111	-	-	47	< 0.001
RI-nonDm + GP-nonDm	772	-	72	-	51	NS (0.07)
GP-Dm + GP-nonDm	965	-	-	85	67	NS (0.17)

* statistically significant at p ≤ 0.05

Table 6.24. Matched pair analyses of study groups according to LBW with all other Bwts as denominator.

| Pair-wise comparison | n pairs | Number of discordant pairs for Bwt <2500 g | | | | McNemar's X^2 p value* |
		RI-Dm	RI-nonDm	GP-Dm	GP-nonDm	
RI-Dm + RI-nonDm	679	34	32	-	-	NS (0.9)
RI-Dm + GP-Dm	786	34	-	61	-	0.008
RI-Dm + GP-nonDm	734	34	-	-	63	0.005
RI-nonDm + GP-nonDm	772	-	35	-	62	0.008
GP-Dm + GP-nonDm	965	-	-	73	75	NS (0.9)

* statistically significant at p ≤ 0.05

6.2.2 Estimation Of Crude ORs

In this section, the three dichotomous birth weight variables (HBW, LBW, HorLBW) were examined in relation to diabetes for the five within and between sample population matched pairs. As determined above, RI people with diabetes had increased HBW rates and decreased LBW rates compared to controls. As I will show, analyses in this section found an association between HBW and diabetes within the RI sample but not among GP subjects (Table 6.25). An association between LBW and diabetes was not found within either of the RI or GP groups.

Using all other birth weights as denominator, matched pair analyses (Table 6.25) indicate a progressively stronger statistically significant relationship between HBW and RI diabetics, when compared to each of the three control groups: RI diabetics are more likely to have HBW than RI non-diabetics (OR=1.63), GP diabetics (OR=1.84) and GP non-diabetics (OR=2.36). On the other hand, RI diabetics are less likely to have LBW than GP diabetics (OR=0.56) and GP non-diabetics (OR=0.54). Among the two non-diabetic groups, RI people are less likely to have LBW than GP subjects (OR=0.57).

Using normal birth weights as denominator (Table 6.26) the significant relationships between HBW and LBW within the study groups follow the same pattern as described in the paragraph above. In addition, RI diabetics are more likely to have HorLBW than RI non-diabetics (OR=1.49) and GP non-diabetics (OR=1.38).

Table 6.25. Matched pair analyses for HBW and LBW with all other Bwts as denominator.

Pair wise comparisons	n pairs	OR (CI) for HBW (>4000 g) vs. all other Bwts	OR (CI) for LBW (<2500 g) vs. all other Bwts
RI-Dm + RI-nonDm	679	1.63 (1.20, 2.24)*	1.06 (0.66, 1.72)
RI-Dm + GP-Dm	786	1.84 (1.36, 2.50)*	0.56 (0.37, 0.85)*
RI-Dm + GP-nonDm	734	2.36 (1.68, 3.32)*	0.54 (0.36, 0.82)*
RI-nonDm + GP-nonDm	772	1.41 (0.99, 2.02)	0.57 (0.37, 0.85)*
GP-Dm + GP-nonDm	965	1.27 (0.92, 1.75)	0.97 (0.71, 1.34)

* statistically significant at p ≤ 0.05

Table 6.26. Matched pair analyses for HBW and/or LBW with normal Bwts as denominator.

Pair wise comparisons	HBW (>4000 g) vs. normal Bwts		LBW (<2500 g) vs. normal Bwts		HBW or LBW vs. normal Bwts	
	n pairs	OR (CI)	n pairs	OR (CI)	n pairs	OR (CI)
RI-Dm + RI-nonDm	612	1.53 (1.10, 2.14)*	503	1.38 (0.79, 2.40)	679	1.49 (1.13, 1.96)*
RI-Dm + GP-Dm	687	1.82 (1.31, 2.55)*	592	0.57 (0.35, 0.93)*	786	1.25 (0.96, 1.61)
RI-Dm + GP-nonDm	633	2.44 (1.67, 3.57)*	573	0.54 (0.33, 0.87)*	734	1.38 (1.05, 1.80)*
RI-nonDm + GP-nonDm	672	1.37 (0.93, 2.01)	643	0.58 (0.37, 0.91)*	772	0.94 (0.72, 1.24)
GP-Dm + GP-nonDm	811	1.29 (0.91, 1.82)	806	0.97 (0.69, 1.37)	965	1.12 (0.89, 1.42)

* statistically significant at p ≤ 0.05

The inclusion of subjects born prior to 1957 (where the proportion of available birth weight information was low) appeared to dilute the observed study effect. In comparison to the analyses with the 1950-57 group, the matched pair analyses without the 1950-57 group (Tables 6.27, 6.28) revealed a similar trend of statistically significant relationships, but mostly stronger. When comparing the analyses with and without the 1950-57 group, Tables 6.27 and 6.28 show additional statistically significant relationships for HBW analyses between RI and GP non-diabetics and within the GP sample population. Because inclusion of the 1950-57 group tended to underestimate the study effect, which was considered to be a less dangerous source of bias, it was decided that subsequent analyses would include the 1950-57 group. By doing this, the advantages of a maximized sample size and a longer time span of observation were achieved.

Table 6.27. Matched pair analyses for HBW and LBW with all other Bwts as denominator, excluding 1950-56 YOB subjects.

Pair wise comparisons	n pairs	OR (CI) for HBW (>4000 g) vs. all other Bwts	OR (CI) for LBW (< 2500 g) vs. all other Bwts
RI-Dm + RI-nonDm	628	1.66 (1.19, 2.32)*	0.94 (0.55, 1.59)
RI-Dm + GP-Dm	688	1.94 (1.38, 2.74)*	0.52 (0.32, 0.84)*
RI-Dm + GP-nonDm	658	2.74 (1.86, 4.04)*	0.47 (0.29, 0.75)*
RI-nonDm + GP-nonDm	654	1.71 (1.11, 2.66)*	0.62 (0.39, 0.99)*
GP-Dm + GP-nonDm	708	1.58 (1.03, 2.42)*	0.88 (0.60, 1.30)

* statistically significant at p ≤ 0.05

Table 6.28. Matched pair analyses for HBW and/or LBW with normal Bwts as denominator, excluding 1950-56 YOB subjects.

Pair wise comparisons	HBW (> 4000 g) vs. normal Bwts n pairs	OR (CI)	LBW (< 2500 g) vs. normal Bwts n pairs	OR (CI)	HBW or LBW vs. normal Bwts n pairs	OR (CI)
RI-Dm + RI-nonDm	565	1.55 (1.10, 2.19)*	461	1.21 (0.68, 2.14)	628	1.45 (1.09, 1.94)*
RI-Dm + GP-Dm	604	1.92 (1.34, 2.75)*	517	0.53 (0.31, 0.91)*	688	1.27 (0.96, 1.69)
RI-Dm + GP-nonDm	570	2.74 (1.82, 4.13)*	513	0.49 (0.29, 0.83)*	658	1.43 (1.07, 1.92)*
RI-nonDm + GP-nonDm	570	1.73 (1.10, 2.71)*	554	0.62 (0.38, 1.00)*	654	1.08 (0.78, 1.47)
GP-Dm + GP-nonDm	593	1.54 (1.00, 2.38)*	605	0.91 (0.61, 1.35)	708	1.16 (0.87, 1.55)

* statistically significant at p ≤ 0.05

A summary of all estimated adjusted ORs calculated for this study are presented in Tables 6.38 and 6.40. To facilitate the integration of all information, results derived from the multivariate analyses using conditional logistic regression are discussed in section 6.4 of this chapter.

6.3   Analyses for Differences in Strength of Association

The analyses in this section answer research questions #1.1, #1.2 and #2.1 which are directed at within sample population differences. For consistency throughout the thesis, the analyses were done for each of the five age and sex matched pairs. As I will show, for RI people, the strength of association between HBW and diabetes increased over time when compared to all three control groups (Table 6.32). When the data was stratified according to gender, this association was significant for RI females only (Table 6.36).

For the analyses of birth weight over time, the data was stratified into three time frames (birth "cohorts") that ranged from a relatively older group to a younger group of subjects. The overall mean age of subjects (Table 6.29) in each of the birth cohorts 1950-59, 1960-69 and 1970-84 was 39.2, 30.6 and 19.8 years respectively. In each birth cohort, the overall mean age generally reflected the individual group mean age of subjects.

Table 6.30 summarizes a descriptive analyses of birth weight over time according to study group. Overall, in both diabetic groups, the mean birth weight has increased over time (↑33 g. for RI, ↑37 g. for GP) whereas both non-diabetic groups reveal a decrease in mean birth weight over time (↓112 g. for RI, ↓65 g. for GP). Only RI diabetics show progressively increasing rates of HBW over time (↑ 4.8% overall) whereas the other three groups show decreasing rates of HBW (an overall ↓ of 2.3%, 2.5% and 2.9% for RI controls, GP diabetic controls and GP non-diabetic controls respectively). With respect to LBW, both RI groups have increased rates of LBW over time (an overall ↑ of 1.5% for diabetics, ↑ 3.3% for non-diabetics). Among the GP groups, diabetics have decreased LBW rates (↓ 4.4% overall) and non-diabetics show effectively little change.

Using the three birth cohorts 1950-59, 1960-69 and 1970-84, a X^2 for linear trend over time was performed according to study group (Table 6.31). For the

proportions of HBW compared to all other birth weights, no significant trends over
time were found within any of the study groups. For the time trend of LBW
proportions compared to all other birth weights, only the decreasing trend within the
GP diabetic group was found to be statistically significant (p=0.03).

Table 6.29. Mean age of subjects within each birth cohort.

