Macrosomic Infants Born to Non-diabetic Mothers in Nova Scotia: Determinants and Development of a Risk Prediction Model

by

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This thesis is dedicated to my parents, Alan and Glenna for their continued support. Without your love and encouragement this would not have been possible. Thank you for always believing in me.

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ABSTRACT

This retrospective cohort study investigated the rates and risk factors of macrosomia in non-diabetic women and developed a clinically relevant model to predict macrosomia in mid-pregnancy. Logistic regression was used to identify risk factors of macrosomia. Risk scoring systems were developed for nulliparous and multiparous women separately using linked Atlee Perinatal Database and IWK lab data from glucose challenge tests (GCT). The scoring systems were validated by the c-statistic.

Of the infants, 15.3% were macrosomic. In nulliparous women, the largest number of points was assigned for pre-pregnancy weight $\geq$90 kg, (OR: 4.8; 95% CI: 3.9-6.0). Other factors contributing points were increasing rate of weight gain and GCT results, male sex, married or common-law and absence of a psychiatric illness, smoking and asthma. The resulting risk score corresponded to a range of estimated risk of 0.2% to 47.0%, depending on the factors present. The *c* statistic for the model was 0.70.

LIST OF ABBREVIATIONS AND SYMBOLS USED

AOR	Adjusted Odds Ratio
BMI	Body Mass Index
CI	Confidence Interval
GCT	Glucose Challenge Test
GDM	Gestational Diabetes Mellitus
LBW	Low Birth Weight
LGA	Large for Gestational Age
MIREC	Maternal-Infant Research on Environmental Chemicals
MSAFP	Maternal Serum Alpha-fetoprotein
NSAPD	Nova Scotia Atlee Perinatal Database
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
QAIPPE	Quintile of Annual Income Per Person Equivalent
ROC	Receiver Operating Characteristic

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Chapter 1 INTRODUCTION

1.1 Thesis Overview

Macrosomia is a term used to describe an infant born with an excessively high birth weight. It is common to define macrosomia as a birth weight greater than 4000 g (approximately the 90th percentile at 40 weeks gestation). However the definition remains debated and some studies choose to report macrosomia with higher limits (greater than 4500 g or 5000 g) (1,2). Other studies suggest macrosomia be categorized by birth weights which are predictive of specific complications and outcomes. They propose a progressive categorization (grade 1, 2 and 3, indicating birth weights of >4000, >4500 and >5000 g respectively), which are based on increasing risk of healthcare utilization, morbidity and death (4).

The overgrowth of a fetus can lead to significant complications during and after delivery for both the mother and the infant. Mothers of macrosomic infants are more likely to have prolonged deliveries and require operative vaginal deliveries (use of forceps or vacuum device during vaginal delivery) and caesarean sections (1,3). A prolonged delivery, described as >10 hours for the first stage of labour or >2 hours for the second stage of labour were observed by Jolly et al. to be significantly more common in the birth of macrosomic infants (defined as >4000 g), when compared to infants of 2500-4000 g (OR: 1.57; 99% CI: 1.51-1.63 and OR: 2.03; 99% CI: 1.88-2.19 respectively) in a study of births in the North West Thames Region of England and Wales (1). The study also demonstrated that the delivery of macrosomic infants is more likely to require induction of labour (OR: 1.59; 99% CI: 1.54-1.63), instrumental vaginal delivery (OR: 1.76; 99% CI: 1.68-1.85) and emergency caesarean sections (OR: 1.84; 99% CI: 1.75-1.93) (1).

The birth of a macrosomic infant is additionally more likely to result in perineal tears, anal sphincter ruptures, postpartum hemorrhaging and pudendal nerve damage to the mother (1).

Macrosomia is associated with many adverse conditions affecting the infant such as shoulder dystocia, skeletal injuries, hypoglycemia, neonatal asphyxia, brachial nerve palsy, meconium aspiration as well as other birth traumas and fetal death (1,2,4). Jolly et al. observed that the delivery of a macrosomic infant is more likely to result in admission to the special care baby unit (SCBU) (OR: 1.51; 99% CI: 1.38-1.66) and a prolonged postnatal stay (OR: 1.16; 99% CI: 1.11-1.22) (1).

In addition to these conditions, several notable long-term consequences face macrosomic infants including obesity, diabetes and heart disease later in life (2). Macrosomic infants are significantly more likely to become overweight and obese (5). A study demonstrated this relationship by comparing children who were born macrosomic to those born of normal weight. Macrosomic children were 1.52 times more likely (95% CI: 1.24-1.86) to be overweight and 1.50 times more likely (95% CI: 1.19-1.92) to be obese at age seven when compared to non-macrosomic children (5).

Macrosomia causes considerable challenges for physicians. Because the birth weight of an infant is usually not known until very close to or until after delivery, interventions to reduce the effects of macrosomia are often not possible (1). Several methods exist for estimating fetal weight; however, they are not reliable until late in pregnancy and are prone to significant error. Estimates of fetal weight can be made using sonography, by palpation of the hand or by asking a parous mother for an estimate based on a comparison with the weight of her previous infant (6). The inaccuracy of the clinical methods for identifying cases of macrosomia and the inability to do so early in pregnancy increases the need for research focused on risk factors. Research

focused on building predictive models has the potential to assist clinicians in identifying possible cases of macrosomia at an earlier stage in pregnancy. This would be advantageous over existing methods because it would allow for time for interventions that may help prevent the condition.

1.2 Literature Review

1.2.1 Macrosomia vs. Large for Gestational Age

As previously mentioned, macrosomia is used to indicate excessive intrauterine growth beyond a specific threshold value (usually $\geq$4000 g) (1). This definition uses a crude measure to describe a point where complications and morbidity severely increase but disregard gestational age. On the other hand, the term large for gestational age (LGA) describes infants who are above the 90th percentile birth weight for gestational age and sex (7). Since an infant born early in gestation can be large for gestational age despite being well below 4000 g, an LGA infant is not necessarily a macrosomic one. Using the definitions of birth weight for gestational age by Kramer et al., an LGA female infant would also be classified as macrosomic at 40 weeks gestation and a male infant at 39 weeks gestation (7).

1.2.2 Prevalence of Macrosomia

The prevalence of macrosomia has been increasing in recent decades. Studies have shown this trend in most developed countries, despite a rise in preterm births (8). This suggests that the observed rise in birth weight is in fact due to an increase in fetal growth and birth weight for gestational age. A Danish study investigating the trends in birth weight over a ten-year period found that the mean birth weight was in fact rising (9). In their study population, the mean birth weight for all infants increased by 45 g between 1990 and 1999 (from 3474 g to 3519 g).

Increasing mean birth weight is typically an indication that a society is healthy and can be attributed to a decrease in infants with low birth weight, an indicator of poor antenatal care and low standard of living. However, it can also be caused by an increase of infants with high birth weight or a combination of the two, indicating the potential for additional health problems as previously mentioned. The Danish study also considered the prevalence of macrosomic infants ($\geq$ 4000 g) and determined that between 1990 and 1999, the proportion of macrosomic infants increased from 16.7% to 20%, independent of gestational age (9).

Previous to the Danish study, Johar et al. revealed a significant increase in the rate of macrosomia during a 50-year period at the University of Nebraska Medical Centre. During the final 15 years of the study (1970-1985), the incidence of macrosomia was noted to increase from 3% to 14% (10). Similarly, a Canadian study of the trends in birth weight, showed an increase in mean birth weight and proportion of high birth weight infants between 1981 and 1997 (11). Mean birth weight increased from 3372 g to 3407 g over the duration of the study, a difference of 35 g (11). Meanwhile, the incidence of macrosomia has remained consistently high in Nova Scotia, affecting approximately 15% of all deliveries in the province over the past decade (12).

1.2.3 Diabetes and Macrosomia

Both pre-existing and gestational diabetes are well-established risk factors for macrosomia and the study of these relationships is prominent in existing research. This results in a significant gap in literature surrounding the non-diabetic population, despite the considerable challenge they pose in research and to physicians. Unlike the diabetic population, there is no common agreement on the prediction or management of cases. Furthermore, since estimation of fetal weight and the diagnosis of macrosomia can be difficult and often only possible very close to, or at delivery, this leaves no time for preventative strategies (13).

Previous studies have focused on the diabetic population most likely because of two reasons: 1) The incidence of macrosomia is more prevalent in the diabetic population and 2) there are recognized interventions designed to treat mothers diagnosed with pre-existing and gestational diabetes (13,14).

The incidence of macrosomia in diabetics has been shown to be higher compared to non-diabetic mothers, with some studies observing an incidence rate of almost double that of non-diabetics (15). A 2014 cohort study, designed to quantify the independent association between pre-pregnancy BMI, gestational weight gain and gestational diabetes mellitus (GDM) with macrosomia found that of the women diagnosed with gestational diabetes and pre-existing diabetes, 14.2% and 16.7%, respectively, delivered macrosomic infants (14). Legardeur et al. additionally reported an increased association between GDM and the birth of a macrosomic infant, with an odds ratio of 1.72 (95% CI: 1.23-2.40) for women with GDM, compared to no GDM, adjusting for age, BMI, ethnicity, parity and weight gain (15). Similarly, a meta-analysis, including 12 observational studies showed that GDM is an independent risk factor for

macrosomia with a pooled adjusted odds ratio of 1.63 (95% CI: 1.42-1.88) for birth weight ≥4000 g and 1.89 (95% CI: 1.40-2.25) for birth weight ≥4500 g (16).

There are numerous proposed interventions, such as dietary and lifestyle counseling, blood glucose self-monitoring and insulin therapies designed for the diabetic population (13, 17). They aim to decrease adverse neonatal outcomes in this population, such as the incidence of macrosomia. A multicenter Australian randomized controlled trial of more than 1000 women (recruited between September 1993 and June 2003) with GDM, randomly assigned individuals to treatment or no treatment groups (18). Treatment included individual dietary counseling, self-monitoring of glucose levels and insulin therapy when needed, replicating the care received for GDM in areas where universal screening and treatment was available. Compared to individuals who received no treatment, the treatment group was statistically less likely to deliver a macrosomic infant, when adjusted for maternal age, race or ethnic group and parity (18). The study demonstrated that the number needed to treat (NNT) for this intervention is 9, indicating that in order for one infant to benefit from this intervention, 9 women must be treated (18). Similarly, a systematic review including five randomized controlled trials and six cohort studies, studied the benefits and harms of treating GDM (19). All studies favoured treatment for lessening the outcome of macrosomia. The systematic review revealed an overall statistically significant reduction of macrosomia when comparing diet modification, glucose monitoring and insulin therapy with no treatment (19).

1.2.4 Macrosomia among Non-diabetic Women

Although many studies have identified a clear association between GDM and macrosomia, the majority of macrosomic births are to non-diabetic women. Considering maximum incidence rates of pre-existing and gestational diabetes (0.9% and 4.5% respectively) for Nova Scotia, 94.6% of births in the province are to non-diabetic women, approximately 8514 births per year (12). Utilizing the prevalence of macrosomia among non-diabetics (7.4%) provided by Legardeur et al., this would result in the birth of 630 macrosomic infants to non-diabetic women (approximately 90%) and 71 to women with pre-existing diabetes or gestational diabetes, per year in Nova Scotia (15).

Current literature on the determinants of macrosomia lacks focus on non-diabetic mothers. To date one study has investigated the risk factors of macrosomia in a population restricted to healthy, non-diabetic pregnancies (20). Li et al. aimed to attain results that would be more applicable to the general population than previous studies, which were compiled of both diabetic and non-diabetic pregnancies. The study identified weight gain during pregnancy, maternal age and gestational age as independent risk factors of macrosomia. However, their study had very few participants (n=1041) and they were selected from only one hospital, therefore not allowing for any differences in region (20).

1.2.5 Established Maternal Risk Factors of Macrosomia

Many risk factors for macrosomia have been reported in the current literature. There is a tendency for these studies to focus on the factors that are modifiable and have increased in recent years, such as obesity and diabetes (3,14,21). Given the limitations of existing methods for estimating fetal weight, identifying and quantifying the significance of risk factors is important for determining high-risk individuals (22). Ideally, once high-risk individuals have been identified, interventions would be in place to decrease the risk of delivering a macrosomic infant. It is important that high-risk individuals be identified in mid-pregnancy rather than late in gestation when an intervention may be less effective.

1.2.5.1 Maternal Obesity

With the development of obesity as a significant health problem in the Western world, attention to its relationship with adverse pregnancy outcomes has been a priority. Maternal obesity has been shown to be a significant predictor of macrosomia in studies of the delivery and outcomes of mixed diabetic and non-diabetic populations (14). Alberico et al. and Ng et al. estimated a 1.7 (95% CI: 1.4-2.2) and 2.73 (95% CI: 1.49-5.01) times increase in the outcome in women with pre-pregnancy obesity when compared to women of normal weight (14, 21). Additionally, a London study of almost 300,000 births was able to demonstrate an increasing gradient of risk with increasing pre-pregnancy BMI, while adjusting for GDM as well as pre-existing diabetes (23). An increase in the outcome (birth weight >90th percentile) of 1.57 (99% CI: 1.50-1.64) was observed for those who were overweight (BMI 25-30) prior to pregnancy and

2.36 (99% CI: 2.23-2.50) for those who were obese (BMI >30), when compared to normal weight individuals (BMI 20-25) (23).

1.2.5.2 Gestational Weight Gain

The Institute of Medicine provides recommendations for gestational weight gain during pregnancy, centered on the health of both the mother and the infant (24). The guidelines are based on the World Health Organization's BMI categories with weight gain ranges for underweight, normal weight, overweight and obese individuals. Those who are outside the recommendation for both pre-pregnancy weight and gestational weight gain are at an increased risk of experiencing adverse pregnancy outcomes (24). Alberico et al. found that women with gestational weight gain above the Institute of Medicine's recommended cutoff were 1.9 times more likely to deliver a macrosomic infant than those who fell within the suggested limits (14).

1.2.5.3 Maternal Age

In the past decades, the developed countries have seen a movement towards increasing childbearing age (25). Advanced maternal age has been attributed to improved birth control methods and assisted reproductive technology, women's pursuit of higher education and career advancement as well as delayed marriage and higher rates of divorce (26). Advanced maternal age is typically defined as a maternal age of 35 or older at the time of pregnancy and has been

consistently associated with adverse pregnancy outcomes (25). A multicenter American study of the effect of maternal age on obstetric outcomes compared three age groups of women (less than 35 years, 35-39 years and 40 years and older) (26). The outcome of macrosomia (>4500 g) was significantly higher (OR: 1.4; 95% CI: 1.1-1.8) for those women aged 35-39, when compared to women less than 35 years old; however, a positive relationship was not observed in the adjusted model between the outcome and the age group of 40 years and older (26). Similarly, in investigating the risk factors of macrosomia, Stotland et al. found a significant increase in the outcome of an infant greater than 4000 g (OR: 1.11; 95% CI: 1.07-1.14) and greater than 4500 g (OR: 1.16; 95% CI: 1.07-1.25) among women 30-39, when compared to those ages 20-29 (27). Again, there was no statistical significance found in the relationship between the highest age group (>39 years) and macrosomia at either level of the outcome (27). The absence of a positive, statistically significant relationship in the highest age group may be a result of early delivery in older women, which would reduce the likelihood of delivering a macrosomic infant (1).