Study Group	Mean age of subjects (yrs)		
	YOB 1950-59 (age grp 35-44 yrs)	YOB 1960-69 (age grp 25-34 yrs)	YOB 1970-84 (age grp 10-24 yrs)
RI-Dm	38.1	30.6	19.8
RI-nonDm	38.6	30.6	19.7
GP-Dm	39.7	30.7	19.8
GP-nonDm	39.7	30.5	19.7
OVERALL	39.2	30.6	19.8

Table 6.30. Descriptive analyses of Bwt over time according to study group.

Group according to Birth cohorts	n	Bwt (g) mean (SD)	low, normal & high Bwt (% of n)		
			< 2500 g	2500-4000 g	> 4000 g
RI-Dm					
1950 - 59	275	3456 (607)	3.6	81.8	14.5
1960 - 69	374	3452 (603)	5.6	78.6	15.8
1970 - 84	197	3489 (677)	5.1	75.6	19.3
RI-nonDm					
1950 - 59	304	3410 (520)	3.0	85.5	11.5
1960 - 69	372	3380 (552)	5.4	83.9	10.8
1970 - 84	206	3298 (558)	6.3	84.5	9.2
GP-Dm					
1950 - 59	541	3289 (610)	10.5	78.7	10.7
1960 - 69	403	3311 (575)	7.2	82.9	9.9
1970 - 84	220	3326 (546)	6.4	85.5	8.2
GP-nonDm					
1950 - 59	504	3299 (535)	8.3	83.1	8.5
1960 - 69	382	3244 (556)	7.9	85.1	7.1
1970 - 84	214	3234 (520)	8.4	86.0	5.6
OVERALL	3992	3342 (577)	6.8	82.4	10.7

Table 6.31. X^2 for linear trend in Bwt over time, using three birth cohorts, according
to study group.

Study Group	X^2 for linear trend on birth cohorts 1950-59, 1960-69, 1970-84	
	P value* for HBW (> 4000 g) vs. all other Bwts	P value* for LBW (< 2500 g) vs. all other Bwts
RI-Dm	NS	NS
RI-nonDm	NS	0.06
GP-Dm	NS	0.03*
GP-nonDm	NS	NS

* statistically significant at p ≤ 0.05

The birth weight comparisons within and between sample populations over time (Tables 6.32 and 6.33) use the same three birth cohorts defined above in matched pair analyses. A progressively stronger relationship is seen between HBW and RI diabetics, over time, when compared to each of the three control groups (Table 6.32). This relationship is most significant in the youngest age group where RI diabetics are more likely to have HBW than RI non-diabetics (OR=2.54), GP diabetics (OR=2.83) and GP non-diabetics (OR=3.27). On the other hand, the relationship between LBW and the study groups appears to generally weaken over time (Table 6.33) and is only significant for some comparisons within the oldest age groups: RI diabetics are less likely to have LBW than GP diabetics (OR=0.32) and for older non-diabetics, RI people are less likely to have LBW GP subjects (OR=0.36).

Table 6.32. Comparison of three age groups for HBW using all other Bwts as denominator in matched pair analyses.

Pair wise comparisons	Oldest age group 35-44 years		Middle age group 25-34 years		Youngest age group 10-24 years	
	n pairs	OR (CI)	n pairs	OR (CI)	n pairs	OR (CI)
RI-Dm + RI-nonDm	169	1.28 (0.66, 2.47)	327	1.47 (0.92, 2.36)	183	2.54 (1.29, 5.08)*
RI-Dm + GP-Dm	241	1.43 (0.79, 2.59)	352	1.73 (1.08, 2.78)*	193	2.83 (1.41, 5.78)*
RI-Dm + GP-nonDm	211	1.60 (0.81, 3.20)	334	2.43 (1.43, 4.17)*	189	3.27 (1.61, 6.82)*
RI-nonDm + GP-nonDm	244	1.24 (0.67, 2.28)	331	1.63 (0.89, 3.00)	197	1.36 (0.59, 3.17)
GP-Dm + GP-nonDm	397	1.03 (0.63, 1.68)	358	1.55 (0.88, 2.73)	210	1.50 (0.64, 3.58)

* statistically significant at $p \le 0.05$

Table 6.33. Comparison of three age groups for LBW using all other Bwts as denominator in matched pair analyses.

Pair wise comparisons	Oldest age group 35-44 years		Middle age group 25-34 years		Youngest age group 10-24 years	
	n pairs	OR (CI)	n pairs	OR (CI)	n pairs	OR (CI)
RI-Dm + RI-nonDm	169	1.50 (0.38, 6.30)	327	1.06 (0.52, 2.15)	183	0.91 (0.36, 2.30)
RI-Dm + GP-Dm	241	0.32 (0.13, 0.74)*	352	0.70 (0.35, 1.37)	193	0.77 (0.31, 1.87)
RI-Dm + GP-nonDm	211	0.44 (0.18, 1.08)	334	0.57 (0.30, 1.09)	189	0.59 (0.25, 1.35)
RI-nonDm + GP-nonDm	244	0.36 (0.16, 0.81)*	331	0.67 (0.34, 1.30)	197	0.77 (0.31, 1.87)
GP-Dm + GP-nonDm	397	1.21 (0.72, 2.03)	358	0.86 (0.49, 1.52)	210	0.76 (0.35, 1.66)

* statistically significant at $p \le 0.05$

Tables 6.34 and 6.35 summarize a descriptive analyses of birth weight for males and females. Overall, males have a mean birth weight 106 grams higher than females, 4.6% higher rates of HBW and 1.5% lower rates of LBW. However, the only striking exception to this trend is among RI diabetics, where 17% females have HBW; a rate that is 2.3% higher than their male counterparts and considerably higher than all female controls. Also of note is that GP diabetic females have the highest rate of LBW (10%).

Table 6.34. Descriptive analyses of Bwt for Males.

Group	n	Bwt (g) Mean (SD)	low, normal & high Bwt (% of n)		
			< 2500 g	2500-4000 g	> 4000 g
RI-Dm	292	3464 (573)	3.8	81.5	14.7
RI-nonDm	311	3453 (599)	4.5	79.1	16.4
GP-Dm	427	3406 (574)	6.1	80.3	13.6
GP-nonDm	405	3341 (576)	8.1	81.0	10.9
OVERALL	1435	3410 (581)	5.9	80.5	13.7

Table 6.35. Descriptive analyses of Bwt. for Females.

Group	n	Bwt (g) Mean (SD)	low, normal & high Bwt (% of n)		
			< 2500 g	2500-4000 g	> 4000 g
RI-Dm	554	3461 (648)	5.4	77.6	17.0
RI-nonDm	571	3327 (506)	4.9	87.6	7.5
GP-Dm	737	3244 (585)	10.0	82.1	7.9
GP-nonDm	695	3225 (514)	8.2	86.3	5.5
OVERALL	2557	3304 (571)	7.4	83.5	9.1

Matched pair analyses (Table 6.36) indicate a significant relationship between HBW and RI diabetics for females but not for males. For females, RI diabetics are more likely to have HBW than RI non-diabetics (OR=2.53), GP diabetics (OR=2.65) and GP non-diabetics (OR=3.41). The relationship between LBW and the study groups (Table 6.37) is significant for the same pair wise comparisons as when both sexes were combined (refer to Table 6.25). However in the gender specific analyses, significant relationships for pair wise comparisons exist for either males (more prominently) or females but not for both.

Table 6.36. Comparison of Males & Females for HBW using all other Bwts as denominator in matched pair analyses.

Pair wise comparisons	Males		Females	
	n pairs	OR (CI)	n pairs	OR (CI)
RI-Dm + RI-nonDm	235	0.82 (0.49, 1.36)	444	2.53 (1.66, 3.87)*
RI-Dm + GP-Dm	277	1.06 (0.66, 1.72)	509	2.65 (1.75, 4.00)*
RI-Dm + GP-nonDm	254	1.44 (0.87, 2.40)	480	3.41 (2.12, 5.48)*
RI-nonDm + GP-nonDm	273	1.41 (0.86, 2.31)	499	1.42 (0.84, 2.39)
GP-Dm + GP-nonDm	355	1.29 (0.83, 2.03)	610	1.24 (0.79, 1.97)

* statistically significant at p ≤ 0.05

Table 6.37. Comparison of Males & Females for LBW using all other Bwts as denominator in matched pair analyses.

Pair wise comparisons	Males		Females	
	n pairs	OR (CI)	n pairs	OR (CI)
RI-Dm + RI-nonDm	235	0.67 (0.27, 1.63)	444	1.30 (0.73, 2.33)
RI-Dm + GP-Dm	277	0.64 (0.28, 1.49)	509	0.53 (0.33, 0.86)*
RI-Dm + GP-nonDm	254	0.39 (0.19, 0.80)*	480	0.65 (0.39, 1.08)
RI-nonDm + GP-nonDm	273	0.46 (0.23, 0.94)*	499	0.63 (0.38, 1.05)
GP-Dm + GP-nonDm	355	0.62 (0.35, 1.12)	610	1.20 (0.81, 1.77)

* statistically significant at p ≤ 0.05

6.4   Estimation of Adjusted ORs and Final Predictive Models

In this section, the three dichotomous birth weight variables (HBW, LBW, HorLBW) were examined in relation to diabetes, taking into account the potential confounding variables identified in section 6.2.1, namely, maternal age, paternal age, parity and previous stillbirth. For each of the five within and between sample population paired datasets, a multivariate analyses using conditional LR was used to estimate adjusted ORs and their corresponding 95% CIs (Table 6.38). The analyses were repeated for males and females separately. As I will show, in most situations, the adjusted OR was less than the crude OR.

In the final study sample, an overall strong correlation was found to exist between maternal age and paternal age (r = .77, calculations not shown) which lead to the decision to exclude paternal age from the group of potential confounding variables. This decision was made in keeping with the general goals of multivariate analyses outlined in section 5.8.2.3 and specifically applies to the following points:

1. A strong correlation between two independent covariates can lead to multicollinearity and a risk of unreliable regression coefficients.
2. A high proportion of paternal age data is missing (34% RI diabetics) which could decrease the sample size for matched pair analyses and minimize statistical power.
3. There is no literature to support that paternal age is an important biological factor in the relationship between birth weight and T2DM; at most, it's importance may be marginal.
4. Given the numerous other variables already in the model, paternal age would add an unnecessary factor to the development of a final model.
5. Exclusion of paternal age would minimize the number of potential variables in the model and thereby respect the law parsimony in conformity with Occam's Razor: "...the simplest of competing theories is preferred to the more complex"[188].

To review the analyses in Sections 6.2.2 and 6.3 (crude ORs, Table 6.28) for within group comparisons, among RI people, an association between birth weight and diabetes was found for both HBW and HorLBW but not for LBW. When the data was stratified by sex, this pattern of significant relationships gained strength for females but lost statistical significance for males. For GP subjects, no association between HBW, LBW or HorLBW and diabetes was found, which remained the same when the data was stratified by sex. After accounting for potential confounders using a forward stepwise LR technique (adjusted ORs, Table 6.38), the relationship between HBW and HorLBW and diabetes remained significant only for RI females.

In the between sample population comparisons for HBW and LBW (all, and stratified by sex, Table 6.38), the crude ORs that indicated significant relationships remained significant (usually to a lesser degree) when adjusted for potential confounders. The adjusted ORs for HorLBW resulted in statistical significance for only the comparison between female RI diabetics and female GP non-diabetics.

The final predictive models for birth weight and adult onset diabetes mellitus for each of the five within and between sample population matched paired datasets include the covariates indicated in Table 6.38.

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Table 6.38 Summary of multivariate analyses using conditional logistic regression (CLR) for HBW and/or LBW.

Pair wise comparisons		Covariates included ⊕	n pairs	HBW (>4000g) vs. all other Bwts OR (CI)	LBW (<2500g) vs. all other Bwts OR (CI)	HBW or LBW vs. normal Bwts OR (CI)
RI-Dm + RI-nonDm						
all	crude		679	1.63 (1.20, 2.24) *	1.06 (0.66, 1.72)	1.49 (1.13, 1.96) *
	adj.	Mat	678	1.33 (0.96, 1.86)	1.00 (0.61, 1.66)	1.25 (0.93, 1.66)
Males	crude		235	0.82 (0.49, 1.36)	0.67 (0.27, 1.63)	0.88 (0.70, 1.10)
	adj.	Mat	235	0.70 (0.41, 1.19)	0.63 (0.25, 1.58)	0.82 (0.65, 1.04)
Females	crude		444	2.53 (1.66, 3.87) *	1.30 (0.73, 2.33)	2.21 (1.54, 3.17) *
	adj.	Mat	443	1.99 (1.27, 3.12) *	1.23 (0.67, 2.28)	1.80 (1.23, 2.64) *
RI-Dm + GP-Dm						
all	crude		786	1.84 (1.36, 2.50) *	0.56 (0.37, 0.85) *	1.25 (0.96, 1.61)
	adj.	Mat, Par, SB	779	1.66 (1.20, 2.30) *	0.54 (0.34, 0.85) *	1.15 (0.87, 1.51)
Males	crude		277	1.06 (0.66, 1.72)	0.64 (0.28, 1.49)	0.93 (0.61, 1.43)
	adj.	Mat, Par	274	1.13 (0.68, 1.89)	0.51 (0.21, 1.25)	0.92 (0.58, 1.45)
Females	crude		509	2.65 (1.75, 4.00) *	0.53 (0.33, 0.86) *	1.46 (1.06, 2.01) *
	adj.	Mat, Par	505	2.19 (1.42, 3.38) *	0.57 (0.34, 0.97) *	1.33 (0.95, 1.88)
RI-Dm + GP-nonDm						
all	crude		734	2.36 (1.68, 3.32) *	0.54 (0.36, 0.82) *	1.38 (1.05, 1.80) *
	adj.	Par	730	2.01 (1.41, 2.85) *	0.52 (0.34, 0.80) *	1.20 (0.91, 1.59)
Males	crude		254	1.44 (0.87, 2.40)	0.38 (0.19, 0.80) *	0.89 (0.58, 1.36)
	adj.	Par	251	1.32 (0.79, 2.22)	0.35 (0.17, 0.74) *	0.80 (0.51, 1.24)
Females	crude		480	3.41 (2.12, 5.48) *	0.65 (0.39, 1.08)	1.82 (1.28, 2.57) *
	adj.	Par	479	2.76 (1.69, 4.50) *	0.68 (0.40, 1.15)	1.59 (1.11, 2.28) *
RI-nonDm +GP-nonDm						
all	crude		772	1.41 (0.99, 2.02)	0.57 (0.37, 0.85) *	0.94 (0.72, 1.24)
	adj.	Mat, Par	772	1.37 (0.95, 1.98)	0.57 (0.38, 0.87) *	0.93 (0.70, 1.23)
Males	crude		273	1.41 (0.86, 2.31)	0.46 (0.23, 0.94) *	0.96 (0.63, 1.45)
	adj.	Mat, Par	273	1.42 (0.85, 2.38)	0.46 (0.22, 0.95) *	0.95 (0.62, 1.47)
Females	crude		499	1.42 (0.84, 2.39)	0.63 (0.38, 1.05)	0.93 (0.65, 1.34)
	adj.	Mat, Par	499	1.33 (0.78, 2.28)	0.67 (0.40, 1.12)	0.93 (0.64, 1.35)
GP-Dm + GP-nonDm						
all	crude		965	1.27 (0.92, 1.75)	0.97 (0.71, 1.34)	1.12 (0.89, 1.42)
	adj.	Mat, Par	963	1.23 (0.89, 1.72)	1.03 (0.74, 1.44)	1.14 (0.89, 1.46)
Males	crude		355	1.29 (0.83, 2.03)	0.62 (0.35, 1.12)	0.98 (0.68, 1.41)
	adj.	Mat, Par	354	1.34 (0.84, 2.15)	0.61 (0.33, 1.13)	1.00 (0.69, 1.46)
Females	crude		610	1.24 (0.79, 1.97)	1.20 (0.81, 1.77)	1.23 (0.91, 1.68)
	adj.	Mat, Par	609	1.16 (0.72, 1.85)	1.30 (0.87, 1.94)	1.25 (0.91, 1.72)

* statistically significant at p ≤ 0.05

⊕ only those covariates statistically significant at p ≤ 0.05, in the presence of all other potential confounding variables, are included in the final CLR model

Covariates: maternal age (Mat), maternal parity (Par), previous stillborn (SB)

Upon review of the results in Table 6.38, it seemed possible that significant LBW relationships could be influenced by premature and twin births and significant HBW relationships could be influenced by postmature births. This was investigated further although it was not planned for in the analytic strategy.

Table 6.39 summarizes the comparison of birth weight distribution using all-birth weight data (n=3992) and data restricted to singleton births with gestational age 38-41 weeks (n=2804). No significant differences were found between datasets for HBW rates. However, in all groups, LBW rates were significantly less in the sub-sample of singleton-term births and this difference was greatest for GP subjects (p <0.001). The reduction in LBW rates increased the proportion of "normal" birth weights and resulted in a significant difference only for GP subjects.

Table 6.39. Comparison of dataset using all Bwts vs. dataset using only singleton births and gestational age 38-41 wks.

Group	n	Bwt category		
		< 2500 g	2500-4000 g	> 4000 g
% of n distribution for all Bwt dataset				
RI Dm	846	4.8 %	79 %	16.2 %
RI nonDm	882	4.8 %	84.6 %	10.7 %
GP Dm	1164	8.6 %	81.4 %	10 %
GP nonDm	1100	8.2 %	84.4 %	7.5 %
Total	**3992**	**6.8 %**	**82.4 %**	**10.7 %**
% of n distribution for singleton & gest.age 38-41 wks dataset				
RI Dm	601	2.7 %	81 %	16.5 %
RI nonDm	622	2.3 %	88 %	10.3 %
GP Dm	820	4.1 %	85 %	10.6 %
GP nonDm	761	4.3 %	88 %	7.2 %
Total	**2804**	**3.5 %**	**86 %**	**10.9 %**

Comparison of datasets	% difference	X^2 p value*	% difference	X^2 p value*	% difference	X^2 p value*
RI Dm	2.1 %	0.05 *	2 %	NS	0.3 %	NS
RI nonDm	2.5 %	0.02 *	3.4 %	NS	0.4 %	NS
GP Dm	4.5 %	<0.001 *	3.6 %	0.03 *	0.6 %	NS
GP nonDm	3.9 %	<0.001 *	3.6 %	0.02 *	0.3 %	NS
Total	**4.5 %**	**<0.001 ***	**3.6 %**	**<0.001 ***	**0.2 %**	**NS**

* statistically significant at p ≤ 0.05

Analyses of the crude and adjusted ORs for HBW and LBW given in Table 6.38 were repeated using the singleton-term birth dataset (see Table 6.40 for results). In effect, the LBW relationships previously significant using all birth weight data, lost statistical significance using the singleton-term sub-sample data. However, for HBW, the same relationships remained statistically significant in both datasets (and were generally stronger in the singleton-term birth dataset) except for the within RI population comparison where the adjusted OR for RI females marginally lost statistical significance.