1.2.5.4 Characteristics of Previous Pregnancies

In addition to the maternal variables mentioned above, variables related to a woman's previous pregnancies have been investigated as potential risk factors for macrosomia. Such variables include parity (the number of births prior to the current), interpregnancy interval (time between pregnancies), the previous birth of a macrosomic infant, as well as a previous diagnosis of gestational diabetes in an earlier pregnancy. Multiparous woman have been shown to be more likely to deliver infants weighing more than 4000 g (OR: 1.6; 95% CI: 1.60-1.71) and more than

4500 g (OR: 1.75; 95% CI: 1.62-1.89) (25). Similarly, women who have previously given birth to a macrosomic infant have been shown to be significantly more likely to deliver a macrosomic infant (4). The relationship presented by Boulet et al. demonstrates that there is increasing likelihood of developing the outcome, with each increasing grade of macrosomia (4000-4499 g, 4500-4999 g and $\geq$5000 g) among those who previously delivered a macrosomic infant ($p<0.05$) (4).

1.2.5.5 Maternal Diseases and Behaviours

Risk factors that affect the outcomes macrosomia and large for gestational age are the primary focus of this study; however, risk factors that affect low birth weight (LBW) must also be considered in order to fully understand the relationship. Maternal diseases that exist prior to pregnancy may adversely influence several pregnancy outcomes including birth weight. For example, the relationship between mood disorders such as depression and anxiety and neonatal outcomes including birth weight and preterm birth have been studied. Depression during pregnancy has been linked to adverse behaviours such as smoking, a known risk factor for LBW (28). In addition to behaviours associated with depression, anti-depressive medications may affect neonatal outcomes (28).

Several studies have demonstrated a relationship between depression and LBW (28). A meta-analysis of the effects of depression during pregnancy on the risk of preterm birth, low birth weight and intrauterine growth restriction found an overall significant relationship between depression and LBW, using the random-effects analysis. Of the eleven studies evaluated, six

studies found no significant association. Significant heterogeneity was found across the studies with a presented I^2 of 70% (28). Similar to mood disorders, autoimmune diseases such as asthma, lupus, Crohn's disease and inflammatory bowel disease may increase the risk of adverse pregnancy outcomes including LBW (29). This relationship is likely related to both the maternal disorder and the management, which includes immunosuppressive therapy (29).

The relationship between polyhydramnios, excess accumulation of amniotic fluid during pregnancy, and macrosomia has been demonstrated in both diabetic and non-diabetic mothers (30). A study of non-diabetic women demonstrated that there was a statistically significant relationship ($p<0.01$) between macrosomia and polyhydramnios, with macrosomia occurring more than 3 times more often in individuals with the condition than without it (31).

1.2.5.6 Fetal Sex

Fetal sex has additionally been shown to be an independent risk factor for macrosomia. Male infants tend to weigh more than female infants at any gestational age (5). Gu et al. and Sheiner et al. have both demonstrated that compared to female infants, male infants are significantly more likely to be macrosomic (OR: 1.61; 95% CI: 1.47-1.75 and OR: 2.0; 95% CI: 1.8-2.1 respectively) (5,32).

1.2.5.7 Socioeconomic Risk Factors

Socioeconomic factors such as income and marital status can have an effect on an individual's likelihood of having a macrosomic infant through a number of mechanisms. Socioeconomic status can be associated with the mother's characteristics at the time of conception as well as her behaviours throughout pregnancy. Maternal characteristics that may vary with socioeconomic status and have the potential to influence macrosomia include age, parity and maternal weight. Similarly, some of the previously described behaviours such as weight gain and smoking during pregnancy may likewise differ by socioeconomic status.

It is widely accepted in literature that socioeconomic factors such as income and marital status affect low birth weight, however little research has been conducted on how these factors influence high birth weight (33). Boulet et al. found that mothers of macrosomic infants were significantly more likely to be married than mothers of normal weight infants (4). Similarly, the effect of other socioeconomic factors such as ethnicity and educational attainment on macrosomia have been observed in literature. Boulet et al. found that mothers of white race and those with high educational attainment ($\geq$ 12 years) were significantly more likely to deliver macrosomic infants (4).

1.2.6 Recommendations for Diagnosing Gestational Diabetes (Pre-2013)

The Canadian Diabetes Association's recommendation for diagnosing gestational diabetes includes a two-step approach (35). This method incorporates a series of two laboratory

blood tests; a screening test (the glucose challenge test (GCT)) and a diagnostic test (the oral glucose tolerance test (OGTT)). It is recommended that a 1-hour 50 g GCT be administered to all pregnant women between 24-28 weeks gestation as a screening test for GDM. Previous to the 2013 adaptation of guidelines, values <7.8 mmol/L indicated a normal screen and values >10.3 mmol/L indicated a positive diagnosis of GDM. Values falling between 7.8 mmol/L and 10.3 mmol/L required further diagnostic testing using the 75 g OGTT. A diagnosis of GDM was given if two or more values were abnormal (fasting $\geq$5.3 mmol/L, 1 hour $\geq$10.6 mmol/L, 2 hours $\geq$8.9 mmol/L). If only one value was met or exceeded, the patient was to be given the diagnosis of impaired glucose tolerance (IGT) (35).

1.2.7 New Recommendations for Diagnosing Gestational Diabetes (Post-2013)

The Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study was designed to assess the risks of maternal glucose intolerance less severe than what was being captured by the diagnostic criteria for GDM at that time (34). The study demonstrated that a continuous graded relationship exists between increasing maternal glucose levels and adverse maternal, fetal and neonatal outcomes. The results of the study prompted a change in screening, focused on identifying pregnancies with increased risk for adverse perinatal outcomes (34).

While strong evidence exists for the benefit of treating GDM, a common approach to the diagnosis is not available internationally and has recently been revised within the Canadian guidelines. The current recommendation of the Canadian Diabetes Association is a modification of the previously described two-step approach. It is recommended that a 1-hour 50 g GCT be

administered to all pregnant women between 24-28 weeks gestation as a screening method for GDM. Values <7.8 mmol/L indicate a normal screen and values ≥11.1 mmol/L indicate a positive diagnosis of GDM. Values falling between 7.8 mmol/L and 11.0 mmol/L require further diagnostic testing using the 75 g OGTT. A diagnosis of GDM is given if one or more values is abnormal (fasting ≥5.3 mmol/L, 1 hour ≥10.6 mmol/L, 2 hours ≥9.0 mmol/L) (36). This method does not include a category of impaired glucose tolerance.

The change in threshold values for the 75 g OGTT were proposed based on the glucose concentrations at which the odds ratio of the four primary outcomes of the HAPO study (birthweight >90 percentile, primary caesarean section, neonatal hypoglycemia and cord C-peptide levels >90%) were 2.00 (36). This adaptation to the recommendations was decided upon after initially applying the threshold values, which resulted in an odds ratio of 1.75 to the HAPO cohort. Using the values corresponding to an OR of 1.75, an incidence rate of 17.8% for GDM was calculated, almost four times the rate we observe in the Nova Scotia population (approximately 4.5%) (12, 36). This change would have huge implications to the Canadian healthcare system, healthcare providers and patients. There remains considerable controversy regarding the diagnosis of GDM and no clear single threshold to predict adverse outcomes in pregnancy. For this reason and implications on cost and workload, the 2013 Canadian Diabetes Association expert committee selected a preferred approach (described above) using thresholds that result in an OR of 2.00 (36).

1.2.8 Gestational Diabetes Screening and Macrosomia

While both the GCT and OGTT are defined by threshold values of what establishes GDM, they can also be perceived as continuous in nature (37). Several studies have successfully demonstrated an association between increasing maternal glucose intolerance in non-diabetic mothers and adverse neonatal conditions such as macrosomia. The Toronto Tri-Hospital Gestational Diabetes Project studied the glucose intolerance of 3637 non-diabetic women and their pregnancy outcomes and determined there was a significant graded relationship between GCT and OGTT values and macrosomia (38). Following a multivariate analysis, only the fasting value on the OGTT remained significant. The results of this analysis revealed that for each 1 mmol/L increase in fasting plasma glucose level the odds of macrosomia increased by 100% when defined as >4000 g and by 140% when defined as >4500 g (95% CI: 1.61-2.58 and 95% CI: 1.69-4.11 respectively) (38).

1.2.9 Risk Prediction Models

Clinical prediction models are becoming more and more common applications (39). They combine characteristics of the patient, the disease or treatment in a statistical model to predict a diagnostic or prognostic outcome. Historically, a limited number of predictors were considered, often including standard qualities such as age, sex and family history (39, 40). But recently, more complex clinical measures such as biomarkers, imaging and pathological variables are being incorporated into prediction models (40).

Predictive models are useful for informing patients and physicians about the probability of an outcome (39). Specifically, they can be used for planning the remaining lifetime of a terminal patient, giving hope to individuals likely to recover and useful for directing preventive interventions to individuals who show to be at high risk of developing an outcome (39). A points system, based on the work of the Framingham Heart Study and development of a risk score function has been established to simplify the complex statistical models used to quantify the impact of risk factors on an outcome for clinicians (41). The points system is very easy to use and does not require a calculator, making it practical for busy clinicians.

The development of a risk prediction model includes two key phases. The first phase is comprised of model development and second is comprised of model validation (40). Validation is essential to confirm that the model is accurate to the population of individuals that it is designed for. Internal validation occurs when the same data that was used for developing the model is used for validation. It is anticipated that the model will perform optimally on the dataset for which it was developed and less accurately when it is tested on a distinct set of individuals, known as overfitting (39). External validation, however, addresses the generalizability of the model by measuring the performance of the model on a different population from the one in which the model was developed. It is common for risk prediction models to provide in depth model development but lack external validation. Although there is an abundance of research in predictive models, relatively few are being used in clinical practice (40).

1.3 Summary

Given the prevalence of macrosomia and the complications that can result, it is an important area of research for improving the health and well being of women and children. This is especially true among non-diabetics who have the majority of macrosomic infants. Based on the reviewed literature, it is evident that understanding the risk factors associated with macrosomia is important. As outlined above, several risk factors have been examined; however, limitations have been noted in the existing research.

A method for predicting macrosomia among diabetics in mid-pregnancy would be a useful tool that would help guide the management of pregnancies at high risk of macrosomia. The existing methods for identifying macrosomic infants, such as sonography are only utilized during the later stages of pregnancy and have been shown to give poor estimates of the outcome and are therefore not reliable or useful for preventing cases (13). These methods are typically used as a means of planning labour and delivery strategies and cannot contribute to the prevention of macrosomia.

Chapter 2 OBJECTIVES

The current study investigated the determinants and trends of macrosomic infants born to non-diabetic mothers in Nova Scotia between 1988 and 2014 with the purpose of developing a risk prediction model.

Specifically, the three main objectives were to:

I. Determine the prevalence and the change in rates over time of macrosomia in non-diabetic women in Nova Scotia.
II. Determine the maternal and pregnancy risk factors of macrosomia in non-diabetic women in Nova Scotia.
III. Build and validate a risk prediction model incorporating both maternal factors and laboratory data to estimate the risk of developing macrosomia for non-diabetic women.

Chapter 3 METHODOLOGY

3.1 Overview of Study Design and Ethics

Utilizing The Nova Scotia Atlee Perinatal Database (NSAPD) as the primary data source, a retrospective cohort of non-diabetic, Nova Scotia residents who delivered an infant between 1988 and 2014 was formed. This cohort was used to determine the prevalence and trends in prevalence of macrosomia (objective 1) and to determine the risk factors of macrosomia (objective 2) at the population level. A second cohort, composed of only those individuals for whom prenatal glucose screening results were available, was used to build the risk prediction model (objective 3).

The project received ethics approval from the Joint Data Access Committee (JDAC) of the Reproductive Care Program (RCP) and approval from the IWK Health Centre Research Ethics Board.

3.2 Data Sources

3.2.1 Nova Scotia Atlee Perinatal Database (NSAPD)

The NSAPD is a high quality database, administered by the Reproductive Care Program of Nova Scotia. It compiles information from hospital charts using standardized collection forms and trained health record personnel. The database contains records of all hospital births of infants 500 g or greater or of a gestational age of 20 weeks or greater in Nova Scotia since 1988, as well

as information on home births since 2009. This results in approximately 9,000 births per year and a very small percentage of missing values. The database is of extremely high quality and undergoes continuous data quality assurance checks, including reabstraction and validation studies to ensure its reliability.

For each individual in the NSAPD, demographic variables, information on procedures and interventions undergone, maternal and newborn diagnoses and reports of morbidity and mortality are available. In the current study, the NSAPD provided the means to measure the prevalence of macrosomia in non-diabetic women at the population level in Nova Scotia. In addition, maternal and pregnancy factors related to the outcome were determined and incorporated into the development of a risk prediction model.

3.2.2 IWK Health Centre Laboratory Data

Laboratory results of glucose challenge test (GCT) for gestational diabetes screening and diagnosis were used to supplement the data obtained from the NSAPD. This allowed for the association between subclinical diabetic levels and macrosomia to first be determined, and then incorporated into the development of the risk prediction model. The data was previously linked with the NSAPD by the Reproductive Care Program and included women who received their pre-natal glucose screening at the IWK Health Centre for the years 1998-2005. The unique NSAPD ID for each individual and date were used to correctly link the laboratory data with the appropriate Atlee data for each individual and pregnancy.

3.2.3 Maternal-Infant Research on Environmental Chemicals (MIREC)

Data from the Maternal-Infant Research on Environmental Chemicals (MIREC) study was used as an external data source to validate the prediction model. The MIREC study is a national longitudinal cohort that recruited 2001 women during their first trimester of pregnancy from 10 sites in 6 provinces across Canada. Women were recruited between 2008 and 2011 and followed through pregnancy and up to eight weeks after birth. During each trimester of pregnancy, data and specimens were collected via questionnaires, medical history and maternal blood and urine samples. The sample of individuals used to validate the predictive model was composed of MIREC participants without GDM or pre-existing diabetes, whose pregnancy resulted in a singleton, live birth and who had sufficient data from gestational diabetes screening. In order to have sufficient data the individual must have undergone at least the GCT.

3.3 Inclusion and Exclusion Criteria

The NSAPD includes information on all births to Nova Scotia residents. Births were excluded from the study if (a) the mother had a pre-existing diagnosis of type 1 or type 2 diabetes, or (b) the mother had a diagnosis of gestational diabetes for the current pregnancy. The study population included only singleton live births. Multiple births were excluded from the study population because their growth patterns may lag behind that of a singleton birth in the third trimester (the period of maximum fetal growth), and very rarely result in a macrosomic infant (42). Births with one or more major anomalies were also excluded.

The current study used all available years of data, incorporating all eligible births between the start of data collection in 1988 and the most recent available data for 2014 for objective 1 and 2. The analysis of the relationship between glucose screening/diagnosis results and macrosomia restricted the study population further to women who met all previously stated criteria and for which access to pre-natal laboratory results was available. As previously mentioned laboratory results for the GCT were only available for those women who had their glucose screening completed at the IWK Health Centre and were included in the previously linked 1998-2005 data. Therefore this subset of women, for which all data was available, was used to develop the risk prediction model.

3.4 Variables

3.4.1 Dependent Variables

The primary outcome variable, macrosomia, was derived from infant birth weight, which is available directly from the NSAPD. The database provides the birth weight as a continuous variable in grams. Participants were coded as having a macrosomic infant if the birth weight was greater than or equal to the cutoff and not having a macrosomic infant if the birth weight was less than the cutoff. The primary measure of macrosomia used in the study defines a macrosomic infant as one born with a weight greater than or equal to 4000 g and not macrosomic if it is less than 4000 g. A second and third definition of macrosomia, demonstrating increasing grades of risk, were defined as: (1) an infant born with a weight greater than or equal to 4500 g and (2) an infant born with a weight greater than or equal to 5000 g.

A secondary outcome, LGA was defined as an infant with birth weight greater than the 90th percentile for their gestational age and sex (8). The variable was obtained from the NSAPD as birth weight for gestational age, categorized by percentiles. All analyses were completed using both the primary and secondary outcomes.