Table 6.40. Summary of multivariate analyses using CLR for HBW and LBW for gestational age 38-41 wks and singleton births only

Pair wise comparisons	Covariates included ⊕	n pairs	HBW (>4000g) vs. all other Bwts OR (CI)	LBW (<2500g) vs. all other Bwts OR (CI)
RI-Dm + RI-nonDm				
all crude		384	1.77 (1.17, 2.68) *	1.22 (0.51, 2.95)
adj.	Mat	383	1.24 (0.79, 1.95)	1.30 (0.51, 3.33)
Males crude		123	1.00 (0.50, 2.00)	0.33 (0.35, 3.21)
adj.	Mat	123	0.69 (0.32, 1.49)	0.19 (0.02, 2.20)
Females crude		261	2.42 (1.42, 4.13) *	1.67 (0.61, 4.59)
adj.	Mat	260	1.71 (0.96, 3.06)	2.04 (0.69, 6.06)
RI-Dm + GP-Dm				
all crude		449	1.92 (1.30, 2.84) *	0.67 (0.30, 1.48)
adj.	Mat, Par, SB	446	1.77 (1.17, 2.68) *	0.64 (0.27, 1.50)
Males crude		154	1.06 (0.55, 2.01)	1.00 (0.14, 7.10)
adj.	Mat, Par	152	1.07 (0.54, 2.11)	0.59 (0.08, 4.49)
Females crude		295	2.70 (1.62, 4.51) *	0.62 (0.26, 1.49)
adj.	Mat, Par	294	2.45 (1.43, 4.21) *	0.66 (0.26, 1.70)
RI-Dm + GP-nonDm				
all crude		415	2.71 (1.70, 4.33) *	0.79 (0.40, 1.55)
adj.	Par	412	2.20 (1.35, 3.56) *	0.83 (0.41, 1.69)
Males crude		134	1.43 (0.72, 2.83)	0.29 (0.06, 1.38)
adj.	Par	132	1.26 (0.62, 2.54)	0.27 (0.54, 1.34)
Females crude		281	4.50 (2.27, 8.93) *	1.08 (0.49, 2.37)
adj.	Par	280	3.49 (1.72, 7.07) *	1.23 (0.54, 2.79)
RI-nonDm + GP-nonDm				
all crude		427	1.71 (1.03, 2.83) *	0.53 (0.24, 1.19)
adj.	0		▪	▪
Males crude		130	1.64 (0.77, 3.47)	0.25 (0.03, 2.24)
adj.	0		▪	▪
Females crude		297	1.77 (0.90, 3.50)	0.62 (0.26, 1.49)
adj.	0		▪	▪
GP-Dm + GP-nonDm				
all crude		544	1.51 (0.99, 2.32)	0.64 (0.36, 1.16)
adj.	Mat, Par	544	1.45 (0.93, 2.25)	0.65 (0.35, 1.20)
Males crude		190	1.87 (0.99, 3.50)	0.33 (0.09, 1.23)
adj.	0 ; Mat, Par	190	▪	0.31 (0.08, 1.18)
Females crude		354	1.25 (0.69, 2.25)	0.79 (0.40, 1.55)
adj.	Mat	354	1.11 (0.61, 2.04)	0.86 (0.43, 1.73)

* statistically significant at p ≤ 0.05
⊕ only those covariates statistically significant at p ≤ 0.05, in the presence of all other potential confounding variables, are included in the final CLR model
Covariates: maternal age (Mat), maternal parity (Par), previous stillborn (SB)

7.   DISCUSSION

7.1   Methodological Issues: Strengths and Limitations

7.1.1   Overview of Study Strengths and Limitations

The methodology used in this study has both strengths and limitations which
may have affected the study results. First, the main strengths of the study will be
identified. A discussion of relevant limitations will follow.

Given the long lag time from birth to the development of T2DM, the case
control design offered a relatively quick and cost effective way to study the area of
interest. The use of Saskatchewan Health's administrative databases had several
advantages: the data covered the entire provincial population which enhanced the
capture of a representative sample, and elevated the validity and generalizability of
the study; the structure for the DRSV-HIRF-UID record linkage was in place and
could be linked to other data sources such as vital statistics; the identification of
diabetics was based on physician diagnosis which can be more reliable and valid
than self-report; experienced, impartial programmers were involved in data extraction
therefore enhancing the objectivity and validity of the data; no interviews were
necessary which eliminated the problem of recall bias; and no interventions were
necessary, hence, no risk to study subjects.

Using a comprehensive administrative database also enabled a large study
sample to be captured, thereby increasing the study power. Cases and controls were
identified from the same source population using the same inclusion criteria which
increased the validity of case-control comparisons. All identified cases (RI-Dm) were
entered and suitable one to one matched controls were randomly selected for each of
the three control groups from a large pool of potential candidates. Since age is a
strong predictor of diabetes, and sex is related to both diabetes and birth weight,
matching on age and sex eliminated potential biases that could otherwise be
attributed to these factors. A 1:3 case-control matching also provided balance in the
numbers of cases and controls that occurred at each level of age and sex, resulting

in a more precise estimation of the OR. The data analyses accounted for pair wise matching which enhanced the validity of results.

The limitations of this study relate primarily to two vulnerable features of case-control studies, namely the sampling scheme and the retrospective sequence of observations[189]. These two features make case-control studies susceptible to systematic errors (biases) which could result in erroneously rejecting the null hypothesis when it is in fact true (type I error) or erroneously failing to reject the null hypothesis when it is in fact false (type II error). The biases that pertain to this study fall into the general categories of selection bias, misclassification bias and the effects of extraneous confounding factors. The use of macrosomia as a proxy measure for GDM and the definition of HBW used in this study could also limit the interpretation of results.

In this study an observed association between high and/or low birth weight and diabetes can not be taken as proof of a cause-effect relationship between the intrauterine environment and T2DM. However, a cause-effect relationship is unlikely if an association cannot be shown, unless a type II error is present.

7.1.2 Selection Bias

Selection bias can occur if the manner in which subjects are sampled for investigation is questionable[189]. All subjects in the study were those who survived birth. Given the high mortality associated with LBW infants, particularly in earlier decades, LBW infants could be underrepresented and could affect the degree of association between LBW and T2DM. If the underrepresentation of LBW occurred among both cases and controls equally, (as would be expected for "within" RI and GP sample population comparisons) only a slight underestimation of the LBW/T2DM association could result. If the underrepresentation of LBW occurred more frequently among cases than controls, then the observed measure of association between LBW and T2DM could be underestimated to a large degree. This would be the situation expected in the comparisons between sample populations where the underrepresentation of LBW would be greater for RI than GP subjects. Similarly, a proportion of infants from diabetic pregnancies who died as a result of GDM related complications could have been HBW infants, resulting in a potential underestimation

of the observed association between HBW and T2DM. Again, because neonatal and infant mortality was greater for RI compared to GP, particularly in earlier decades, only the between sample population comparisons would be expected to possibly result in an underestimation of the true HBW/T2DM effect.

The DRSV registry used to identify diabetics is based on cases of clinically diagnosed diabetes, which could underestimate the frequency of diabetes by as much as 50%[61] and subsequently dilute the observed study effect. The reliability of ICD9 codes for accurate diagnosis was not validated; however, the number of falsely diagnosed cases was probably minimal. In addition to variable screening practices, diagnosed diabetics could have been subjects with more overt risk factors for diabetes, such as obesity, thereby making them more likely to have been screened. Also, more recent and more rigorous diabetic screening among Aboriginal people (both RI and non-RI) combined with an increased birth rate among Aboriginal peoples, could result in an unknown variation in the proportion of GP subjects who are in fact Aboriginal. This may underestimate the effect observed in the between sample population comparisons.

All diabetics were identified according to the first ICD9 250 or 362 event between January 1, 1991 through December 31, 1994. No distinction was made between first ever event and recurring event, thus diabetics identified were essentially prevalent cases, not incident cases. No measures were taken to assure diabetics were newly diagnosed, although capture of the first ICD9 event within the 4 year period enhanced the likelihood that those captured towards the end of the time frame were incident cases. Not only were diabetic subjects prevalent cases, but they were also diabetics who had survived at least until January 1, 1991. This survival bias must be taken into account during the interpretation of results.

Use of the 4 year period to select diabetics may have contributed to further biases. Subjects with an ICD9 250 or 362 event before January 1, 1991 who did not reappear within the 4 year period, were not captured as diabetic and could have fallen into the potential non-diabetic population. The ensuing misclassification could underestimate the true effect. No measures were taken to assure that subjects in the potential non-diabetic control sample were in fact non-diabetic, such as linkage with Prescription Drug Services Branch (PDSB) for the use of oral hypoglycemic agents or

insulin. In any event, RI would not be captured in PDSB because the pharmaceutical database for RI is federal, not provincial.

The fact that birth weights were not recorded prior to 1950 excluded subjects older than age 45 from the study, therefore narrowing the times pan from which birth cohorts were formed. This could make it more difficult to show a change in the association between birth weight and T2DM over time.

The unavailability of birth weight data for the initial study sample entailed a loss of information and a reduction in size of the final study sample. Because unmatched case-control pairs could not be analyzed, the sample groups that ultimately made it to the matched pair analysis entailed a further loss of information. The loss of birth weight data was greatest for RI diabetics which reduced the number of pair wise comparisons with each control group to almost half. A reduction in sample size could lower the power of the study and limit the generalizability of results as well as increase the risk of making a type II error.

The loss of birth weight data tended to make the final study sample younger with relatively more females; mothers of these subjects also tended to have lower parity and relatively more previous stillbirths. Thus, older subjects, male subjects, high parity and no previous stillbirth may be underrepresented and observations pertaining to these factors could be underestimated.

7.1.3   Misclassification Bias

Misclassification bias can occur if the exposure or disease status is inaccurately assigned[189]. In this study there are three main sources of possible misclassification of disease status that could lead to an underestimation of the true effect. First, the ICD9 codes used to determine diabetic status were unable to differentiate between T1DM and T2DM. As discussed in the literature review, the relationship between birth weight and T1DM remains unclear. Given that essentially all RI diabetics are T2DM and 85-90% GP diabetics are T2DM, the effect of birth weight and T1DM, if any, would be minimal. Second, the *362-only* problem resulted in leaving 95 RI presumed diabetics and 24 GP presumed diabetics in the original study sample. This could have resulted in non-diabetics being included in the

diabetic group. Finally, the non-diabetic population inevitably included diabetics not captured, undiagnosed diabetics and people destined to be future diabetics.

Misclassification of subjects according to the racial groupings used in this study was also a potential source of bias. The sample representing Aboriginal people was confined to subjects with RI status identified as such in the HIRF. Some of these individuals could have been non-Aboriginal women who gained RI status through marriage. It was not possible to distinguish any other Aboriginal groups apart from RI so that Métis and Aboriginal people without RI status were incorporated into the GP sample. HIRF is a subset of the federal Medical Services Branch (MSB) database and is known to have a smaller denominator of RI people than MSB by 10-20%[190]. Consequently, RI who were not captured by HIRF were incorporated into the GP sample, which further "muddied" the sample populations. These circumstances would tend to make the study effect more conservative for observations between populations (due to unclean groups). Alternately, the chance of type I error could increase for observations within the GP sample because the effect attributed to non-Aboriginal is really due to Aboriginal (Métis, non-RI or RI not captured).

The method of obtaining exposure data is an important source of information bias and can result in misclassification[189]. The deterministic methodology used to link DRSV-HIRF-UID data with vital Statistics data sources involved many manual searches and a large quantity of data transcription from birth registration forms. This could increase the error factor and decrease the number of data matches found. Although accurate transcription of data was validated by cross checking a random sample of 118 birth registrations, validity of the match of vital statistics data to primary records was not assessed. It is not possible to estimate the degree to which this could affect the chance of type I or type II error.

Errors in birth weight measure could have lead to the misclassification of high or low birth weight. Inaccurate birth weight measures could have originated from a number of sources, including unknown variability in equipment (quality of scale, calibration), method (inter / intra-agency standardization, trends according to era, period of time between birth and birth weight measure, rounding off, conversion from imperial to metric measure) and person (experience, eyesight, personal technique). It was impossible to assess the reliability or validity of birth weight measures as indicated on birth registrations. There is no reason to believe that misclassification of

birth weight would be differentially distributed among cases and controls; therefore, potential errors in birth weight would not be expected to affect the observed results.

7.1.4 Confounding

Confounding refers to a distortion in the study effect which results from the mixing of the exposure-disease association with the effect(s) of extraneous variable(s)[189]. In this study, control for the effects of potential confounding was limited to the dataset variables and was partially achieved through the use of a matched study design, the method of subject selection, and analytical adjustment. Because the dataset for this study did not include information on important risk factors related to T2DM (i.e. obesity, lifestyle, genetic predisposition) and birth weight (i.e. maternal weight), it was not possible to control for all potential confounding factors extraneous to the association between birth weight and T2DM. Consequently, the study effect could have been distorted resulting in either type I or type II error.

7.1.5 Macrosomia as a Proxy for GDM

The use of macrosomia as an indirect marker of GDM is another limitation of this study. As stated in the literature review, many HBW infants are born to mothers without GDM and many mothers with GDM deliver normal weight infants. The inability to assess the effect of important confounding factors (maternal obesity) and the lack of a clearly defined attributable risk for HBW by GDM in the literature adds to the complexity of the problem. In addition, increased rates of macrosomia among Canadian Aboriginal women compared to non-Aboriginal women, as indicated in the literature, raises the issue of using uniform birth weight standards for between population comparisons. This issue is discussed further below.

Lack of a universally accepted definition of macrosomia may limit the comparability of results to other studies. The measure for HBW in this study was based on an absolute birth weight > 4000 g. Although this is the most commonly used definition of macrosomia, it fails to consider the influence of gestational age on birth weight. Macrosomia could have been defined using the 90th percentile birth weight for gestational age (LGA); however, this would have been problematic for

subjects with missing gestational age and could have resulted in misclassification bias or a reduction in sample size.

For comparisons of birth weight between sample populations, the issue of "race-specific birth weight standards" comes forth. Because normal birth weights for gestational ages may vary with geography and ethnicity[191], an infant that is LGA using a set of normative data derived from one population may not meet the criteria using a set of normative data derived from another population. Alternate birth size indices such as the ponderal index (PI) and birth symmetry index (SI) are considered to be relatively free of influence of race, gender and gestational age and have been suggested as a rational means of comparing birth weight data derived from different populations[191]. However, it was not possible to use PI or SI measures in this study because the information required to calculate these measures, namely, the length of the infant, was not available on birth registrations.

7.2   Interpretation of Results

The results of this study will be discussed in relation to the research questions set out for this thesis in chapter 4.

Primary Research Question:
1.   Among Saskatchewan RI people, is there an association between HBW or LBW and T2DM?
        1.1   Has the strength of this association changed from the middle to the latter part of this century?
        1.2   Is the strength of this association the same between males and females?

This study shows an association between HBW and T2DM among Saskatchewan RI people. This association is considered to be a conservative estimate in view of the various biases that could underestimate the study effect, as discussed in section 7.1. The most common risk factors for Macrosomia are maternal obesity, gestational age >42 weeks, GDM and male sex[117 192]. The study findings cannot be explained by male sex because the cases and controls were matched on gender which therefore controlled for this factor. Differences in rates of prolonged gestation are also unlikely to explain the results because the association between HBW and T2DM remained using the sub-sample of singleton subjects with 38-41

weeks gestation. Hence, differences in rates of maternal obesity and /or GDM probably account for the study observations. Independent genetic factors may also be possible.

It is difficult to discern the relative importance of obesity versus GDM in causing HBW given that both maternal obesity and GDM are risk factors for macrosomia and maternal obesity is also a risk factor for GDM. However, it seems very plausible that pregnancy induced maternal carbohydrate intolerance may be an important factor in the effect observed in this study. The finding that RI diabetics tended to have mothers with characteristics associated with GDM or GDM recurrence (older, higher parity, previous stillbirths) compared to RI non-diabetics also support this hypothesis.

The HBW / T2DM association is consistent with previous findings among the Pima Indians[42] and in animal models[161]. In these studies respectively, the observed effect was attributed to maternal diabetes and GDM specific factors, which further supports the hypothesis that GDM is an important factor in the observed effect of this study. Gestational IGT could also be contributing to the study effect since it is also independently associated with macrosomia[149][150][140].

After controlling for maternal age, the association between HBW and T2DM was no longer significant. Taken at face value, one could interpret this to mean that the observed association could be attributed to maternal age. However, the adjustment for maternal age could be disputed because the literature does not support the basis for it to be a confounder: it is not known to be an independent predictor of T2DM in the offspring. Instead, increased maternal age is a risk factor for GDM and is associated with macrosomia. It can therefore be argued that what appears to be a primary relationship between maternal age and T2DM is actually reflected through birth weight. The same reasoning would apply to the variables parity and previous stillbirth.

The strong association between HBW and T2DM for RI females but not for RI males may be due in part to a smaller sample size for male RI subjects resulting in a lower statistical power. Two factors that contributed to this smaller sample size were the greater number of female versus male RI cases identified at the outset of this study and the greatest loss of birth weight information that occurred for RI male diabetic subjects. The strong association between HBW and T2DM for RI females

could also reflect a (diagnostic) selection bias for females with risk factors for T2DM through earlier and more frequent encounters with health services. Alternately, this may be a new finding that reflects sex differences for exposure of the developing fetus to the diabetogenic intrauterine environment. Previous studies[24] have suggested that Aboriginal females, particularly adolescent girls and women during child bearing years[95], were the first to be consistently affected by lifestyle changes during early stages of acculturation. The intrauterine environment may play a key role in the initial expression of this adaptation. If this were true, sex differences would be expected to be less apparent where nontraditional lifestyles were adopted earlier. Another explanation for this finding could be that the interactive effect of intrauterine environmental factors, genetic predisposition and lifestyle factors throughout the lifecycle differentially affects RI males and females with respect to T2DM development in adulthood.

The notion of significant gender differences with respect to the link between birth weight and T2DM was observed in the British studies in which the LBW / T2DM relationship was found to be stronger in men than in women[34]. It is possible that more intense exposure to intrauterine environmental conditions not yet fully identified differentially affect male and female fetuses with respect to T2DM development in later life. Using birth weight as the crude surrogate index of unknown environmental conditions, this phenomenon would appear at extreme values of the birth weight spectrum so that male LBW infants and female HBW infants would represent the highest risk for T2DM in adulthood.

The association between HBW and T2DM increased in strength from the middle to the latter part of this century. This trend was evident despite the following two conditions. First, the data was partitioned into three smaller sub-samples which reduced the statistical power to detect differences between birth cohorts. Second, the more recent birth cohorts were younger than the earlier cohorts at the time of this study having therefore had less time to develop T2DM. What has essentially been shown here is that the younger the age of T2DM diagnosis, the stronger the relationship with HBW and the significant association between HBW and T2DM has occurred only in recent years. This observation supports the hypothesis of Dyck and Tan[24] that GDM may be one of the initial manifestations of carbohydrate intolerance in the Aboriginal population, a finding that is apparent among Aboriginal people in

Saskatchewan because in this part of Canada, the diabetes epidemic is at a relatively early stage and is probably still evolving. The increased HBW / T2DM relationship over time may also be an indication of the phenomenon of diabetic pregnancy contributing to the cyclic transference of diabetogenic effects on subsequent generations as observed among the Pima by Pettitt et al[28].