3.4.2 Predictors

Variables containing information on sociodemographic and behavioural factors, pregnancy history as well as pre-existing medical conditions were obtained from the NSAPD in order to investigate the potential risk factors of macrosomia. A full description of the treatment of covariates and outcome variables is available in Table 3-1 (p. 32-33). Each variable was chosen as a covariate based on associations found in past research, as described previously in the literature review.

As height was only introduced as a variable captured by the NSAPD in 2003 a significant amount of missing data existed for our study population. Therefore the covariate pre-pregnancy weight was used instead of body mass index. The rate of weight gain at 26 weeks (GWG_{rate}) was predicted using a previously established formula that considers overall gestational weight gain and gestational age of the fetus.

$$GWG_{rate} = 2kg + [13weeks * \text{(delivery weight (kg)- prepregnancy weight (kg)- 2kg)/ (length of gestation (weeks)- 13 weeks)}] \quad (43)$$

This formula accounts for the varying lengths in gestation of women who deliver before or after 40 weeks (43). The calculation of a rate of weight gain early in pregnancy (26 weeks) assumes a constant weight gain through the second and third trimester and allows for the variable to be practically used in a prediction model where the goal is early detection in pregnancy. Again, due to the large amount of missing height data, it was not possible to categorize this rate according to the Institute of Medicine's recommendations of inadequate, adequate and excessive pregnancy weight gain, by pre-pregnancy BMI (44). Maternal smoking was dichotomized into non-smoker and smoker. Mothers were coded as non-smokers if they reported not smoking any cigarettes at the first pre-natal visit or at the time of admission for delivery. Mothers who reported smoking $\geq$1 cigarette at the first pre-natal visit and/or smoking $\geq$1 cigarette at the time of admission for delivery were coded as smokers during pregnancy.

3.4.3 Laboratory Variables

As previously mentioned, laboratory results of the GCT are defined by cutoff values, representing a positive or negative test result. However, their values are in fact continuous in nature and were obtained from the linked data in mmol/L. The GCT results were categorized into quartiles with the maximum value of 10.3 mmol/L (above which a woman is given a diagnosis of GDM).

3.5 Sample Size and Smallest Detectable Relative Risk

Sample size calculations were carried out for the binary outcome variable macrosomia. The population size for the current study was predetermined by the number of live births of women residing in Nova Scotia during the study period. During the study period 1988-2014 there were 263,914 births to Nova Scotia residents. After excluding women who had a stillbirth, multiple birth, a fetus with a major anomaly, or pre-existing or gestational diabetes, 240,765 mother-infant pairs were included in the study. Sample size calculations were carried out using the available sample size and approximating a rate of 4% for macrosomia in non-diabetic women based on previous measurements (45). Assuming an alpha error of 0.05 and 80% power, the smallest detectable relative risk of developing macrosomia for the risk factor of obesity is 1.08. Prevalence of those exposed was based on NSAPD reported obesity by BMI (12). This example indicates that the available sample size was sufficient for detecting a very small increase in the relative risk of developing macrosomia when comparing obese women with normal weight women. Similarly, the sample size was sufficient to detect fairly small effect sizes, even for less prevalent risk factors.

As explained previously, the analysis of objective 3 was performed on a smaller sample size, including only those women who met all criteria for inclusion in the study and were captured by the previously linked 1998-2005 IWK and NSAPD dataset. This cohort contained laboratory information on 24,038 individuals. After considering the exclusion criteria mentioned above, 23,857 mother-infant pairs were included in the second cohort. Maintaining the same parameters as above, this sample size would result in a smallest detectable relative risk for the risk factor obesity of 1.25. Therefore, even though the sample size is reduced for this analysis, it

was still sufficient to detect a small increase in relative risk. All power analyses were conducted using OpenEpi software.

3.6 Statistical Analysis

3.6.1 Software

All analyses were completed using STATA 13.1 software (Stata Corp., College Station, TX, US).

3.6.2 Repeated Response

The longitudinal nature of the study results in women contributing multiple observations if they delivered more than one infant during the time frame of the study. The repeated observations from a single subject, results in within-subject responses that are correlated and cannot be treated as independent observations. To account for repeated observations (births) in multiparous women, generalized estimating equations (GEE) were used. The GEE method allows for more accurate standard errors to be calculated by accounting for the similarity of within-subject observations (46).

3.6.3 Outcome Measure

All analyses were conducted on the primary outcome macrosomia (using cutoffs of ≥4000 g, ≥4500 g and ≥ 5000 g) as well as the secondary outcome, LGA (>90th percentile for their gestational age and sex). For this study, the analysis using LGA included all gestational ages, whereas the analyses using macrosomia were limited to term infants (≥37 weeks).

3.6.4 Analysis of Objective 1

Descriptive statistics were used to estimate the prevalence of macrosomia by year of delivery. Rates of macrosomia over time were summarized in graphs to display any changes in prevalence over the study period.

3.6.5 Analysis of Objective 2

To compare variables of interest between the two outcome groups (i.e., macrosomic, not macrosomic), the Chi-square test was used for categorical variables and Wilcoxon Mann-Whitney U Test for continuous variables. Using the NSAPD data for the years 1988-2014, logistic regression was used to analyze the relationship between all covariates and the outcome of macrosomia. Unadjusted odds ratios (OR) and 95% confidence intervals (CI) for each risk factor on the outcome were calculated. A multivariable model was developed using backwards

stepwise regression. All covariates were included in the initial model. To develop a parsimonious model, at each step the factor with the largest p-value, determined from the likelihood ratio test, was eliminated until only factors with p-values <0.05 remained.

Interaction terms were added to the regression model to test biologically plausible effect modification. Two possible interactions were explored, hypothesizing that the relationship between the amount of weight gain and macrosomia is different for male and female infants; and similarly that the relationship between weight gain and macrosomia is different depending on pre-pregnancy weight. The likelihood ratio test was used to test for the significance of the interaction term in the model by comparing the model before and after elimination of the interaction term.

The final model included all risk factors that were found to be significant using the likelihood ratio test. Any observations deleted for missing values among variables in the model development were reintroduced if the variable was not included in the final model. In the final model, referent categories were determined based on lowest risk. ORs and 95% CI were estimated from the final multivariable model.

3.6.6 Analysis of Objective 3

A scoring system for predicting macrosomia in non-diabetic women was developed using the linked IWK lab data and NSAPD for the years 1998-2005 and previously established methods (41). In order to utilize the additional information from previous births of a multiparous woman, two separate scoring systems were created, separating nulliparous women and

multiparous women. Estimates of the regression coefficients, odds ratios and 95% confidence intervals for each risk factor were determined using backward stepwise regression, as previously described in the analysis of objective 2 (Section 3.6.5). For continuous variables, categories were created and the mid-point was determined for each level of category and called W_{ij} (e.g., ages 25-29 would have a mid-point value of 27). In order to minimize the influence of extreme values for the first and last category of continuous variables, mid-point values were determined using the 1st percentile and the 99th percentile, respectively (e.g., reference value for pre-pregnancy weight <60 kg was 52 kg and the reference value for pre-pregnancy weight ≥90 kg was 103 kg). The base category (lowest risk) of each risk factor was chosen and assigned 0 points in the scoring system (called $W_{i\text{REF}}$). In the case of dichotomous variables (e.g., sex), one level was considered the base category (e.g., female). Subsequently, for each risk factor, the distance from the base category to each additional category was computed in terms of regression units ($\beta_i(W_{ij}-W_{i\text{REF}})$), where β_i is the regression coefficient). Using the following equation, the points associated with each category of each risk factor were computed and rounded to the nearest integer. In this equation B reflects the number of regression units that corresponds to one point. Here, the constant B was set to 0.2.

$$\text{Points}_{ij} = \beta_i(W_{ij}-W_{i\text{REF}})/\ B \tag{41}$$

Finally, the range of all possible total scores was calculated and the associated risk of macrosomia ($\hat{p}$) was estimated for each total score, based on the final regression model coefficients and using the equation:

$$\hat{p} = \frac{1}{1+\exp\left(-\sum_{i=0}^{p}\beta_i X_i\right)} \tag{41}$$

The performance of the risk prediction model was assessed according to its ability to discriminate between those who develop the outcome, from those who do not (42). The model was internally validated by calculating the *c* statistic (area under the ROC curve) to measure the probability that the model assigns a higher risk to those who deliver a macrosomic infant than those who do not (42). The model was externally validated using data from the MIREC study. Since the MIREC cohort does not have information on the weight of previous births, validation was only completed for the nulliparous model using macrosomia $\geq$4000 g. The regression coefficients generated by applying the NSAPD developed prediction model to the MIREC cohort were compared to those obtained using the NSAPD cohort and the *c* statistic was calculated.

Optimal cut-points were created to categorize patients into high and low-risk groups. The Youden Index (the point for which sensitivity and specificity are maximized) on the ROC curve and the corresponding test characteristics (sensitivity and specificity) were calculated.

Table 3-1 Treatment of variables in the Nova Scotia Atlee Perinatal Database

Variable	Description	Treatment of Variable
Birth weight	Weight of infant delivered	Dichotomized: macrosomic or not macrosomic
Fetal sex	Sex of infant delivered	Remained dichotomized: male or female
Maternal age	Mother's age at time of delivery	Categorized into <20, 20-24, 25-29, 30-34, 35-39, ≥40
Pre-pregnancy weight	Mother's self reported weight at first prenatal visit	Categorized into <60 kg, 60-69 kg, 70-79 kg, 80-89 kg, ≥90 kg
Weight gain during pregnancy	Mother's weight gain per week at 26 weeks	Categorized into quartiles
Smoking status during pregnancy	Smoking status of mother at first pre-natal visit and at admission for delivery	Dichotomized: non-smoker or smoker
QAIPPE (Quintile of Annual Income Per Person Equivalent)	Neighbourhood income from Canadian census data, based on postal code of mother	Remained in quintiles
Marital status	Marital status of mother	Dichotomized: married/common law or single/widowed/ divorced/separated
Parity	Number of live and still births not including current pregnancy	Dichotomized: nulliparous or multiparous
Previous overweight infant	Previous birth of an infant weighing >4080g	Remained dichotomized: yes or no
Previous low birth weight infant	Previous birth of an infant weighing <2500g	Remained dichotomized: yes or no
GDM in previous pregnancy	Yes or no	Remained dichotomized: yes or no
Previous abortion/miscarriage	Yes or no	Remained dichotomized: yes or no
Pre-existing hypertension	Yes or no	Remained dichotomized: yes or no
Depression/anxiety	Yes or no	Remained dichotomized: yes or no
Asthma	Yes or no	Remained dichotomized: yes or no

Variable	Description	Treatment of Variable
Lupus	Yes or no	Remained dichotomized: yes or no
Crohn's disease	Yes or no	Remained dichotomized: yes or no
Inflammatory bowel disease	Yes or no	Remained dichotomized: yes or no
Polyhydramnios	Yes or no	Remained dichotomized: yes or no

Chapter 4 OBJECTIVE 1 RESULTS

4. OBJECTIVE 1: To determine the prevalence and the change in rates over time of macrosomia in non-diabetic women in Nova Scotia.

4.1 Prevalence of Macrosomia

During the study period 1988-2014, there were 263,914 births to Nova Scotia residents. After excluding stillbirths, multiple births, presence of a major anomaly, and pre-existing or gestational diabetes), 240,765 mother-infant pairs were included in the study (Figure 4-1, p. 38). Of the 240,765 mothers included in the study, 36,796 (15.3%) delivered a macrosomic (≥4000 g) infant, 6,266 (2.6%) women delivered a macrosomic infant using the ≥4500 g definition and 761 (0.3%) using the ≥5000 g definition of macrosomia. Figure 4-2 (p.39) shows the prevalence of macrosomia in Nova Scotia among non-diabetic women from 1988 to 2014 using all three definitions of the primary outcome (≥4000 g, ≥4500 g and ≥5000 g). The prevalence of macrosomia did not change substantially during the study period, ranging from 12.6% to 17.3% for macrosomia ≥4000 g, 2.2% to 3.1% for macrosomia ≥4500 g and 0.2% to 0.5% for macrosomia ≥5000 g.

4.2 Description of Cohort

A detailed description of the characteristics of the study cohort is provided in Table 4-1 (p. 36-37). For each covariate obtained from the NSAPD, the frequency and percentage of missing values are displayed. In the covariates that contained missing data, the percent missing ranged from 0.01% for the variable parity to 22.0% for the variable depicting the rate of weight gain. The mean (SD, range) for mother's age was 28.3 (5.5, 12-50), mean pre-pregnancy weight was 67.0 kg (15.7, 29-187) and mean rate of weight gain was 0.48 kg/week (0.25, -3-26).

Table 4-1 Characteristics of Cohort

Variable		Frequency (%)
Maternal age		
	<20 years	17,381 (7.2)
	20-24 years	51,950 (21.6)
	25-29 years	78,000 (32.4)
	30-34 years	65,315 (27.1)
	35-39 years	24,420 (10.1)
	≥40 years	3,699 (1.5)
Parity		
	Nulliparous	108,280 (45.0)
	Multiparous	132,461 (55.0)
	*Missing	24 (0.01)
Pre-pregnancy weight		
	<60 kg	82,516 (34.3)
	60-69 kg	57,533 (23.9)
	70-79 kg	33,264 (13.8)
	80-89 kg	17,245 (7.2)
	≥90 kg	18,592 (7.7)
	*Missing	31,615 (13.1)
Pre-existing hypertension	No	240,342 (99.8)
	Yes	423 (0.2)
Marital status		
	Single/widowed/divorced	58,247 (24.2)
	Married/common-law	167,955 (69.8)
	*Missing	14,563 (6.0)
Neighbourhood income quintile		
	Lowest	41,215 (17.1)
	Lower-middle	43,707(18.2)
	Middle	46,108 (19.2)
	Middle-upper	41,704 (17.3)
	Highest	27,288 (11.3)
	*Missing	40,743 (16.9)
Sex of infant		
	Male	122,826 (51.0)
	Female	117,939 (49.0)
Smoked during pregnancy		
	No	172,472 (71.6)
	Yes	62,953 (26.2)
	*Missing	5,340 (2.2)
Asthma		
	No	236,637 (98.3)
	Yes	4,128 (1.7)
Gastrointestinal disorders	No	239,919 (99.6)
	Yes	846 (0.4)

Variable		Frequency (%)
Polyhydramnios		
	No	239,885 (99.6)
	Yes	880 (0.4)
Placenta previa		
	No	24,368 (99.8)
	Yes	397 (0.2)
Psychiatric illness		
	No	237,190 (98.5)
	Yes	3,575 (1.5)
Previous abortion/miscarriage	No	178,485 (74.1)
	Yes	62,233 (25.8)
	*Missing	47 (0.02)
Previous GDM		
	No	240,235 (99.8)
	Yes	530 (0.2)
Previous birth <2050g		
	No	227,843 (94.6)
	Yes	8,951 (3.7)
	*Missing	3,971 (1.6)
Previous birth >4080g	No	220,332 (91.5)
	Yes	16,535 (6.9)
	*Missing	3,898 (1.6)
Rate of weight gain at 26 weeks		
	<0.3243	42,935 (17.8)
	0.3243-<0.4531	45,979 (19.1)
	0.4531-<0.5868	45,041 (18.7)
	≥0.5868	53,790 (22.3)
	*Missing	53,020 (22.0)