Contrary to findings in the recent literature[33 34 35 36 37 39 40 41], an association between LBW and T2DM was not observed in the RI sample population. This could be explained in part by selective survival bias due to higher neonatal and infant mortality that has been documented among Saskatchewan RI people[45]. The large loss of birth weight data for older RI subjects and the exclusion of subjects > 44 years could also account for the absence of a LBW / T2DM association because LBW rates were probably higher in earlier years when poor maternal / fetal nutrition was more likely and health care was less accessible[46]. Lack of a LBW / T2DM relationship in this study reinforces the considerations of McCance et al[42] : the excess of T2DM in the Pima found to be associated with LBW accounted for only 6% of diabetes in this population and most Pima who develop diabetes have birth weights that fall within the usual range.

Secondary Research Question:
2.   Is there a similar association between HBW or LBW and T2DM among GP
         people in Saskatchewan?
         2.1   Is there a difference in the degree of these associations between
                  RI and GP people in Saskatchewan?

No association between either HBW or LBW and T2DM was observed among GP subjects in this study. The absence of a HBW / T2DM association is consistent with the findings of other studies involving predominantly Caucasian populations [22-29]. As suggested in other studies[175], a lower prevalence of GDM among GP women possibly explains this observation.

The absence of a LBW / T2DM association is inconsistent with findings in the recent literature[33 34 35 36 37 39 40 41]. The loss of birth weight data for older aged subjects and the exclusion of subjects > 44 years could possibly account for this observation because LBW rates in Saskatchewan were slightly higher two decades ago[46] and were probably even higher in earlier years. Also, because the onset of diabetes in GP Canadians tends to occur in mid-life (as opposed to early adulthood in Aboriginal

people), misclassification of diabetic status as well as other potential biases discussed in section 7.1 could contribute to an underestimation of the observed effect.

Secondary Research Questions

3.   Among those with T2DM, is there a difference in the rates of HBW or LBW between RI and GP people in Saskatchewan?

4.   Among non-diabetics, is there a difference in the rates of HBW or LBW between RI and GP people in Saskatchewan?

5.   Is there a difference in the rates of HBW or LBW between RI people with T2DM and GP people without diabetes?

The patterns of HBW rates in RI and GP samples are generally consistent with the patterns found in other studies in Saskatchewan[156]. The fact that HBW rates are highest for RI diabetics and appear to be increasing in more recent generations gives additional support to the hypothesis that maternal carbohydrate intolerance could partially account for these findings.

The patterns of LBW rates in the RI and GP samples were not consistent with the patterns found in other studies in Saskatchewan[45,46]. Instead, LBW rates were generally higher among GP subjects than RI subjects and the trend for LBW appeared to be increasing over time within the RI population. Selective survival bias due to higher neonatal and infant mortality among Saskatchewan RI people in earlier decades may partially account for these findings.

Critics may suggest that the use of uniform birth weight standards for between sample population comparisons invalidates the differences observed in this study. There appears to be a general impression that infants born to Aboriginal women are heavier than infants of non-Aboriginal women. How are we to know if this is a true difference or an apparent difference subject to recall bias? If Aboriginal infants are truly heavier, it may in fact be largely attributable to higher rates of maternal obesity and/or GDM. In addition, clearly defined "race-specific" birth weight standards have not been established for Aboriginal peoples nor is there any indication that they will be. If separate standards should ever be developed, the results of this study could be reassessed at that time.

7.3 Relevance and Practical Significance

This study adds to the epidemiological information in this field by providing further evidence for an association between HBW and later development of T2DM. This study also gives additional support for the hypothesis that GDM may play a significant role in the inter-generational cyclic transference of diabetogenic effects. There are two new findings that have resulted from this study: the observed association between HBW and T2DM in RI people increased in strength over time and was stronger for RI females than for RI males. This study provides an impetus to target modifiable risk factors for GDM, such as obesity, for which effective primary prevention strategies should be developed. Programs to prevent GDM and to diagnose and optimally manage diabetes during pregnancy could help to reduce the occurrence of T2DM among future generations of Saskatchewan Aboriginal peoples.

APPENDIX I

Word Health Organization classification of diabetes mellitus and allied categories of glucose intolerance.*

A. Clinical classes

    1) Diabetes mellitus

        Insulin-dependent diabetes mellitus

        Non-insulin-dependent diabetes-mellitus
            a) Non-obese
            b) Obese

        Malnutrition-related diabetes mellitus

        Other types of diabetes associated with certain conditions and syndromes
            1) pancreatic disease
            2) disease of hormonal etiology
            3) drug or chemical induced conditions
            4) abnormalities of insulin or its receptors
            5) certain genetic syndromes
            6) miscellaneous

    2) Impaired glucose tolerance
            a) Non-obese
            b) Obese
            c) Associated with certain conditions and syndromes

    3) Gestational diabetes mellitus

B. Statistical risk classes (normal glucose tolerance but substantially increased risk of developing diabetes

    1) Previous abnormality of glucose tolerance
    2) Potential abnormality of glucose intolerance

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* Kahn CR, Weir GC, editors. Joslin's diabetes mellitus. 13th edition. Pennsylvania:Lea & Feber, 1994.

APPENDIX II

Calculations for derivations of relative risk (RR) for birth weight > 4000 g (HBW) and attributable risk (AR) for birth weight > 4000 g by GDM in the Aboriginal and non-Aboriginal populations of pregnant women in Saskatchewan.

Presentation of cohort data with count denominator in 2 x 2 table

		Disease (HBW) +	–	Total
Exposure	+	A	B	A+B
(GDM)	–	C	D	C+D
	total	A+C	B+D	N=(A+B+C+D)

Relative Risk (RR) = $\dfrac{\text{incidence rate among exposed } (I_e)}{\text{incidence rate among nonexposed } (I_o)}$ = $\dfrac{A / A+B}{C / C+D}$

Attributable risk (AR) = $I_e - I_o$ = (A / A+B) - (C / C+D)

A) For non-Aboriginal women

1. incidence GDM = 3%
   rate of bwt >4000 g in GDM = 20%,
   overall pop. rate bwt >4000 g = 12%

		+ HBW -		Tot
GDM	+	6	24	30
	–	114	856	970
		120		1000

RR = (6/30) / (114/970)   AR = 0.2 - 0.118
    = 0.2 / 0.118   = .082
    = 1.7

2. incidence GDM = 4%
   rate of bwt >4000 g in GDM = 20%
   overall pop. rate bwt >4000 g = 12%

		+ HBW -		Tot
GDM	+	8	32	40
	–	112	848	960
		120		1000

RR = (8/40) / (112/960)   AR = 0.2 - 0.117
    = 0.2 / 0.117   = .083
    = 1.7

B) For Aboriginal women

3. incidence GDM = 10%
   rate of bwt >4000 g in GDM = 30%
   overall pop. rate bwt >4000 g = 16%

		+	HBW -	Tot
GDM	+	30	70	100
	-	130	770	900
		160		1000

RR = (30/100) / (130/90)   AR = 0.3 - 0.144
   = 0.3 / 0.144   = 0.156
   = 2.1

4. incidence GDM = 15%
   rate of bwt >4000 g in GDM = 30%
   overall pop. rate bwt >4000 g = 16%

		+	HBW -	Tot
GDM	+	45	105	150
	-	115	735	850
		160		1000

RR=(45/150) / (115/850)   AR = 0.3 - 0.135
   = 0.3 / 0.135   = 0.165
   = 2.2

5. incidence GDM = 10%
   rate of bwt >4000 g in GDM = 40%
   overall pop. rate bwt >4000 g = 16%

		+	HBW -	Tot
GDM	+	40	60	100
	-	120	780	900
		160		1000

RR=(40/100) / (120/900)   AR = 0.4 - 0.133
   = 0.4 / 0.133   = 0.267
   = 3.0

6. incidence GDM = 15%
   rate of bwt >4000 g in GDM = 40%
   overall pop. rate bwt >4000 g = 16%

		+	HBW -	Tot
GDM	+	60	90	150
	-	100	750	850
		160		1000

RR=(60/150) / (100/850)   AR = 0.4 - 0.118
   = 0.4 / 0.118   = 0.282
   = 3.4

ICD-9* codes used to identify Diabetic population

<u>Code 250</u>:

Diabetes Mellitus
   Adult onset
   Juvenile type
   Unspecified whether Adult onset or Juvenile Type
Diabetes Mellitus without mention of complication
Diabetes with Ketoacidosis
   Diabetic Acidosis
   Diabetic Ketosis
Diabetes with coma
   Diabetic Coma
   Diabetes with Hyperosmolar Coma
Diabetes with Renal Manifestations
   Diabetic Nephropathy
   Intracapillary Glomerulosclerosis
   Kimmelsteil-Wilson Syndrome
Diabetes with Opthalmic Manifestations
   Diabetic Cataract
   Diabetic Retinopathy
Diabetes with Neurological Manifestations
   Diabetic Amyotrophy
   Diabetic Neurpoathy
Diabetes with Peripheral Circulatory Disorders
   Diabetic Gangrene
   Diabetic Peripheral Angiopathy
Diabetes with other specified manifestations
Diabetes with unspecified complications

<u>Code 362</u>:   Diabetic Retinopathy

   plus 51 conditions other than Diabetic Retinopathy such as:

      Other Retinal Disorders
      Other Background Retiopathy and retinal vascular changes

      Other Proliferative Retinopathy
         Retinal Vascular Occlusion
      Separation of Retinal Layers
      Degeneration of Macula and Posterior Pole
      Peripheral Retinal Degenerations
      Hereditary Retinal Dystrophies
      Unspecified Retinal Disorders

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*International Classification of Diseases 9th Revision, World Health Organization, 1977 (vol. 1)

Variables in "Study Subject File"

5464 subjects = 1366 complete quartets

Study ID	unique identifier number
Sex	
Year of Birth	
Month of Birth	
Day of Birth	not available - all coded as "01"
Enrollment date	Sask. Health coverage enrollment date
Termination date	Sask Health coverage termination date
Death	
Diagnosis	according to ICD-9 code
Diagnosis date	Date of diagnosis of diabetes

## Variables in "Birth Registration file"

(study subject file merged with birth registration data)
4833 subjects; incomplete quartets

Year of Birth	as reported in Study Subject File
Month of Birth	as reported in Study Subject File
Sex	as reported in Study Subject File
Study ID	as reported in Study Subject File
Date of Birth	as reported on birth registration
Single/twin/triplet	
Pounds	birth weight in imperial measure
Ounces	birth weight in imperial measure
Grams	birth weight in metric measure
Gestation	at delivery
Born Alive	birth order of this child among live births
Now Living	number of children still living including this child
Stillborn*	number of stillborn deliveries prior to this child
Father's Age	at time of delivery
Mother's Age	at time of delivery

* Prior to 1970, stillborn was defined as born dead after 28 weeks. From 1970-72 until the present, stillborn has been defined as born dead after 20 weeks.