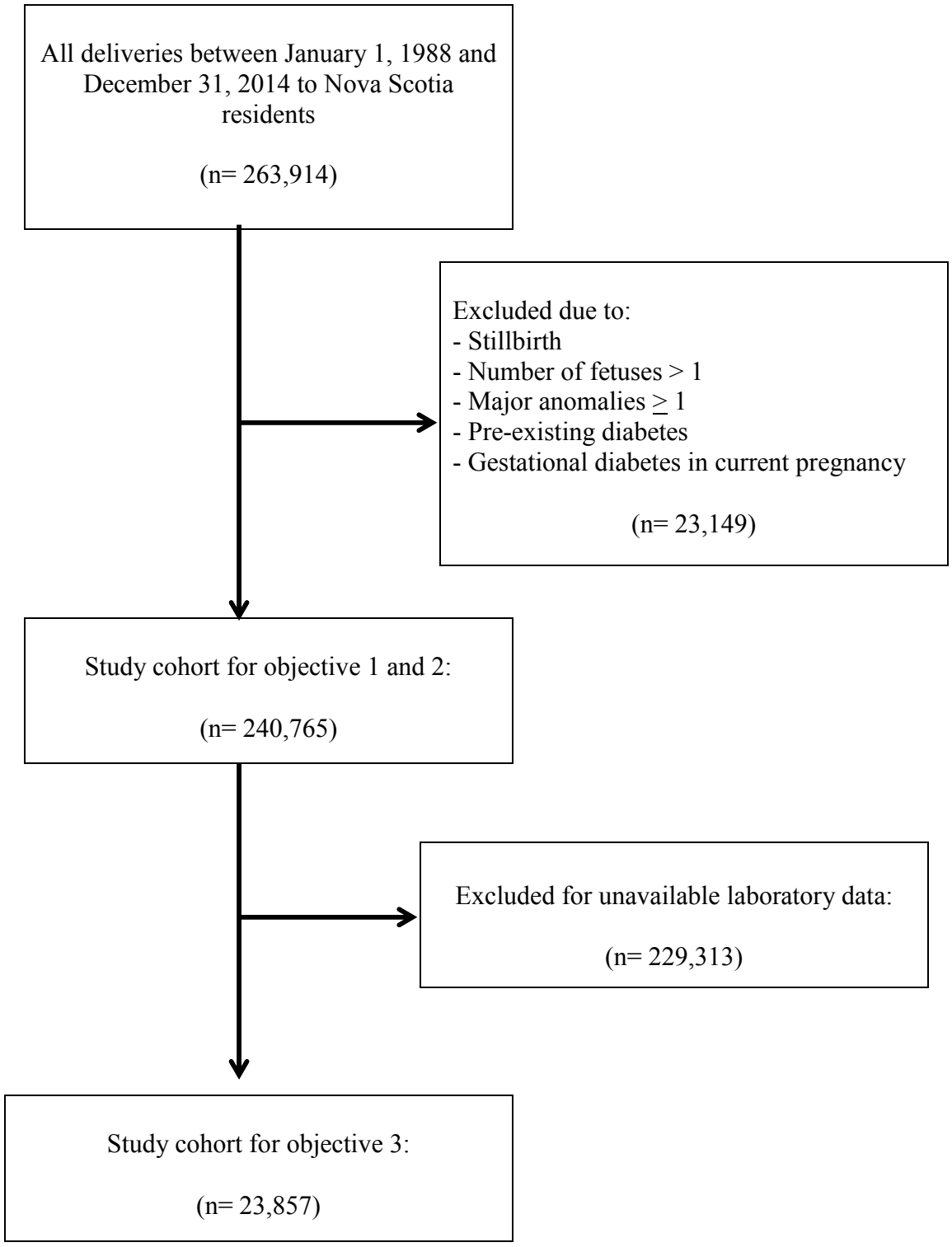

Figure 4-1 Flow diagram of participant exclusion for study cohorts for objectives 1 and 2 and objective 3.

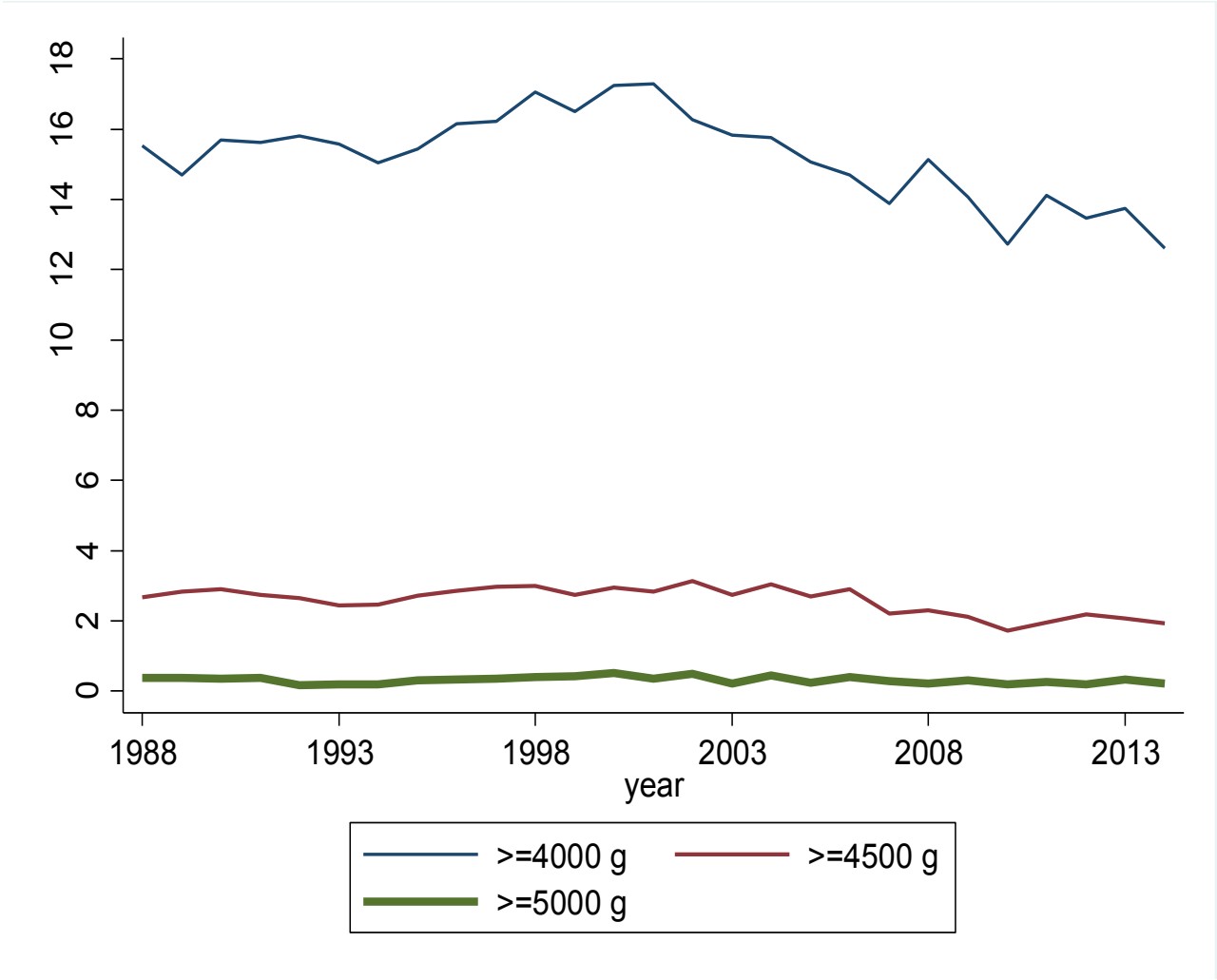

Figure 4-2 Per cent of births affected by macrosomia, among non-diabetic Nova Scotia residents, by year, 1988-2014

Chapter 5 OBJECTIVE 2 RESULTS

5. OBJECTIVE 2: To determine the maternal and pregnancy risk factors of macrosomia in non-diabetic women in Nova Scotia.

5.1 Characteristics of Cohort by Macrosomia Status

Table 5-1 (p. 44-45) shows the associations between macrosomia (≥4000 g) and the covariates obtained from the NSAPD. Results of the univariate logistic regression are expressed as odds ratios and 95% confidence intervals. Almost all variables were shown to be significantly different, comparing those who delivered a macrosomic infant and those who did not, at a significance level of $p<0.05$.

The previous birth of a large infant (defined as over 9 lbs or >4080 g) (OR: 5.53; 95% CI: 5.35-5.72) and pre-pregnancy weight ≥90 kg (OR: 3.15; 95% CI: 3.02-3.28) exhibited the strongest positive associations, while the previous birth of an infant <2500 g (OR: 0.36; 95% CI: 0.33-0.39), placenta previa (OR: 0.34; 95% CI: 0.22-0.52) and smoking during pregnancy (OR: 0.42; 95% CI: 0.41-0.44) were identified as the variables with the strongest inverse relationship. The smallest odds ratios were observed for the variables previous abortions and miscarriages (OR: 1.02; 95% CI: 1.00-1.05; p= 0.051) and pre-existing hypertension (OR: 1.06; 95% CI: 0.82-1.38; p=0.065), both of which were non-significant at $p<0.05$.

5.2 Associations between Covariates and Macrosomia >4000 g

Two separate multivariable logistic regression models were developed for nulliparous and multiparous women for each definition of macrosomia. The starting models included all factors shown in Table 5-1 with variables pertaining to previous pregnancies only included in the models for multiparous women.

The adjusted odds ratios and 95% confidence intervals for macrosomic infants ≥4000 g are presented in Tables 5-2 and 5-3 (p.46-49). Due to missing values, 66,843 nulliparous women and 74,550 multiparous women were included in the analyses involving macrosomia ≥4000 g. Among nulliparous women, being married or common-law, the birth of a male infant, presence of polyhydramnios and increasing pre-pregnancy weight, rate of weight gain and neighbourhood income level, were all associated with an increase risk of macrosomia. In the same model, an inverse relationship was observed between smoking, placenta previa, the presence of psychiatric illness and asthma and macrosomia. All of the variables mentioned in the nulliparous model remained in the model for multiparous mothers. As well, the previous birth of a large infant became the factor with the largest odds ratio and previous birth of a low birth weight infant was the factor with the smallest odds ratio associated with macrosomia. In addition, an inverse relationship emerged between gastrointestinal disorders and macrosomia. Of the biologically plausible interactions that were explored, neither the interaction between fetal sex and weight gain or pre-pregnancy weight and weight gain were significant.

5.3 Associations between Covariates and Macrosomia >4500 g

Table 5-4 (p.50) presents the nulliparous multivariable model with macrosomia ≥4500 g. In this model 85,752 women were included in the analysis. Among nulliparous women, increasing pre-pregnancy weight, infant sex, polyhydramnios and rate of weight gain were associated with an increase risk of macrosomia. In the same model, an inverse relationship was observed between smoking and psychiatric illness and macrosomia. In the multiparous model with macrosomia ≥4500 g (Table 5-5, p. 51-52), the number of women included was 74,550. Unlike the nulliparous model, marital status, asthma and neighbourhood income remained in the model, along with pre-pregnancy weight, infant sex, smoking, gastrointestinal disorders, polyhydramnios, rate of weight gain and previous birth of an infant <2500 g and previous birth of an infant >4080 g. Of the biologically plausible interactions that were explored, neither the interaction between fetal sex and weight gain or pre-pregnancy weight and weight gain were significant.

5.4 Associations between Covariates and Macrosomia >5000 g

The multivariable model for macrosomia ≥5000 g among nulliparous women is shown in Table 5-6 (p.53). Among nulliparous women, increasing pre-pregnancy weight, infant sex, and rate of weight gain were all associated with an increased risk of macrosomia while smoking during pregnancy was associated with a decreased risk of macrosomia. The multivariable model for macrosomia ≥5000 g among multiparous women is shown in Table 5-7 (p.54). Risk factors

identified to be significantly associated with macrosomia included pre-pregnancy weight, neighbourhood income level, infant sex, smoking status, polyhydramnios, previous birth of an infant <2500 g, previous birth of an infant >4080 g and rate of weight gain. In the analyses of both the nulliparous and multiparous mothers for macrosomia ≥5000 g, the total number of women were 85,752 and 74,550, respectively. Of the biologically plausible interactions that were explored, neither the interaction between fetal sex and weight gain or pre-pregnancy weight and weight gain were significant.

5.5 Associations between Covariates and Large for Gestational Age (LGA)

Among the 70,734 women included in the nulliparous model (Table 5-8, p. 55), increasing pre-pregnancy weight and rate of weight gain, previous abortions or miscarriages, polyhydramnios and having a neighbourhood income level in the two highest quintiles were all positively associated with increased risk of LGA (≥90^{th} percentile for age and sex). Smoking during pregnancy and the presence of asthma and psychiatric illness were negatively associated with LGA. In the 74,550 women in the multiparous model (Table 5-9, p. 56-57), pre-pregnancy weight, weight gain, smoking and the presence of polyhydramnios and psychiatric illness remained in the model of risk factors of LGA. In addition, marital status, the previous birth of a small infant and the previous birth of a large infant were significantly associated. Of the biologically plausible interactions that were explored, neither the interaction between fetal sex and weight gain or pre-pregnancy weight and weight gain were significant.

Table 5-1 Frequencies and unadjusted odds ratios (and 95% confidence intervals) between macrosomia (≥4000 g) and covariates

Variable	Macrosomia (N= 36,796) N[a] (%)	No macrosomia (N=203,969) N[a] (%)	Significance (p-value)	UOR (95% CI)
Maternal age				
<20 years	1,810 (4.9)	15,571 (7.6)	<0.0001[b]	1 (Ref)
20-24 years	6,713 (18.2)	45,237 (22.2)		1.28 (1.02-1.35)
25-29 years	12,172 (33.1)	65,828 (32.3)		1.59 (1.51-1.67)
30-34 years	11,402 (31.0)	53,913 (26.4)		1.82 (1.72-1.92)
35-39 years	4,124 (11.2)	20,296 (10.0)		1.75 (1.65-1.85)
≥40 years	575 (1.6)	3,124 (1.5)		1.58 (1.43-1.75)
Maternal age (continuous)				
Mean (SD)	28.99(5.3)	28.16(5.6)	<0.0001[c]	1.03(1.02-1.03)
Parity				
Nulliparous	13,288 (36.1)	94,992(46.6)	<0.0001[b]	1 (Ref)
Multiparous	23,504 (63.9)	108,957 (53.4)		1.54 (1.51-1.58)
Pre-pregnancy weight				
<60 kg	7,936 (21.6)	74,580 (36.6)	<0.0001[b]	1 (Ref)
60-69 kg	9,351 (25.4)	48,182 (23.6)		1.82 (1.77-1.88)
70-79 kg	6,533 (17.8)	26,731 (13.1)		2.30 (2.22-2.38)
80-89 kg	3,848 (10.5)	13,397 (6.6)		2.70 (2.59-2.82)
≥90 kg	4,668 (12.7)	13,924 (6.8)		3.15 (3.02-3.28)
Pre-pregnancy weight (continuous)				
Mean (SD)	72.44(16.9)	65.96(15.3)	<0.0001[c]	1.02 (1.02-1.02)
Pre-existing hypertension				
No	36,728 (99.8)	203,614 (99.8)	0.65[b]	1 (Ref)
Yes	68 (0.2)	355 (0.2)		1.16 (0.82-1.38)
Marital status				
Single/widowed/divorced	6,867 (18.7)	51,380 (25.2)	<0.0001[b]	1 (Ref)
Married/common-law	27,828 (5.7)	140,127 (68.7)		1.48 (1.44-1.53)
Neighbourhood income quintile				
Lowest	5,524 (15.0)	35,691 (17.5)	<0.0001[b]	1 (Ref)
Lower-middle	6,534 (17.8)	37,173 (18.2)		1.14 (1.09-1.18)
Middle	6,925 (18.8)	39,183 (19.2)		1.14 (1.10-1.19)
Middle-upper	6,959 (18.9)	34,745 (17.0)		1.29 (1.24-1.34)
Highest	4,447 (12.1)	22,841 (11.2)		1.26 (1.20-1.31)
Sex of infant				
Female	13,781 (37.4)	104,158 (51.1)	<0.0001[b]	1 (Ref)
Male	23,015 (62.6)	99,811 (48.9)		1.74 (1.70-1.78)
Smoked during pregnancy				
No	30,712 (83.5)	141,812 (69.5)	<0.0001[b]	1 (Ref)
Yes	5,316 (14.4)	57,637 (28.3)		0.42 (0.41-0.44)

Variable	Macrosomia (N= 36,796) N[a] (%)	No macrosomia (N=203,969) N[a] (%)	Significance (p-value)	UOR (95% CI)
Asthma				
No	36,254 (98.5)	200,383 (98.2)	<0.0001[b]	1 (Ref)
Yes	542 (1.5)	3,586 (1.8)		0.84 (0.76-0.91)
Gastrointestinal disorders				
No	36,698 (99.7)	203,221 (99.6)	0.003[b]	1 (Ref)
Yes	98 (0.3)	748 (0.4)		0.72 (0.59-0.90)
Polyhydramnios				
No	36,491 (99.2)	203,394 (99.7)	<0.0001[b]	1 (Ref)
Yes	305 (0.8)	575 (0.3)		2.96 (2.57-3.40)
Placenta Previa				
No	36,773 (99.9)	203,595 (99.8)	<0.0001[b]	1 (Ref)
Yes	23 (0.06)	374 (0.2)		0.34 (0.22-0.52)
Psychiatric illness				
No	36,384 (98.9)	200,806 (98.4)	<0.0001[b]	1 (Ref)
Yes	412 (1.1)	3,163 (1.6)		0.72 (0.65-0.80)
Previous abortion/miscarriage				
No	27,145 (73.8)	151,340 (74.2)	0.051[b]	1 (Ref)
Yes	9,648 (26.2)	52,585 (25.8)		1.02 (1.00-1.05)
Previous GDM				
No	36,696 (99.7)	203,539 (99.8)	0.022[b]	1 (Ref)
Yes	100 (0.3)	430 (0.2)		1.29 (1.04-1.60)
Previous birth <2500 g				
No	35,648 (96.9)	192,195 (94.2)	<0.0001[b]	1 (Ref)
Yes	560 (1.5)	8,391 (4.1)		0.36 (0.33-0.39)
Previous birth >4080 g				
No	28,690 (78.0)	191,642 (94.0)	<0.0001[b]	1 (Ref)
Yes	7,489 (20.4)	9,046 (4.4)		5.53 (5.35-5.72)
Rate of weight gain at 26 weeks				
<0.3243 kg/week	4,727 (12.8)	38,208 (18.7)	<0.0001[b]	1 (Ref)
0.3243-<0.4531 kg/week	6,136 (16.7)	39,843 (19.5)		1.24 (1.20-1.30)
0.4531-<0.5868 kg/week	7,183 (19.5)	37,858 (18.6)		1.53 (1.47-1.60)
≥0.5868 kg/week	11,176 (20.6)	42,614 (20.9)		2.12 (2.04-2.20)

[a] Frequency may not total sample size due to missing values
[b] p-value based on Chi-square Test
[c] p-value based on Wilcoxon Mann-Whitney U Test

UOR- Unadjusted odds ratio

Table 5-2 Adjusted odds ratios and 95% confidence intervals for the multivariable association between covariates and macrosomia (≥4000 g) among nulliparous mothers (N=66,843)[a]

Risk Factor	Adjusted Odds Ratio [b]	95% Confidence Interval	p-value
Maternal age			
<20 years	1.10	1.00-1.20	0.049
20-24 years	1.02	0.96-1.09	0.452
25-29 years	1	-	-
30-34 years	0.97	0.91-1.04	0.358
35-39 years	0.82	0.74-0.91	<0.001
≥40 years	0.76	0.57-1.01	0.055
Pre-pregnancy weight			
<60 kg	1	-	-
60-69 kg	1.66	1.56-1.77	<0.001
70-79 kg	2.27	2.11-2.43	<0.001
80-89 kg	2.96	2.71-3.23	<0.001
≥90 kg	4.08	3.75-4.43	<0.001
Marital status			
Single/widowed/divorced	1	-	-
Married/common-law	1.10	1.03-1.17	0.004
Neighbourhood income quintile			
Lowest	1	-	-
Lower-middle	1.13	1.05-1.21	0.002
Middle	1.06	0.98-1.14	0.130
Middle-upper	1.18	1.10-1.28	<0.001
Highest	1.20	1.10-1.30	<0.001
Infant sex			
Female	1	-	-
Male	1.78	1.70-1.87	<0.001
Smoked during pregnancy			
No	1	-	-
Yes	0.50	0.47-0.53	<0.001
Asthma			
No	1	-	-
Yes	0.74	0.62-0.88	0.001
Polyhydramnios			
No	1	-	-
Yes	3.60	2.58-5.03	<0.001

Risk Factor	Adjusted Odds Ratio [b]	95% Confidence Interval	p-value
Placenta previa			
No	1	-	-
Yes	0.16	0.04-0.67	0.012
Psychiatric illness			
No	1	-	-
Yes	0.71	0.57-0.87	0.001
Rate of weight gain at 26 weeks			
<0.3243 kg/week	1	-	-
0.3243-<0.4531 kg/week	1.58	1.44-1.73	<0.001
0.4531-<0.5868 kg/week	2.04	1.87-2.22	<0.001
≥0.5868 kg/week	3.13	2.89-3.40	<0.001

[a] Does not total sample size due to missing values
[b] Adjusted for all variables in model

Table 5-3 Adjusted odds ratios and 95% confidence intervals for the multivariable association between covariates and macrosomia (≥4000 g) among multiparous mothers (N=74,550)[a]

Risk Factor	Adjusted Odds Ratio [b]	95% Confidence Interval	p-value
Maternal age			
<20 years	1.02	0.84-1.23	0.838
20-24 years	1.01	0.94-1.08	0.758
25-29 years	1	-	-
30-34 years	1.02	0.98-1.08	0.306
35-39 years	0.90	0.84-0.96	0.002
≥40 years	0.88	0.76-1.01	0.074
Pre-pregnancy weight			
<60 kg	1	-	-
60-69 kg	1.60	1.51-1.68	<0.001
70-79 kg	2.02	1.90-2.15	<0.001
80-89 kg	2.59	2.41-2.79	<0.001
≥90 kg	3.44	3.20-3.69	<0.001
Marital status			
Single/widowed/divorced	1	-	-
Married/common-law	1.24	1.16-1.32	<0.001
Neighbourhood income quintile			
Lowest	1	-	-
Lower-middle	1.01	0.94-1.07	0.823
Middle	0.97	0.91-1.03	0.329
Middle-upper	1.01	1.01-1.15	0.017
Highest	1.00	0.93-1.07	0.994
Infant sex			
Female	1	-	-
Male	1.81	1.73-1.88	<0.001
Smoked during pregnancy			
No	1	-	-
Yes	0.46	0.44-0.49	<0.001
Asthma			
No	1	-	-
Yes	0.76	0.64-0.90	0.002
Gastrointestinal disorders			
No	1	-	-
Yes	0.53	0.35-0.82	0.004

Risk Factor	Adjusted Odds Ratio [b]	95% Confidence Interval	p-value
Polyhydramnios			
No	1	-	-
Yes	2.06	1.62-2.62	<0.001
Placenta previa			
No	1	-	-
Yes	0.25	0.10-0.59	0.001
Psychiatric illness			
No	1	-	-
Yes	0.61	0.50-0.74	<0.001
Previous birth <2500 g			
No	1	-	-
Yes	0.38	0.34-0.43	<0.001
Previous birth > 4080 g			
No	1	-	-
Yes	4.20	4.01-4.41	<0.001
Rate of weight gain at 26 weeks			
<0.3243 kg/week	1	-	-
0.3243-<0.4531 kg/week	1.58	1.48-1.68	<0.001
0.4531-<0.5868 kg/week	2.02	1.90-2.15	<0.001
≥0.5868 kg/week	2.76	2.60-2.93	<0.001

[a] Does not total sample size due to missing values
[b] Adjusted for all variables in model

Table 5-4 Adjusted odds ratios and 95% confidence intervals for the multivariable association between covariates and macrosomia (≥4500 g) among nulliparous mothers (N=85,752)[a]

Risk Factor	Adjusted Odds Ratio [b]	95% Confidence Interval	p-value
Pre-pregnancy weight			
<60 kg	1	-	-
60-69 kg	1.84	1.59-2.14	<0.001
70-79 kg	2.87	2.46-3.35	<0.001
80-89 kg	4.10	3.43-4.89	<0.001
≥90 kg	6.90	5.87-8.10	<0.001
Infant sex			
Female	1	-	-
Male	2.10	1.89-2.34	<0.001
Smoked during pregnancy			
No	1	-	-
Yes	0.48	0.41-0.55	<0.001
Polyhydramnios			
No	1	-	-
Yes	4.10	2.52-6.68	<0.001
Psychiatric illness			
No	1	-	-
Yes	0.51	0.31-0.86	0.011
Rate of weight gain at 26 weeks			
<0.3243 kg/week	1	-	-
0.3243-<0.4531 kg/week	1.46	1.18-1.81	0.001
0.4531-<0.5868 kg/week	2.26	1.85-2.75	<0.001
≥0.5868 kg/week	4.29	3.58-5.14	<0.001

[a] Does not total sample size due to missing values
[b] Adjusted for all variables in model

Table 5-5 Adjusted odds ratios and 95% confidence intervals for the multivariable association between covariates and macrosomia (≥4500 g) among multiparous mothers (N=74,550)[a]

Risk Factor	Adjusted Odds Ratio [b]	95% Confidence Interval	p-value
Pre-pregnancy weight			
<60 kg	1	-	-
60-69 kg	1.80	1.58-2.05	<0.001
70-79 kg	2.68	2.34-3.07	<0.001
80-89 kg	3.66	3.14-4.25	<0.001
≥90 kg	5.29	4.57-6.12	<0.001
Marital status			
Single/widowed/divorced	1	-	-
Married/common-law	1.23	1.08-1.41	0.002
Neighbourhood income quintile			
Lowest	1	-	-
Lower-middle	0.88	0.77-1.01	0.062
Middle	0.87	0.76-0.99	0.043
Middle-upper	1.02	0.89-1.16	0.769
Highest	0.92	0.80-1.07	0.299
Infant sex			
Female	1	-	-
Male	2.10	1.92-2.30	<0.001
Smoked during pregnancy			
No	1	-	-
Yes	0.47	0.42-0.54	<0.001
Asthma			
No	1	-	-
Yes	0.61	0.41-0.90	0.014
Gastrointestinal disorders			
No	1	-	-
Yes	0.12	0.02-0.89	0.038
Polyhydramnios			
No	1	-	-
Yes	3.32	2.34-4.70	<0.001
Previous birth <2500 g			
No	1	-	-
Yes	0.42	0.31-0.56	<0.001

Risk Factor	Adjusted Odds Ratio [b]	95% Confidence Interval	p-value
Previous birth > 4080 g			
No	1	-	-
Yes	5.52	5.07-6.01	<0.001
Rate of weight gain at 26 weeks			
<0.3243 kg/week	1	-	-
0.3243-<0.4531 kg/week	1.78	1.54-2.04	<0.001
0.4531-<0.5868 kg/week	2.40	2.09-2.76	<0.001
≥0.5868 kg/week	3.95	3.47-4.49	<0.001

[a] Does not total sample size due to missing values
[b] Adjusted for all variables in model

Table 5-6 Adjusted odds ratios and 95% confidence intervals for the multivariable association between covariates and macrosomia (≥5000 g) among nulliparous mothers (N=85,752)[a]

Risk Factor	Adjusted Odds Ratio [b]	95% Confidence Interval	p-value
Pre-pregnancy weight			
<60 kg	1	-	-
60-69 kg	1.80	1.16-2.78	0.009
70-79 kg	2.82	1.79-4.44	<0.001
80-89 kg	3.92	2.33-6.59	<0.001
≥90 kg	8.19	5.24-12.78	<0.001
Infant sex			
Female	1	-	-
Male	2.66	1.92-3.68	<0.001
Smoked during pregnancy			
No	1	-	-
Yes	0.45	0.29-0.69	<0.001
Rate of weight gain at 26 weeks			
<0.3243 kg/week	1	-	-
0.3243-<0.4531 kg/week	1.32	0.72-2.45	0.369
0.4531-<0.5868 kg/week	1.84	1.03-3.27	0.039
≥0.5868 kg/week	4.34	2.64-7.16	<0.001

[a] Does not total sample size due to missing values
[b] Adjusted for all variables in model

Table 5-7 Adjusted odds ratios and 95% confidence intervals for the multivariable association between covariates and macrosomia (≥5000 g) among multiparous mothers (N=74,550)[a]

Risk Factor	Adjusted Odds Ratio [b]	95% Confidence Interval	p-value
Pre-pregnancy weight			
<60 kg	1	-	-
60-69 kg	2.24	1.48-3.38	<0.001
70-79 kg	3.98	2.63-6.02	<0.001
80-89 kg	5.58	5.58-8.68	<0.001
≥90 kg	9.19	6.02-14.04	<0.001
Neighbourhood income quintile			
Lowest	1	-	-
Lower-middle	0.66	0.44-0.96	0.032
Middle	0.88	0.61-1.25	0.472
Middle-upper	1.20	0.85-1.67	0.300
Highest	1.00	0.68-1.48	0.985
Infant sex			
Female	1	-	-
Male	2.45	1.91-3.14	<0.001
Smoked during pregnancy			
No	1	-	-
Yes	0.36	0.24-0.54	<0.001
Polyhydramnios			
No	1	-	-
Yes	4.17	2.11-8.21	<0.001
Previous birth <2500 g			
No	1	-	-
Yes	0.41	0.17-0.99	0.049
Previous birth > 4080 g			
No	1	-	-
Yes	6.80	5.39-8.58	<0.001
Rate of weight gain at 26 weeks			
<0.3243 kg/week	1	-	-
0.3243-<0.4531 kg/week	3.37	2.17-5.23	<0.001
0.4531-<0.5868 kg/week	4.28	2.76-6.62	<0.001
≥0.5868 kg/week	7.70	5.11-11.60	<0.001

[a] Does not total sample size due to missing values
[b] Adjusted for all variables in model

Table 5-8 Adjusted odds ratios and 95% confidence intervals for the multivariable association between covariates and LGA (≥90th percentile for age and sex) among nulliparous mothers (N=70,734)[a]

Risk Factor	Adjusted Odds Ratio [b]	95% Confidence Interval	p-value
Pre-pregnancy weight			
<60 kg	1	-	-
60-69 kg	1.61	1.50-1.72	<0.001
70-79 kg	2.20	2.04-2.37	<0.001
80-89 kg	3.15	2.88-3.44	<0.001
≥90 kg	4.28	3.93-4.66	<0.001
Neighbourhood income quintile			
Lowest	1	-	-
Lower-middle	1.05	0.97-1.13	0.250
Middle	1.05	0.97-1.13	0.240
Middle-upper	1.14	1.05-1.23	0.001
Highest	1.15	1.05-1.26	0.002
Previous abortion/miscarriage			
No	1	-	-
Yes	1.08	1.02-1.15	0.009
Smoked during pregnancy			
No	1	-	-
Yes	0.47	0.44-0.51	<0.001
Polyhydramnios			
No	1	-	-
Yes	4.24	3.06-5.88	<0.001
Asthma			
No	1	-	-
Yes	0.81	0.67-0.97	0.021
Psychiatric illness			
No	1	-	-
Yes	0.78	0.63-0.97	0.026
Rate of weight gain at 26 weeks			
<0.3243 kg/week	1	-	-
0.3243-<0.4531 kg/week	1.32	1.20-1.46	<0.001
0.4531-<0.5868 kg/week	1.89	1.72-2.08	<0.001
≥0.5868 kg/week	3.30	3.03-3.58	<0.001