APPENDIX V

Overview of Preparation of "Study Subject file" *
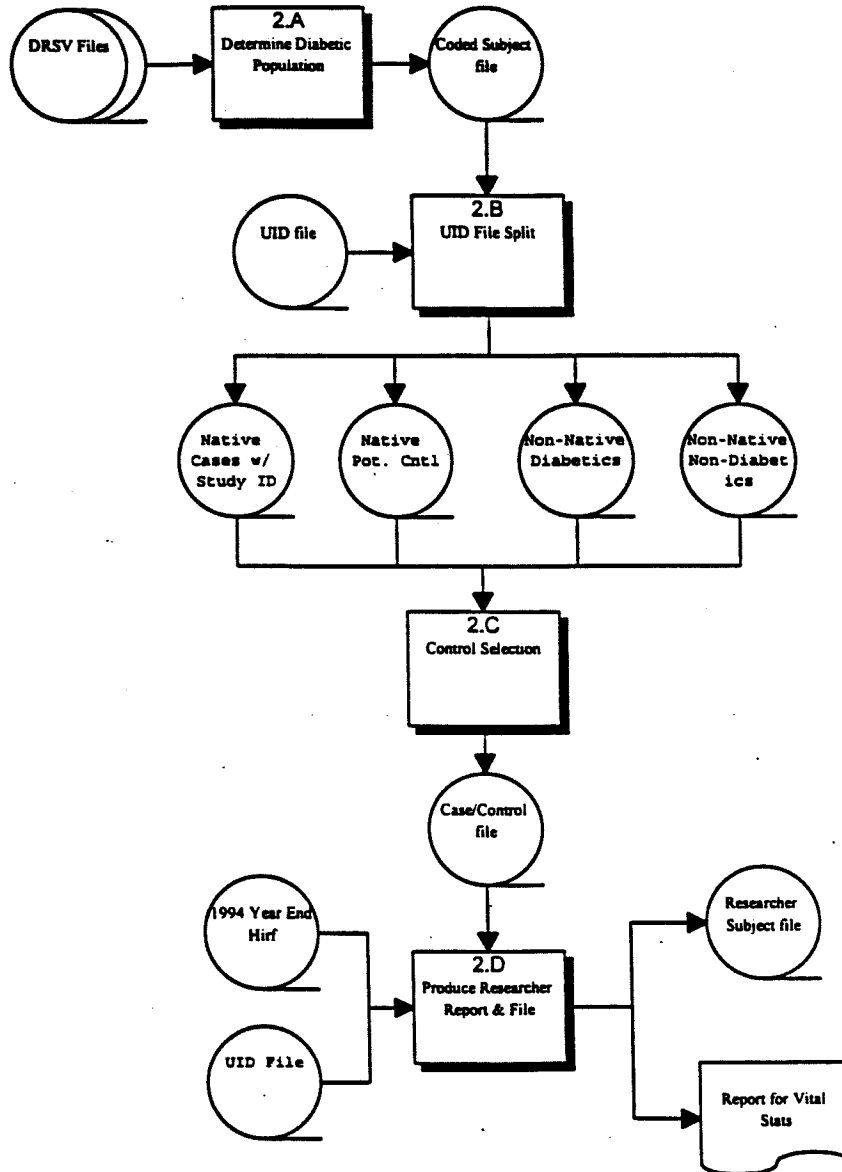
DRSV = Physician' Services File
UID = Unique Identifier File
HIRF = Health Insurance Registration File

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* Provided by: Saskatchewan Health, January, 1995

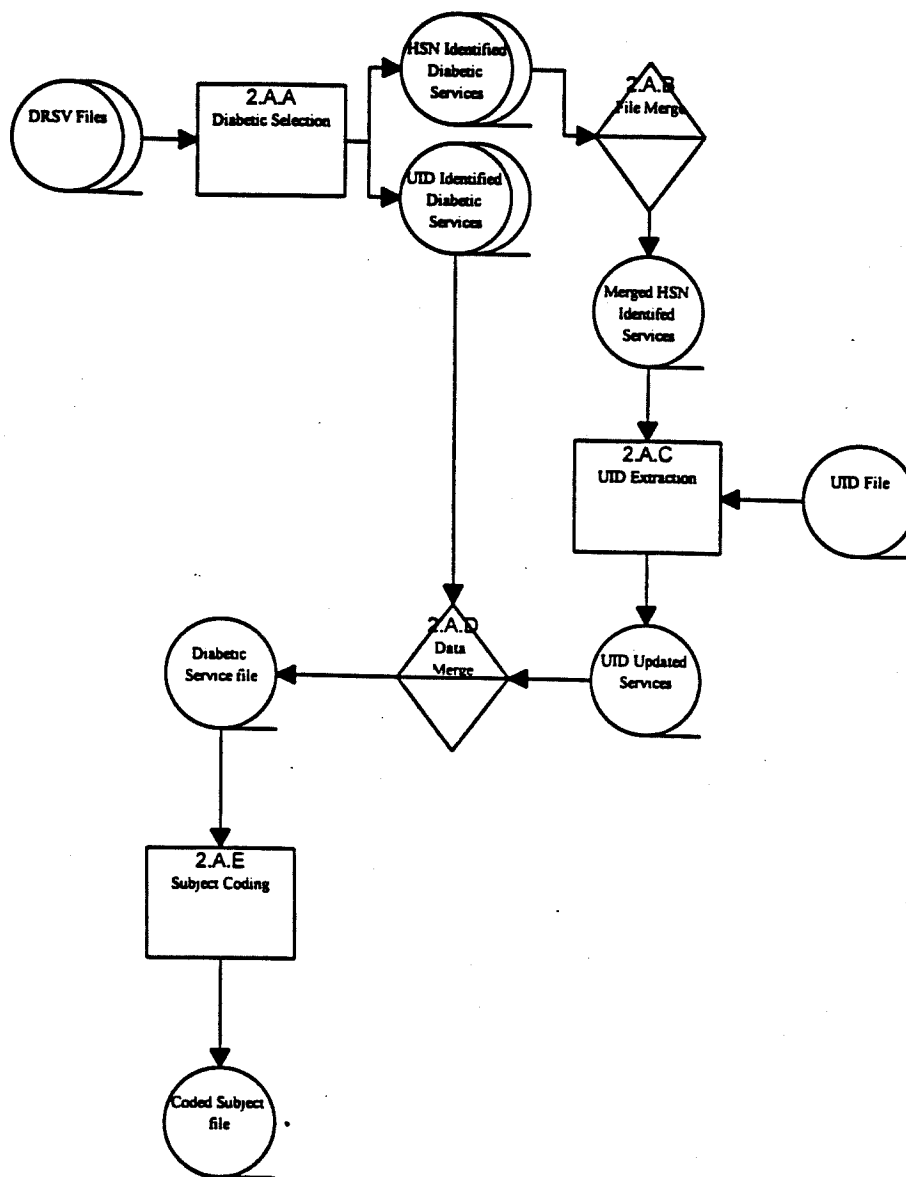# APPENDIX VI

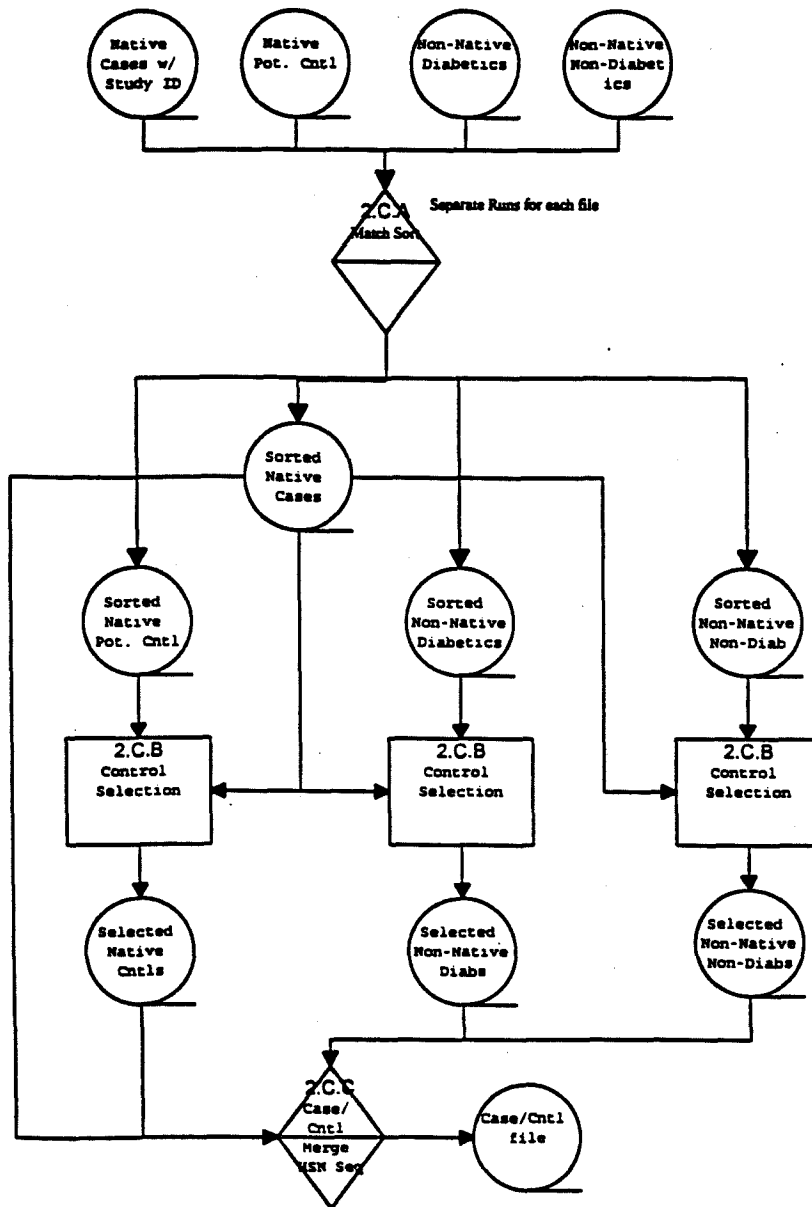## Procedure for Selection of Diabetic Population*