[a] Does not total sample size due to missing values
[b] Adjusted for all variables in model

Table 5-9 Adjusted odds ratios and 95% confidence intervals for the multivariable association between covariates and LGA (≥90th percentile for age and sex) among multiparous mothers (N=74,550)[a]

Risk Factor	Adjusted Odds Ratio [b]	95% Confidence Interval	p-value
Maternal age			
<20 years	1	-	-
20-24 years	1.11	0.90-1.36	0.319
25-29 years	1.05	0.86-1.29	0.615
30-34 years	1.20	0.98-1.46	0.086
35-39 years	1.15	0.93-1.41	0.196
≥40 years	1.11	0.86-1.42	0.416
Pre-pregnancy weight			
<60 kg	1	-	-
60-69 kg	1.54	1.46-1.63	<0.001
70-79 kg	2.20	2.07-2.35	<0.001
80-89 kg	3.01	2.80-3.25	<0.001
≥90 kg	4.14	3.85-4.46	<0.001
Marital status			
Single/widowed/divorced	1	-	-
Married/common-law	1.13	1.06-1.21	<0.001
Neighbourhood income quintile			
Lowest	1	-	-
Lower-middle	0.94	0.88-1.01	0.104
Middle	0.94	0.88-1.00	0.060
Middle-upper	1.04	0.98-1.12	0.213
Highest	1.02	0.95-1.10	0.572
Smoked during pregnancy			
No	1	-	-
Yes	0.47	0.44-0.50	<0.001
Polyhydramnios			
No	1	-	-
Yes	3.09	2.44-3.90	<0.001
Psychiatric illness			
No	1	-	-
Yes	0.78	0.65-0.93	0.007
Previous birth <2500 g			
No	1	-	-
Yes	0.56	0.50-0.62	<0.001

Risk Factor	Adjusted Odds Ratio [b]	95% Confidence Interval	p-value
Previous birth > 4080 g			
No	1	-	-
Yes	3.88	3.69-4.07	<0.001
Rate of weight gain at 26 weeks			
<0.3243 kg/week	1	-	-
0.3243-<0.4531 kg/week	1.54	1.45-1.65	<0.001
0.4531-<0.5868 kg/week	2.09	1.96-2.23	<0.001
≥0.5868 kg/week	3.28	3.08-3.49	<0.001

[a] Does not total sample size due to missing values
[b] Adjusted for all variables in model

Chapter 6 OBJECTIVE 3 RESULTS

6. OBJECTIVE 3: To build and validate a risk prediction model incorporating both maternal factors and laboratory data to estimate the risk of developing macrosomia for non-diabetic women.

6.1 Description of Cohort

As previously described (Section 3.2), laboratory results for pre-natal glucose screening were only available for women who had their testing completed at the IWK Health Centre and were included in the previously linked 1998-2005 data (Figure 4-1, p. 38). Of the 23,857 women included in this cohort, 16.7% delivered a macrosomic (≥4000 g) infant.

6.2 Macrosomia >4000 g

6.2.1 Risk Prediction Model for Macrosomia

Separate multivariable logistic regression models were built for nulliparous and multiparous women, this time utilizing the laboratory data cohort. 8,629 nulliparous mothers were included in the development of a risk prediction model for macrosomia (≥4000 g). Among the nulliparous mothers, being married or common-law, having a male infant and increasing results of the glucose challenge test, pre-pregnancy weight, and rate of weight gain were positively associated with macrosomia. In contrast, smoking during pregnancy and the presence

of asthma and psychiatric illness were negatively associated with macrosomia. Table 6-1 (p. 65) displays the estimates of the regression coefficients, odds ratios (ORs) and 95% confidence intervals (CIs) for the multivariable model of macrosomia (≥4000 g) among nulliparous women.

Table 6-2 (p. 66) shows the risk factors included in the prediction model for nulliparous women and the risk of macrosomia, the categories and reference values and the associated points they each contribute to the model. In this system, the range of total points is -12 to 19. Asthma contributes the largest amount of negative points (-7) and having a pre-pregnancy weight ≥90 kg contributes the largest amount of positive points (7). Table 6-3 (p. 67) displays the risk estimates for having a macrosomic infant attached to each possible point total for the system. The estimated risk ranges from 0.18% for a point total of -12 to 46.9% for a point total of 19.

Tables 6-4 to 6-6 (p. 68-70) show the estimates of the regression coefficients, points associated with each risk factor and estimate of risk for each possible point total for macrosomia (≥4000 g) among multiparous mothers. This model was developed from 8,098 women and significant factors include male infant, the previous birth of a large infant and increasing glucose challenge test results, pre-pregnancy weight and rate of weight gain as risk factors positively associated with macrosomia and smoking during pregnancy, psychiatric illness and the previous birth of a small infant as negatively associated risk factors. The range of total points for this system is -12 to 25. Smoking during pregnancy and the previous birth of a small infant both contribute the largest amount of negative points (-5) and a pre-pregnancy weight ≥90 kg and the previous birth of a large infant both contribute the largest amount of positive points (7). Table 6-5 (p. 69) displays the risk estimate associated with each possible point total for the system. The estimated risk ranges from 0.45% for -12 points to 88.0% for 25 points.

6.2.2 Internal Validation of Risk Prediction Model for Macrosomia

Table 6-7 (p.71) displays the *c* statistic (area under the ROC curve) for the prediction models of macrosomia among nulliparous and multiparous women. The *c* statistic for the nulliparous model is 0.70 and for the multiparous model is 0.75, indicating that the multiparous model is a slightly better at predicting macrosomia.

6.2.3 External Validation of Nulliparous Risk Prediction Model for Macrosomia

Table 6-8 (p.72) presents the odds ratios and 95% confidence intervals of the macrosomia ($\geq$4000 g) risk factors for the NSAPD and the MIREC cohorts. Among the NSAPD cohort, all risk factors were statistically significant. However, among the MIREC cohort, a number of risk factors were not statistically significant, likely because of small sample size. The total sample size for the MIREC cohort included only 452 women, 56 of whom delivered a macrosomic infant. The risk factors asthma and psychiatric illness were excluded from the analysis because of low event rates. Still, the trends in almost all risk factors were similar between cohorts.

Table 6-7 (p.71) displays the *c* statistic for the developed risk prediction model on both the NSAPD and MIREC cohorts. This shows the discrimination that was achieved by applying the developed risk prediction model to the non-NSAPD cohort. For the non-NSAPD cohort (MIREC), the risk prediction model discriminates well, obtaining the same discrimination as the model on the NSAPD cohort from which it was developed. The comparable *c* statistics indicates that the model has similar predictive ability on an external dataset.

6.2.4 Optimal Cut-point

The optimal cut-point, which categorizes nulliparous women as low or high-risk for delivering a macrosomic (≥4000 g) infant, was calculated to be 29%. This indicates that nulliparous women who have an estimated risk <29% are at low-risk of delivering a macrosomic infant while those who have an estimated risk ≥29% are at high-risk of delivering a macrosomic infant. The sensitivity and specificity when using this cut-point were estimated to be 0.66 and 0.63 respectively, resulting in a positive likelihood ratio of 1.8 and a negative likelihood ratio of 0.5. This positive likelihood ratio greater than 1 indicates that the test result is associated with macrosomia; however, since it is somewhat close to 1, it offers only a modest increase in the posttest probability of macrosomia. The negative likelihood ratio of 0.5, indicates that the test offers a modest decrease in the likelihood of macrosomia if the test is negative.

The optimal cut-point for defining multiparous women as low or high-risk for delivering a macrosomic (≥4000 g) infant was calculated to be 36%. Therefore, multiparous women who have an estimated risk of <36% are at low-risk for delivering a macrosomic infant and those who have an estimated risk of ≥36% are at high-risk of delivering a macrosomic infant. The sensitivity and specificity when using this cut-point were estimated to be 0.73 and 0.63 respectively, resulting in a positive likelihood ratio of 2.0 and a negative likelihood ratio of 0.4. The positive likelihood ratio of 2.0 indicates that the test offers a small increase in the posttest probability of macrosomia. Similarly, the negative likelihood ratio of 0.4 indicates that the test offers a small decrease in the likelihood of macrosomia if the test is negative.

6.2.5 Use of Risk Prediction Model for Predicting Macrosomia

6.2.5.1 Nulliparous Model

Table 6-9 (p. 73) illustrates how the scoring system could be used in clinical practice at mid-pregnancy. In this example, the hypothetical patient is an 85 kg married, nulliparous woman, expecting a male infant, with GCT results of 8.3 mmol/L and a rate of weight gain of 0.60 kg/week at 26 weeks. For this example, points were given for marital status of married (1), male infant sex (2), GCT result of 6.8 - 10.3 mmol/L (3), rate of weight gain $\geq$0.59 kg/week (6) and pre-pregnancy weight of 80- 89 kg (5). This example resulted in total points of 17. Using the table of estimated risks (Table 6-3, p. 67), this individual would have an estimated risk of having a macrosomic infant of 37%.

6.2.5.2 Multiparous Model

In this example, a scenario is shown for a multiparous woman (Table 6-10, p. 74). In this scenario, the patient is a 76 kg, multiparous women, with a previous large birth, expecting a male infant. She has an expected weight gain of 0.50 kg/week at 26 weeks and a GCT result of 6.3 mmol/L. Points were given for a GCT result of 5.9-6.8 mmol/L (1), male infant sex (3), rate of weight gain of 0.45-0.59 kg/week (3), pre-pregnancy weight of 70-79 kg (3) and a previous large birth (7). This example resulted in a risk score of 17. Using the table of estimated risks (Table 6-6, p. 70), this individual would have an estimated risk of having a macrosomic infant of 60%.

6.3 Large for Gestational Age (>90th percentile for age and sex)

6.3.1 Risk Prediction Model for LGA

Among nulliparous mothers, increasing pre-pregnancy weight, glucose challenge test results and rate of weight gain were positively correlated with LGA and asthma and smoking during pregnancy were negatively associated with LGA. Table 6-11 (p. 75) displays the estimates of the regression coefficients, odds ratios (ORs) and 95% confidence intervals (CIs) for the multivariable model of LGA among nulliparous mothers. The risk factors, categories and reference values and associated points they each contribute to the model are shown in Table 6-12 (p. 76). In this system, the range of total points is -10 to 18. Similar to the nulliparous macrosomia model, asthma contributes the largest amount of negative points (-7) and having a pre-pregnancy weight ≥90 kg contributes the largest amount of positive points (8). Table 6-13 (p. 77) displays the risk estimate attached to each possible point total for the system. The estimated risk ranges from 0.48% for a point total of -10 to 56.8% for a point total of 18. This model was developed from 8,677 mothers.

Tables 6-14 to 6-16 (p. 78-80) show the estimates of the regression coefficients, points associated with each risk factor and the estimate of risk for each possible point total for LGA among multiparous mothers. This model was developed from 8,098 mothers. The risk factors found to be positively associated with LGA were the previous birth of a large infant, increasing glucose challenge test results, polyhydramnios, pre-pregnancy weight and rate of weight gain. Smoking during pregnancy and the previous birth of a small infant were negatively associated with the risk for LGA. The range of total points for this system is -7 to 28. Smoking during pregnancy contributes the largest amount of negative points (-4) and pre-pregnancy weight ≥90

kg contribute the largest amount of positive points (7). Table 6-16 (p. 80) displays the risk estimate attached to each possible point total for the system. The estimated risk ranges from 1.5% for -7 points to 94.4% for 28 points.

6.3.2 Internal Validation of Risk Prediction Model for LGA

Table 6-7 (p.71) displays the *c* statistic (area under the ROC curve) for the prediction models of LGA among nulliparous and multiparous women. The *c* statistic for the nulliparous model is 0.70 and 0.73 for the multiparous model.

6.4 New Diagnostic Criteria and Macrosomia >4000 g

Table 6-17 (p. 81) displays the risk prediction model for nulliparous women for macrosomia ≥4000 g, using the changed 2013 gestational diabetes diagnostic criteria. Individuals who had previously been classified as having impaired glucose tolerance, using the criteria prior to 2013 were classified as having gestational diabetes and excluded from the model using the new criteria. In both the nulliparous and multiparous models, the same risk factors remained significant as in the model using the old criteria (Section 6.2.1). In both models, the only change was observed in the points associated with the highest level of GCT result. In each model, the points associated with the highest level of GCT results decreased by one point (from 3 to 2 points).

Table 6-1 Regression coefficients, odds ratios and 95% confidence intervals for the multivariable association between risk factors and macrosomia (>4000 g) among nulliparous mothers with glucose screening data (N=8629)[a]

Risk factor	Regression coefficient	OR	95% CI for OR	p-value
Intercept	-6.1012	-	-	-
Male sex	0.4151	1.51	1.33-1.72	<0.001
Married	0.2914	1.34	1.13-1.58	0.001
Pre-pregnancy weight (per kg)	0.0286	1.03	1.02-1.03	<0.001
Smoked during pregnancy	-0.5109	0.60	0.48-0.74	<0.001
Asthma	-1.4150	0.24	0.06-1.03	0.055
Psychiatric illness	-0.4062	0.67	0.45-0.98	0.037
GCT results (per mmol/L)	0.1043	1.11	1.05-1.17	<0.001
Rate of weight gain at 26 weeks (per kg/week)	1.7871	5.97	4.62-7.72	<0.001

[a] Does not total sample size due to missing values

Table 6-2 Points associated with each category of risk factor for macrosomia (≥4000 g) among nulliparous mothers with glucose screening data (N=8629)[a]

Risk Factor	Categories	Reference value (W_{ij})	β_i	$\beta_i(W_{ij} - W_{i\text{REF}})$	Points$_{ij}$ = $\beta_I(W_{ij} - W_{i\text{REF}})/B$
Infant sex			0.4151		
	Female	0= $W_{1\text{REF}}$		0	0
	Male	1		0.4151	2
Marital status			0.2914		
	Not married	0= $W_{2\text{REF}}$		0	0
	Married	1		0.2914	1
Pre-pregnancy weight *			0.0286		
	<60 kg	52= $W_{3\text{REF}}$		0	0
	60-69 kg	65		0.3718	2
	70-79 kg	75		0.6578	3
	80-89 kg	85		0.9438	5
	≥90 kg	103		1.4586	7
Smoked during pregnancy			-0.5109		
	No	0= $W_{4\text{REF}}$		0	0
	Yes	1		-0.5109	-3
Asthma			-1.4150		
	No	0= $W_{5\text{REF}}$		0	0
	Yes	1		-1.4150	-7
Psychiatric illness			-0.4062		
	No	0= $W_{6\text{REF}}$		0	0
	Yes	1		-0.4062	-2
GCT results **			0.1043		
	<5.1 mmol/L	3.7= $W_{7\text{REF}}$		0	0
	5.1-<5.9 mmol/L	5.5		0.1877	1
	5.9-<6.8 mmol/L	6.4		0.2816	1
	6.8-10.3 mmol/L	8.6		0.5111	3
Rate of weight gain at 26 weeks ***			1.7871		
	<0.32 kg/week	0.17= $W_{8\text{REF}}$		0	0
	0.32-<0.45 kg/week	0.38		0.3753	2
	0.45-<0.59 kg/week	0.52		0.6254	3
	≥0.59 kg/week	0.88		1.2688	6

[a] Does not total sample size due to missing values

* The pre-pregnancy weight range in the sample is 29.93-158.30 kg. To minimize the influence of extreme values, the 1st percentile (44.0) and the 99th percentile (116.12) were used to calculate the midpoints of the first and last categories.

** The range of GCT reults in the sample is 2.3-10.3 mmol/L

*** The range of rate of weight gain at 26 weeks is -1.70-3.95 kg/week. To minimize the influence of extreme values, the 1st percentile (0.010) and the 99th percentile (1.18) were used to calculate the midpoints of the first and last categories.

Table 6-3 Estimated risk of macrosomia (≥4000 g) among nulliparous mothers with glucose screening data (N= 8629)[a]

Point total	Estimate of risk	Point total	Estimate of risk
-12	0.001789	4	0.04212
-11	0.002184	5	0.05097
-10	0.002667	6	0.06156
-9	0.003255	7	0.07417
-8	0.003973	8	0.08913
-7	0.004848	9	0.1068
-6	0.005915	10	0.1274
-5	0.007215	11	0.1513
-4	0.008799	12	0.1788
-3	0.01073	13	0.2101
-2	0.01307	14	0.2452
-1	0.01592	15	0.2841
0	0.01937	16	0.3264
1	0.02356	17	0.3718
2	0.02863	18	0.4196
3	0.03475	19	0.4690

[a] Does not total sample size due to missing values

Table 6-4 Regression coefficients, odds ratios and 95% confidence intervals for the multivariable association between risk factors and macrosomia (≥4000 g) among multiparous mothers with glucose screening data (N=8098)[a]

Risk factor	Regression coefficient	OR	95% CI for OR	p-value
Intercept	-4.9472	-	-	-
Male sex	0.6060	1.83	1.62-2.07	<0.001
Previous birth <2500 g	-1.0622	0.34	0.25-0.48	<0.001
Previous birth >4080 g	1.3294	3.78	3.26-4.37	<0.001
Pre-pregnancy weight (per kg)	0.02622	1.03	1.02-1.03	<0.001
Smoked during pregnancy	-0.91795	0.40	0.33-0.49	<0.001
Psychiatric illness	-0.4123	0.66	0.47-0.93	0.019
GCT results (per mmol/L)	0.1098	1.12	1.06-1.17	<0.001
Rate of weight gain at 26 weeks (per kg/week)	-4.9471	3.79	2.65-5.41	<0.001

[a] Does not total sample size due to missing values

Table 6-5 Points associated with each category of risk factor for macrosomia (≥4000 g) among multiparous mothers with glucose screening data (N=8098)[a]

Risk Factor	Categories	Reference value (W_{ij})	β_i	$\beta_i(W_{ij} - W_{i\text{REF}})$	Points$_{ij}$ = $\beta_I(W_{ij} - W_{i\text{REF}})/B$
Infant sex			0.6060		
	Female	0= $W_{1\text{REF}}$		0	0
	Male	1		0.6060	3
Previous birth <2500 g			-1.0622		
	No	0= $W_{2\text{REF}}$		0	0
	Yes	1		-1.0622	-5
Previous birth >4080 g			1.3294	0	0
	No	0= $W_{3\text{REF}}$		1.3294	7
	Yes	1			
Pre-pregnancy weight *			0.02622		
	<60 kg	52= $W_{4\text{REF}}$		0	0
	60-69 kg	65		0.3409	2
	70-79 kg	75		0.6031	3
	80-89 kg	85		0.8653	4
	≥90 kg	104		1.3634	7
Smoked during pregnancy			-0.9180		
	No	0= $W_{5\text{REF}}$		0	0
	Yes	1		-0.9180	-5
Psychiatric illness			-0.4123		
	No	0= $W_{6\text{REF}}$		0	0
	Yes	1		-0.4123	-2
GCT results **			0.1098		
	<5.1 mmol/L	3.8= $W_{7\text{REF}}$		0	0
	5.1-<5.9 mmol/L	5.5		0.1867	1
	5.9-<6.8 mmol/L	6.4		0.2855	1
	6.8-10.3 mmol/L	8.6		0.5270	3
Rate of weight gain at 26 weeks ***			1.3320		
	<0.32 kg/week	0.12= $W_{8\text{REF}}$		0	0
	0.32-<0.45 kg/week	0.38		0.3463	2
	0.45-<0.59 kg/week	0.52		0.5328	3
	≥0.59 kg/week	0.84		0.9590	5

[a] Does not total sample size due to missing values

* The pre-pregnancy weight range in the sample is 30.39-158.76 kg. To minimize the influence of extreme values, the 1st percentile (44.91) and the 99th percentile (118.84) were used to calculate the midpoints of the first and last categories.

** The range of GCT reults in the sample is 2.4-10.3 mmol/L

*** The range of rate of weight gain at 26 weeks is -1.66-4.90 kg/week. To minimize the influence of extreme values, the 1st percentile (-0.088) and the 99th percentile (1.08) were used to calculate the midpoints of the first and last categories.

Table 6-6 Estimated risk of macrosomia (≥4000 g) among multiparous mothers with glucose screening data (N= 8098)[a]

Point total	Estimate of risk	Point total	Estimate of risk
-12	0.004466	7	0.1670
-11	0.005450	8	0.1968
-10	0.006649	9	0.2303
-9	0.008109	10	0.2676
-8	0.009886	11	0.3086
-7	0.01205	12	0.3528
-6	0.01468	13	0.3997
-5	0.01787	14	0.4485
-4	0.02174	15	0.4983
-3	0.02642	16	0.5482
-2	0.03209	17	0.5971
-1	0.03892	18	0.6441
0	0.04712	19	0.6885
1	0.05696	20	0.7297
2	0.06871	21	0.7673
3	0.08266	22	0.8011
4	0.09915	23	0.8311
5	0.1185	24	0.8573
6	0.1410	25	0.8800

[a] Does not total sample size due to missing values

Table 6-7 Summary of discrimination evaluations for internal and external validations

	Macrosomia ≥4000 g		LGA		External validation	
	Nulliparous	Multiparous	Nulliparous	Multiparous	NSAPD	MIREC
C statistic	0.70	0.75	0.70	0.73	0.70	0.70

Table 6-8 Odds ratios and 95% confidence intervals for risk factors of macrosomia (≥4000 g) by source of data

Risk factor	NSAPD OR(95% CI)	MIREC OR(95% CI)
Male sex	1.52 (1.34-1.74)	1.32 (0.73-2.37)
Married	1.33 (1.13-1.57)	1.36 (0.28-6.68)
Pre-pregnancy weight	1.03 (1.02-1.03)	1.04 (1.02-1.06)
Smoked during pregnancy	0.58 (0.47-0.71)	1.22 (0.50-2.97)
GCT results	1.09 (1.04-1.15)	1.00 (0.80-1.24)
Rate of weight gain at 26 weeks	5.94 (4.58-7.70)	3.27 (1.96-5.46)

Table 6-9 Breakdown of associated points and estimated risk of macrosomia for nulliparous example

Risk factor	Value	Points
Fetal sex	Male	2
Marital status	Married	1
Pre-pregnancy weight	85	5
Smoked during pregnancy	No	0
Asthma	No	0
Psychiatric illness	No	0
GCT results	8.3	3
Rate of weight gain at 26 weeks	0.60	6

Point total	17
Estimate of risk	0.3718

Table 6-10 Breakdown of associated points and estimated risk of macrosomia for multiparous example

Risk factor	Value	Points
Fetal sex	Male	3
Previous birth <2500 g	No	0
Previous birth >4080 g	Yes	7
Pre-pregnancy weight	76	3
Smoked during pregnancy	Yes	0
Psychiatric illness	No	0
GCT results	6.3	1
Rate of weight gain at 26 weeks	5.0	3

Point total	17
Estimate of risk	0.5971

Table 6-11 Regression coefficients, odds ratios and 95% confidence intervals for the multivariable association between risk factors and LGA ($\geq 90^{th}$ percentile for age and sex) among nulliparous mothers with glucose screening data (N=8677)[a]

Risk factor	Regression coefficient	OR	95% CI for OR	p-value
Intercept	-5.6454	-	-	-
Pre-pregnancy weight (per kg)	0.02956	1.03	1.02-1.03	<0.001
Smoked during pregnancy	-0.6614	0.52	0.42-0.63	<0.001
Asthma	-1.4161	0.24	0.06-1.04	0.056
GCT results (per mmol/L)	0.1163	1.12	1.07-1.18	<0.001
Rate of weight gain at 26 weeks (per kg/week)	2.0789	8.00	6.18-10.34	<0.001

[a] Does not total sample size due to missing values

Table 6-12 Points associated with each category of risk factor for LGA (≥90th percentile for age and sex) among nulliparous mothers with glucose screening data (N=8677)[a]

Risk Factor	Categories	Reference value (W_{ij})	β_i	$\beta_i(W_{ij} - W_{i\text{REF}})$	$\text{Points}_{ij} = \beta_I(W_{ij} - W_{i\text{REF}})/B$
Pre-pregnancy weight *			0.02956		
	<60 kg	52= $W_{3\text{REF}}$		0	0
	60-69 kg	65		0.3843	2
	70-79 kg	75		0.6799	3
	80-89 kg	85		0.9755	5
	≥90 kg	103		1.5076	8
Smoked during pregnancy			-0.6614		
	No	0= $W_{4\text{REF}}$		0	0
	Yes	1		-0.6614	-3
Asthma			-1.4161		
	No	0= $W_{5\text{REF}}$		0	0
	Yes	1		-1.4161	-7
GCT results **			0.1163		
	<5.1 mmol/L	3.7= $W_{7\text{REF}}$		0	0
	5.1-<5.9 mmol/L	5.5		0.2093	1
	5.9-<6.8 mmol/L	6.4		0.3140	2
	6.8-10.3 mmol/L	8.6		0.5699	3
Rate of weight gain at 26 weeks ***			2.0789		
	<0.32 kg/week	0.17= $W_{8\text{REF}}$		0	0
	0.32-<0.45 kg/week	0.38		0.4366	2
	0.45-<0.59 kg/week	0.52		0.7276	4
	≥0.59 kg/week	0.88		1.4760	7

[a] Does not total sample size due to missing values

* The pre-pregnancy weight range in the sample is 29.93-158.30 kg. To minimize the influence of extreme values, the 1st percentile (44.0) and the 99th percentile (116.12) were used to calculate the midpoints of the first and last categories.

** The range of GCT reults in the sample is 2.3-10.3 mmol/L

*** The range of rate of weight gain at 26 weeks is -1.70-3.95 kg/week. To minimize the influence of extreme values, the 1st percentile (0.010) and the 99th percentile (1.18) were used to calculate the midpoints of the first and last categories.

Table 6-13 Estimated risk of LGA (≥90th percentile for age and sex) among nulliparous mothers with glucose screening data (N= 8677)[a]

Point total	Estimate of risk	Point total	Estimate of risk
-10	0.004847	5	0.08911
-9	0.005914	6	0.1067
-8	0.007214	7	0.1237
-7	0.008797	8	0.1513
-6	0.01072	9	0.1788
-5	0.01307	10	0.2101
-4	0.01591	11	0.2452
-3	0.01937	12	0.2840
-2	0.02356	13	0.3264
-1	0.02862	14	0.3718
0	0.03474	15	0.4196
1	0.04211	16	0.4689
2	0.05095	17	0.5188
3	0.06154	18	0.5684
4	0.07415		

[a] Does not total sample size due to missing values

Table 6-14 Regression coefficients, odds ratios and 95% confidence intervals for the multivariable association between risk factors and LGA ($\geq 90^{th}$ percentile for age and sex) among multiparous mothers with glucose screening data (N=8098)[a]

Risk factor	Regression coefficient	OR	95% CI for OR	p-value
Intercept	-4.9229	-	-	-
Previous birth <2500 g	-0.6728	0.51	0.39-0.67	<0.001
Previous birth >4080 g	1.1545	3.17	2.75-3.66	<0.001
Prep-pregnancy weight (per kg)	0.0287	1.03	1.02-1.03	<0.001
Smoked during pregnancy	-0.7303	0.48	0.40-0.58	<0.001
Polyhydramnios	1.2129	3.36	1.83-6.17	<0.001
GCT results (per mmol/L)	0.1243	1.13	1.08-1.18	<0.001
Rate of weight gain at 26 weeks (per kg/week)	1.5813	4.86	3.29-7.17	<0.001

[a] Does not total sample size due to missing values

Table 6-15 Points associated with each category of risk factor for LGA (≥90th percentile for age and sex) among multiparous mothers with glucose screening data (N=8098)[a]

Risk Factor	Categories	Reference value (W_{ij})	β_i	$\beta_i(W_{ij} - W_{i\text{REF}})$	$\text{Points}_{ij} = \beta_I(W_{ij} - W_{i\text{REF}})/B$
Previous birth <2500 g			-0.6728		
	No	0= $W_{2\text{REF}}$		0	0
	Yes	1		-0.6728	-3
Previous birth >4080 g			1.1545		
	No	0= $W_{3\text{REF}}$		0	0
	Yes	1		1.1545	6
Pre-pregnancy weight *			0.0287		
	<60 kg	52= $W_{4\text{REF}}$		0	0
	60-69 kg	65		0.3731	2
	70-79 kg	75		0.6601	3
	80-89 kg	85		0.9471	5
	≥90 kg	104		1.4924	7
Smoked during pregnancy			-0.7303		
	No	0= $W_{5\text{REF}}$		0	0
	Yes	1		-0.7303	-4
Polyhydramnios			1.2129		
	No	0= $W_{6\text{REF}}$		0	0
	Yes	1		1.2129	6
GCT results **			0.1243		
	<5.1 mmol/L	3.8= $W_{7\text{REF}}$		0	0
	5.1-<5.9 mmol/L	5.5		0.2113	1
	5.9-<6.8 mmol/L	6.4		0.3232	2
	6.8-10.3 mmol/L	8.6		0.5966	3
Rate of weight gain at 26 weeks ***			1.5813		
	<0.32 kg/week	0.12= $W_{8\text{REF}}$		0	0
	0.32-<0.45 kg/week	0.38		0.4111	2
	0.45-<0.59 kg/week	0.52		0.6325	3
	≥0.59 kg/week	0.84		1.1385	6

[a] Does not total sample size due to missing values

* The pre-pregnancy weight range in the sample is 30.39-158.76 kg. To minimize the influence of extreme values, the 1st percentile (44.91) and the 99th percentile (118.84) were used to calculate the midpoints of the first and last categories.

** The range of GCT reults in the sample is 2.4-10.3 mmol/L

*** The range of rate of weight gain at 26 weeks is -1.66-4.90 kg/week. To minimize the influence of extreme values, the 1st percentile (-0.088) and the 99th percentile (1.08) were used to calculate the midpoints of the first and last categories.