DRSV = Physician' Services File
UID = Unique Identifier File
HSN = Health Services Number

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* Provided by: Saskatchewan Health, January, 1995
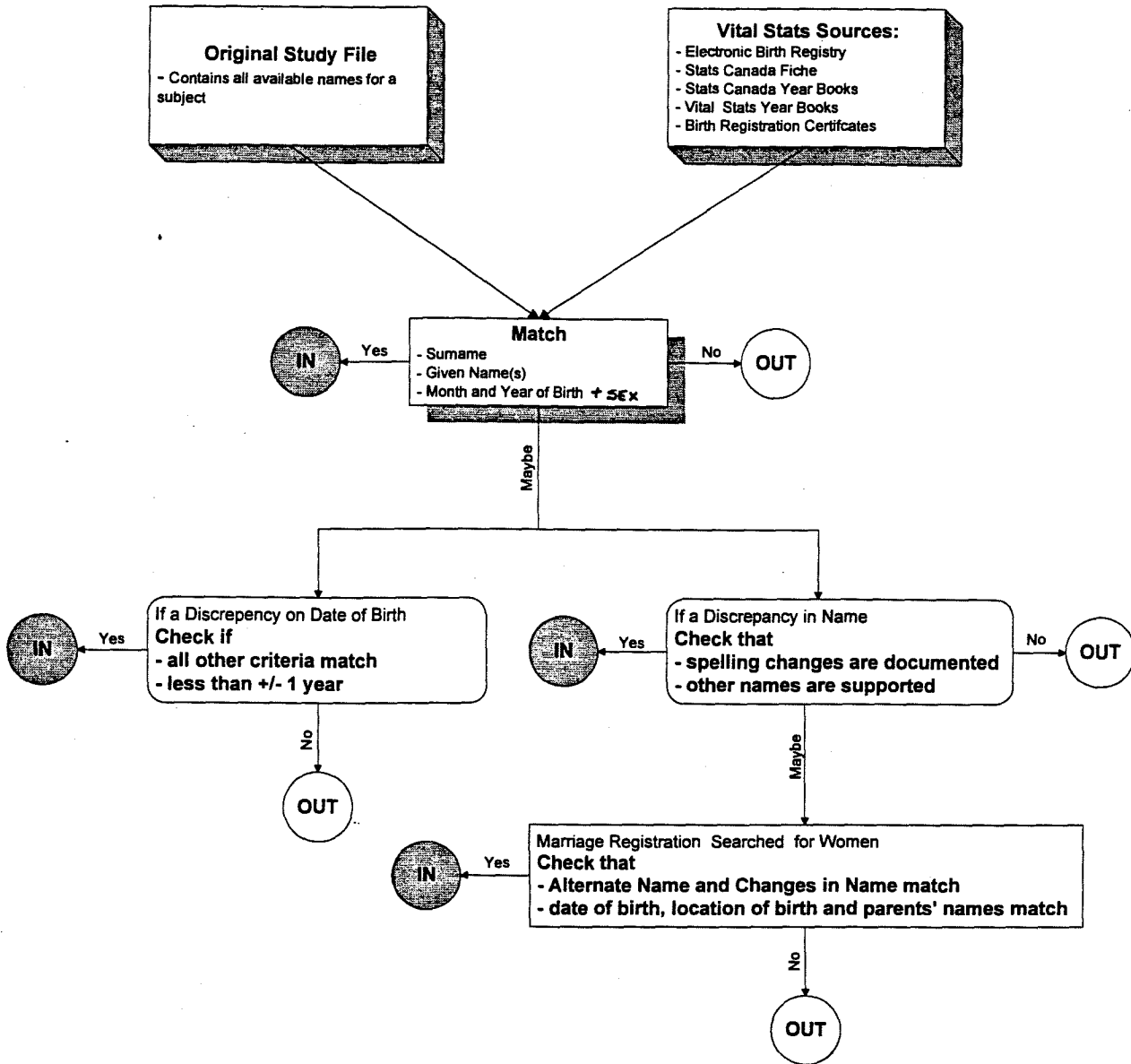
APPENDIX VII

Procedure for Selection of Controls*

* Provided by: Saskatchewan Health, January, 1995

APPENDIX VIII

Procedure for Merging "Study Subject file" with Vital Statistics Sources*

Original Study File
- Contains all available names for a subject

Vital Stats Sources:
- Electronic Birth Registry
- Stats Canada Fiche
- Stats Canada Year Books
- Vital Stats Year Books
- Birth Registration Certifcates

IN ← Yes — **Match**
- Surname
- Given Name(s)
- Month and Year of Birth + Sex

No → **OUT**

Maybe

IN ← Yes — If a Discrepency on Date of Birth
Check if
- **all other criteria match**
- **less than +/- 1 year**

No

OUT

IN ← Yes — If a Discrepancy in Name
Check that
- **spelling changes are documented**
- **other names are supported**

No → **OUT**

Maybe

IN ← Yes — Marriage Registration Searched for Women
Check that
- **Alternate Name and Changes in Name match**
- **date of birth, location of birth and parents' names match**

No

OUT

Provided by: Saskatchewan Health, July 15, 1996

APPENDIX IX

Description Of Study Variables Used In Data Analysis

Study ID   - 6 digit unique identifier as reported in Study Subject File

Quartet   - created by taking the first 4 digits of "Study ID"
- common for each case & 3 corresponding controls in quartet

Group   - created by taking the last 2 digits of "Study ID" which correspond to:
        00 = Aboriginal diabetic
        01 = Aboriginal non-diabetic
        02 = non-Aboriginal diabetic
        03 = non-Aboriginal non-diabetic

Age   - for all 4833 subjects with available birth registration
- calculated at the point of December 31, 1994
- created by transforming "date of birth" expressed in "day-month-year" and using the formula: [(31-Dec-94) - (date of birth)] $\div$ 365.25 days
- rounded up to nearest 10th

Age_   - for all 5464 subjects from Study Subject File
- calculated at the point of December 31, 1994
- created by transforming "date of birth" expressed in "01-month-year" and using the formula: [(31-Dec-94) - (date of birth)] $\div$ 365.25 days
- rounded up to nearest 10th

Sex   - Male (M) converted to "1"; Female (F) converted to "2"

Birth weight   - as documented in metric measure (grams) or converted from imperial measure (pounds, ounces) to metric measure by using the formula:
grams = [pounds +(ounces $\div$ 16)] x 453.6

Gest. age   - Gestational age at delivery; converted into weeks and rounded down (e.g. "36-37" became 36.5 wks. and "36.5" or "36 $^5/_7$" became 36 wks.)
- "full term", "term", "normal" and "complete" were assigned 40 weeks
- "x" months or "x" days were converted into weeks by using the formulas: weeks = ("x" months $\div$ 12) x 52   or   weeks = "x" days $\div$ 7

Stillborn   - number of previous stillborn prior to this child
- was defined as born dead after 28 wks. gestation prior to 1970 but from 1970-72 until the present, it is defined as born dead after 20 wks.

Parity   - Created by adding "Stillborn" (previous stillborn prior to this child) and "Born Alive" (birth order of this child among live births)

Single/Twin   - "Single" converted to "1"; "Twin", "Twin A" or "Twin B" converted to "2"
Mother's Age   - at delivery
Father's Age   - at delivery

APPENDIX X

List of Abbreviations Used in Thesis

AR	Attributable risk
Birth reg.	Birth registration
Bwt	Birth weight
CI	95% Confidence interval
CLR	Conditional logistic regression
DM	Diabetes mellitus
Dm	Diabetic
g	grams
GDM	Gestational diabetes mellitus
Gest	Gestational
GP	General population
HBW	High birth weight
ICD-9	International Classification of Diseases 9th Revision
IGT	Impaired glucose tolerance
LBW	Low birth weight
LGA	Large for gestational age
Mat	Maternal age
MSB	Medical Services Branch
non-Dm	Non-diabetic
OR	Odds ratio
Par	Parity
Pat	Paternal age
PDSB	Prescription Drug Services Branch
RI	Registered Indian
RR	Risk ratio
Sask	Saskatchewan
SB	Stillbirth
T2DM	Type 2 diabetes mellitus
W.H.O.	World Health Organization
Wks	Weeks
YOB	Year of birth
Yrs	Years
>	Greater than
≥	Greater than or equal to
<	Less than
≤	Less than or equal to

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