Table 6-16 Estimated risk of LGA (≥90th percentile for age and sex) among multiparous mothers with glucose screening data (N= 8098)[a]

Point total	Estimate of risk	Point total	Estimate of risk
-7	0.01524	11	0.3616
-6	0.01855	12	0.4089
-5	0.02257	13	0.4580
-4	0.02742	14	0.5079
-3	0.03330	15	0.5576
-2	0.04037	16	0.6062
-1	0.04887	17	0.6528
0	0.05906	18	0.6967
1	0.07120	19	0.7372
2	0.08561	20	0.7741
3	0.1026	21	0.8072
4	0.1226	22	0.8364
5	0.1457	23	0.8620
6	0.1724	24	0.8841
7	0.2029	25	0.9030
8	0.2371	26	0.9192
9	0.2752	27	0.9329
10	0.3168	28	0.9444

[a] Does not total sample size due to missing values

Table 6-17 Points associated with each category of risk factor for macrosomia (≥4000 g) among nulliparous mothers using 2013 diagnostic criteria for GDM (N=8538)[a]

Risk Factor	Categories	Reference value (W_{ij})	β_i	$\beta_i(W_{ij} - W_{i\text{REF}})$	$\text{Points}_{ij} = \beta_I(W_{ij} - W_{i\text{REF}})/B$
Infant sex			0.4274		
	Female	0= $W_{1\text{REF}}$		0	0
	Male	1		0.4274	2
Marital status			0.2828		
	Not married	0= $W_{2\text{REF}}$		0	0
	Married	1		0.2828	1
Pre-pregnancy weight *			0.0285		
	<60 kg	52= $W_{3\text{REF}}$		0	0
	60-69 kg	65		0.3705	2
	70-79 kg	75		0.6555	3
	80-89 kg	85		0.9405	5
	≥90 kg	103		1.4535	7
Smoked during pregnancy			-0.5355		
	No	0= $W_{4\text{REF}}$		0	0
	Yes	1		-0.5355	-3
Asthma			-1.3755		
	No	0= $W_{5\text{REF}}$		0	0
	Yes	1		-1.3755	-7
Psychiatric illness			-0.4027		
	No	0= $W_{6\text{REF}}$		0	0
	Yes	1		-0.4027	-2
GCT results **			0.0908		
	<5.2 mmol/L	4.5= $W_{7\text{REF}}$		0	0
	5.2-<6.2 mmol/L	5.7		0.1090	1
	6.2-<7.8 mmol/L	7.0		0.2270	1
	≥7.8 mmol/L	8.5		0.3632	2
Rate of weight gain at 26 weeks ***			1.7885		
	<0.32 kg/week	0.17= $W_{8\text{REF}}$		0	0
	0.32-<0.45 kg/week	0.38		0.3756	2
	0.45-<0.59 kg/week	0.52		0.6260	3
	≥0.59 kg/week	0.88		1.2698	6

[a] Does not total sample size due to missing values

Chapter 7 DISCUSSION

7.1 Rates of Macrosomia

Of the 240,765 mother-infant pairs included in the study, 36,796 (15.3%) delivered a macrosomic (≥4000 g) infant. Of women in the study, 2.6% delivered a macrosomic infant using the ≥4500 g definition and 0.3% using the ≥5000 g definition of macrosomia. Although rates tend to vary between studies, these results are similar to rates of macrosomia that have been previously reported in literature (9,10,53,54). A Danish study measuring the prevalence of macrosomia (≥4000 g) reported a slightly higher prevalence of 16.7% in 1990, which increased to 20% in 1999 (9). A 2014 systematic review, which aimed to measure the role of maternal obesity on macrosomia, found that in sixteen identified studies, 10.4% of infants were macrosomic, using a ≥4000 g definition (53). When examining the eight studies that measured macrosomia using the ≥4500 g definition, a prevalence of 2.1% was observed (53). Similarly, Prince Edward Island's Reproductive Care Program reported a prevalence of macrosomia of 2.9%, using the ≥4500 g definition (54).

7.2 Determinants of Macrosomia

As predicted, the risk factors identified from previous birth weights were among the strongest predictors of macrosomia in multiparous women. In order to utilize this additional information from previous births in the risk prediction models, the analyses of nulliparous and multiparous women were completed independently and two separate models were developed.

Approximately 20% of women who delivered a macrosomic birth had a previous large birth, compared to 4% who did not have a previous macrosomic infant. In multiparous women, having a previous large birth was among the strongest predictors in all models (with odds ratios ranging from 3.9 (95% CI: 3.7-4.1) in the LGA model to 6.8 (95% CI: 5.4-8.6) in the macrosomia ≥5000 g model). This relationship has been previously recognized in literature (4). In a retrospective cohort study of singleton, live births of US residents by Boulet et al., a previous macrosomic infant was among the two strongest predictors of macrosomia (OR: 3.7-11.6). The second strong predictor identified was diabetes (4).

Consistent with the odds ratios derived for this risk factor, having a previous large birth was one of the largest contributors of points in the risk prediction models for multiparous women. In the model predicting macrosomia among multiparous women, a previous large birth contributed the largest amount of points (7), equal to the number of points given for pre-pregnancy weight ≥90 kg. Similarly, a previous large birth contributed 6 points in the model predicting LGA among multiparous women.

Male infant sex was identified as a significant risk factor for macrosomia in all models. With each increasing grade of macrosomia (≥4000 g, ≥4500 g and ≥5000 g) the magnitude of risk increased (odds ratios ranged from 1.8 (95% CI: 1.7-1.9) to 2.7 (95% CI: 1.9-3.7)). Previous studies have shown similar risk for male infants, stating that genotypic and phenotypic differences explain why male fetuses weigh more than female at any gestational age (47). Studies by Gu et al. and Sheiner et al. both reported similar odds ratios of the relationship between infant sex and macrosomia (OR: 1.61; 95% CI: 1.47-1.75 and OR: 2.0; 95% CI: 1.8-2.1 respectively) (5,30). Male infant sex contributed 2 points in the model predicting macrosomia

among nulliparous women and 3 points among multiparous women. Since the measurement of LGA accounts for infant sex, it does not contribute points to the model for that outcome.

Women with higher pre-pregnancy weight were also significantly more likely to deliver a macrosomic infant. This risk factor was once again significant in all models. With each increasing category of pre-pregnancy weight, the magnitude of risk increased. Similarly, with each increasing grade of macrosomia, the magnitude of risk associated with pre-pregnancy weight increased. The risk prediction models demonstrate that the increase in risk for each increasing category of pre-pregnancy weight was similar within a model, with the difference between two categories of pre-pregnancy weight typically contributing 1-2 points. The lowest category of risk contributed 0 points to the model and the highest category of risk contributed up to 8 points. This increasing gradient of risk with increasing pre-pregnancy weight has been previously observed in literature (23). Sebire et al. demonstrated a similar gradient of risk using BMI categories of underweight, normal weight, overweight and obese (23).

The rate of weight gain during pregnancy (calculated at 26 weeks) also played a significant role in all models. Similar to pre-pregnancy weight, the risk of macrosomia increased with each increasing category of rate of weight gain within a model and also increased with increasing grades of macrosomia. The risk prediction models displayed this gradient of risk, contributing 1-3 points for each increasing category of rate of weight gain (resulting in 0 points for lowest category of risk and up to 7 points for the highest category of risk). Alberico et al. found a similar relationship, comparing the macrosomia outcome of women with gestational weight gain above the Institute of Medicine's recommended cutoff to those who fell within the suggested limits (14). Since accurate BMI measurements were not possible for this study, an

increasing gradient of weight gain was observed via quartiles rather than according to these cutoffs.

7.3 Protective Factors

A number of protective factors were identified in this study. Smoking during pregnancy was strongly protective against macrosomia, using all definitions of the outcome. It remained in all models for both nulliparous and multiparous women and contributed a large number of negative points in each risk prediction model. This does not come as a surprise since smoking is a known risk factor for LBW (28). Similarly, the presence of a psychiatric illness and asthma in the expecting mother were identified as protective risk factors in both nulliparous and multiparous mothers, using the ≥4000 g definition of macrosomia and LGA as the outcome. The risk factors did not remain in the models of higher grades of macrosomia (≥4500 g and ≥5000 g), which may be the result of the low number of identified cases in the smaller macrosomic population, using these definitions. In the risk prediction models, psychiatric illness contributed negative points in both the nulliparous and multiparous model of macrosomia (≥4000 g). Asthma contributed negative points to the nulliparous model of macrosomia and the previous birth of an infant <2500 g contributed negative points to the multiparous risk prediction models.

Psychiatric illnesses such as depression have been linked to adverse behaviours such as smoking (a previously mentioned risk factor for LBW) (28). In addition to behaviours associated with depression, anti-depressive medications may affect neonatal outcomes (28). Similar to depression, the relationship between asthma and macrosomia may have multiple mechanisms.

The association between asthma and macrosomia has been observed in studies on LBW and is likely related to both the maternal disorder and the management, which includes inhaled steroids and bronchodilators (29, 48).

Unfortunately, the protective risk factors that were identified are not clinically useful in reducing the incidence of macrosomia. It would not be possible to modify risk factors such as asthma, psychiatric illness or the birth weight of a previous infant. Smoking during pregnancy, although modifiable, would never be suggested since it would introduce the possibility of a number of other adverse outcomes.

7.4 Risk Factors by Grades of Macrosomia

Risk factors that were common in the majority of models, using increasing grades of macrosomia have so far been discussed. However, several risk factors were significant in one or more definitions of macrosomia but subsequently eliminated from the model as the grade of macrosomia increased or in the development of the risk prediction model, using the linked IWK lab data. These risk factors include maternal age, neighbourhood income (QAIPPE), polyhydramnios and placenta previa. The nulliparous and multiparous models of macrosomia $\geq$4000 g included all risk factors; however, as the degree of macrosomia increased, fewer factors remained. It is likely that as the definition of macrosomia increased, risk factors such as polyhydramnios and placenta previa had low numbers due to their rarity, and were not significant because of low power. Similarly, categories of maternal age and annual income may have had low event rates, making their effects harder to detect. A decrease in power may have also been the reason some risk factors were significant in the models developed using the

NSAPD but were not significant in the development of the risk prediction models, using the linked IWK lab data. This dataset was smaller than the NSAPD data from which the original models were developed. As well, the linked IWK lab data included the GCT results, which was revealed to be among the strongest predictors and could have been associated with some of the variables in the larger NSAPD models. The addition of another strong predictor may have decreased the effect of other less predictive risk factors.

7.5 Changing Diagnostic Criteria for GDM

The primary analysis of objective 3 was conducted using the diagnostic criteria for gestational diabetes that were in place at the time the cohort of women was diagnosed. However, in order for the model to be considered for future use, the new guidelines (adapted in 2013) were considered (36). Both the nulliparous and multiparous models developed using the 2013 guidelines contributed identical points to the pre-2013 criteria models in all risk factor categories except one. The highest level of risk associated with the GCT result contributed 2 points, where in the initial model, using pre-2013 criteria, it contributed 3 points. The highest level of risk of GCT results was changed to fit the new guidelines (now 7.8-<11.1 mmol/L) and no longer included women who would have previously been categorized as having impaired glucose tolerance (considered diagnosed with GDM with new guidelines).

This change to the extent a one-category increase in GCT results would have on the outcome of macrosomia makes sense. As higher risk individuals (IGT) were excluded from the cohort using the new guidelines, the effect the GCT results had on the outcome decreased. This

small change, using the new criteria, demonstrates that with minor adjustments the model would be appropriate for future use.

7.6 Validation of Model and Optimal Cut-points

The developed risk prediction model was internally and externally validated. The internal validation revealed that the model could be considered reasonable at predicting macrosomia (49). With *c* statistics of 0.70 and 0.75 for nulliparous and multiparous women respectively, it was observed that the multiparous model was slightly better at predicting risk than the nulliparous model.

The comparison of odds ratios and the *c* statistics of the developed model on the MIREC data, demonstrated that the model similarly predicts macrosomia on an external dataset. However, there were several limitations to the external validation of the risk prediction model. The MIREC study did not collect information on previous births of multiparous women, and therefore, only the nulliparous model could be externally validated. Additionally, the MIREC cohort had a much smaller sample size. This resulted in the risk factors asthma and psychiatric illness being excluded due to low event rates and is likely the reason for many risk factors not exhibiting statistical significance.

Optimal cut-points for categorizing nulliparous and multiparous women as low or high-risk for delivering a macrosomic ($\geq$4000 g) infant were determined. For nulliparous women, an estimated risk <29% can be used to indicate a woman is low-risk, and $\geq$29% to indicate a woman is high-risk for delivering a macrosomic infant. The sensitivity and specificity when using this

cut-point were calculated to be 0.66 and 0.63 respectively. A sensitivity of 0.66 indicates that the test correctly identifies 66% of women who deliver a macrosomic infant as at risk for delivering a macrosomic infant, therefore missing 34% of cases. Similarly, a specificity of 0.63 indicates that the test correctly identifies 63% of women who do not deliver a macrosomic infant as not at risk for delivering a macrosomic infant.

The optimal cut-point for defining multiparous women as low or high-risk for delivering a macrosomic infant was calculated to be 36%. Therefore multiparous women who have an estimated risk of <36% are at low-risk for delivering a macrosomic infant and those who have an estimated risk of ≥36% are at high-risk of delivering a macrosomic infant. The sensitivity and specificity when using this cut-point were calculated to be 0.73 and 0.63 respectively. Therefore, the sensitivity for the cut-point in the multiparous model was improved compared to the nulliparous model, correctly identifying 73% of women who delivered a macrosomic infant as high risk and missing 27% of cases. Identical to the nulliparous model, the specificity of 0.63 indicates that the cut point correctly identifies 63% of women who do not deliver a macrosomic infant.

7.7 Interventions

There are numerous proposed interventions designed for the diabetic population, aimed at decreasing adverse neonatal outcomes such as macrosomia (13, 17). They include dietary and lifestyle counseling, blood glucose self-monitoring and insulin therapies. Several studies have

demonstrated the effectiveness of these interventions on adverse outcomes including macrosomia (13, 17). A 2013 systematic review commissioned for the U.S. Preventive Services Task Force, observed an overall significant decrease in macrosomia, comparing any treatment of GDM with no treatment (50). The study included five randomized controlled trials and six cohort studies and resulted in a risk ratio of 0.50 (95% CI 0.35-0.71) with the strength of the evidence considered moderate (50).

While interventions exist for the treatment of GDM aimed at decreasing outcomes such as macrosomia, no such interventions currently exist for the non-diabetic population. Possible interventions for the non-diabetic population could be assumed to be similar to the effective interventions for diabetic women and include increased surveillance of high-risk pregnancies (including dietary and lifestyle counseling), scheduled growth ultrasounds and possible early induction of labour if appropriate (50, 51).

7.8 Study Strengths and Limitations

There are several strengths to this study, including the use of the NSAPD as the primary data source. The NSAPD is a population-based dataset that is large in size and contains numerous maternal variables to explore as potential risk factors of macrosomia. The NSAPD contains information on socio-demographic, pre-natal, delivery and postpartum risk factors. As well, the inclusion of laboratory data makes this study unique. Most studies would not have this information.

Evaluating the generalizability of the risk prediction model to other populations, outside of which the model was developed, is another strength of this study. This was done by external validation using the MIREC cohort. Furthermore, since the majority of the risk factors remaining in the final models were biologically based, we can infer that this model is more likely to be generalizable to other populations than a model composed of risk factors that were non-biologically based. Such risk factors include socieoeconomic status, which may be a proxy for different things in different populations.

In 2013 the guidelines for diagnosing gestational diabetes changed. Although the individuals in the cohort were diagnosed using the pre-existing criteria, the changing standards were taken into account. By adapting to the change in diagnostic criteria, the model remains practical for future use.

The recognition of the study's limitations is also important. It is possible that other risk factors, not captured by the NSAPD contribute to the outcome. These relationships would not have been explored. One possible relationship that was not explored due to unavailable data is the effect of very low maternal serum alpha-fetoprotein (MSAFP) and macrosomia. Baschat et al. observed this association in a 2002 retrospective case-control study (52). This study demonstrated that women with very low MSAFP were significantly more likely to deliver a heavier baby (an average increase of 250 g) and an LGA baby than their matched controls ($p<0.05$) (52). Incorporating data such as MSAFP may have the potential to improve the predictive probabilities of the risk prediction model.

In addition, the NSAPD only began the collection of maternal height in 2003. This resulted in a large amount of missing data for pre-pregnancy BMI, a covariate of interest and because of the years of our cohort, made it unusable. Instead, pre-pregnancy weight was used.

Due to the missing height data, it was also not possible to categorize the rate of weight gain according to the Institute of Medicine's recommendations of pregnancy weight gain, by pre-pregnancy BMI. Finally, due to the nature of the MIREC data, external validation was only possible for the nulliparous model.

7.9 Summary

This thesis aimed to investigate the rates and risk factors of macrosomia in a large population of non-diabetic women and develop a clinically relevant model to predict macrosomia in mid-pregnancy. The model can be used to estimate the risk of macrosomia by entering a particular individual's risk factor profile. Risk factors that were included in the model are those identified to be significantly associated with the outcome and readily available in clinical practice at mid-pregnancy.

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