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The Association Between Maternal Obesity and Fetal Size for Gestational Age in Singletons and Twins

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ABSTRACT

Maternal obesity and multiple births have adverse effects on fetal growth; prevalence of both are increasing in Canada. We explored associations between maternal obesity and infant size for gestational age using data from a London perinatal database. Birthweight for gestational age was assessed using standards published by Robertson (2002) to classify Small for Gestational Age (SGA) and Large for Gestational Age (LGA) in 30396 singletons and 1346 twins. Associations were estimated using logistic regression for singletons and the GEE extension of logistic regression for twins. Increased maternal pre-pregnancy BMI was statistically significantly associated with decreased odds of SGA in singletons ($p< 0.0001$), and increased odds of LGA in singletons and twins ($p< 0.0001$, $p= 0.0004$ respectively). Results suggest that maternal BMI may influence size for gestational age differently in singleton and twins.

Keywords: *Singleton, Twin, Pregnancy, Maternal obesity, Fetal growth, Small for gestational age, Large for gestational age)*

LAY SUMMARY

The St. Josephs' Health Care and London Health Sciences Centre Perinatal Database contains valuable information on pregnant mothers and their newborns.

We used this database to explore mothers' body mass index (BMI), and how this affected growth of their babies. While this has been studied in singleton babies (babies that are born following a pregnancy where the mother carried only a single baby), it has not been studied in babies who are twins.

As an additional objective, we wanted to know if mothers' BMI affected the growth of singleton and twin babies in similar ways. A twin pregnancy can be more complicated for the mother, the babies, and the doctors taking care of them, compared to a singleton pregnancy. For this reason, twins are often excluded from research studies. We wanted to compare singleton and twin pregnancies because many studies exclude twins from their research.

We focused on mothers' BMI because this can be related to other medical conditions that can harm the pregnancy. To study growth, we used a measure known as "Size for Gestational Age, which assesses the newborn's weight at birth, relative to the weight we expect for a baby born from a pregnancy of this length (gestational age). This measure allows us to better compare newborn growth. Newborns with below-normal rates of growth are "Small for Gestational Age (SGA)" while newborns with above-normal rates of growth are "Large for Gestational Age (LGA)" compared to the population. Identifying SGA and LGA newborns can help doctors recognize newborns that might need further health care.

We found that heavier mothers were more likely to have a bigger, or LGA singleton or twin baby, and less likely to have a smaller, or SGA singleton baby. However, it is important to remember that some heavier mothers can still have smaller babies, and that some thinner mothers can still have larger babies. This was previously known for singletons, but we found this also to be true for twins. Our results were unable to determine conclusively whether this may just be a random finding because the number of twins in our study was small. Therefore. further study is required. These results are important, because they can help doctors better take care of mothers of all sizes with singleton and twin pregnancies.

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List of Abbreviations

AC	Abdominal Circumference
AGA	Appropriate for Gestational Age
APGAR (Score)	Appearance, Pulse, Grimace, Activity and Respiration Score
BMI	Body Mass Index
CHL	Crown Heel Length
CI	(95%) Confidence Interval
CRL	Crown Rump Length
DA	Diamniotic
DC	Dichorionic
DZ	Dizygotic
GDM	Gestational Diabetes Mellitus
GWG	Gestational Weight Gain
IUGR	Intrauterine Growth Restriction
LGA	Large for Gestational Age
LHSC/SJHC	London Health Sciences Centre/St. Josephs Healthcare Centre
MA	Monoamniotic
MC	Monochorionic
MZ	Monozygotic
OR	Odds Ratio
SD	Standard Deviation
SGA	Small for Gestational Age

1 Chapter 1 – Introduction

1.1 Introduction

This thesis research was undertaken to explore the role of maternal obesity in determining fetal growth in twins and singletons. While, to some degree, studies have examined the relationship between maternal obesity and fetal growth in singletons, there remain some gaps in understanding this relationship. To date, the relationship between maternal obesity and fetal growth has not been studied in twins in this population. Incorporating a comparison between twins and singletons furthers the topic.

Using data from a London Ontario based perinatal database from June 1st 2006, to August 31st 2018, this research explored the association between maternal Body Mass Index (BMI) and infant size for gestational age, in singletons and in twins, with consideration of whether the associations are consistent between singletons and twins. Other higher order multiples (triplets, quadruplets etc.) were not included owing to increased complications and decreased sample sizes.

Chapter one consists of 6 sections: Section 1.1 is a general introduction. Sections 1.2 and 1.3 cover the objectives of this thesis research, section 1.4 presents the hypotheses, and section 1.5 provides a rationale for the objectives. Section 1.6 is an outline of the structure of the remainder of the thesis.

1.2 Research Objectives

Each objective will separately consider singletons and twins.

The objectives of this thesis are:

1. To describe pre-pregnancy, pregnancy related, birth and delivery and infant related factors in the London Ontario maternal and birth population, stratified by multiple births.
2. **a)** To determine the population-specific prevalence of being born in one of three categories: Small for Gestational Age (SGA; defined as birth weight <10th percentile for gestational age); Appropriate for Gestational Age (AGA; defined as birth weight 10th-90th percentile for gestational age) or Large for Gestational Age (LGA; defined as birth weight >90th percentile for gestational age), using an external (1) Canadian size for gestational age standard.
   b) To compare these prevalence estimates for infants born to mothers across six maternal BMI classes; (underweight: (BMI 16.0-18.49 kg/m^2); normal weight (BMI 18.50-24.99); overweight

(BMI 25.0-29.99); and obese (class I: BMI 30.0-34.99; class II: BMI: 35.0-39.99; class III: BMI 40.0-60.0)) in singletons and in twins.

3. To identify whether there is an association between maternal pre-pregnancy BMI class and infant size for gestational age in singletons and in twins, after adjustment for relevant confounders.
4. To explore the effects of multiple births on modifying the association between maternal pre-pregnancy BMI class and infant size for gestational age.

1.3 Hypotheses

It was hypothesized that an association would be present between maternal BMI and infant size for gestational age. In particular, decreasing maternal BMI was hypothesized to be associated with decreasing size for gestational age, and increasing maternal BMI was hypothesized to be associated with increasing size for gestational age.

1.4 Rationale

Both maternal obesity and multiple births can have an adverse effect on fetal growth.

Fetal growth and size are significant determinants of health (2,3). Increased risks of morbidity and mortality exist for both excessively and insufficiently grown babies(4–7), as opposed to those that are 'optimally' grown (8–10). Fetal size for gestational age is one measure that allows for assessment of fetal growth that incorporates birthweight and gestational age.

According to Canadian Community Health Survey data, as of 2014, 27.5% of Canadian women reported being overweight, and 18.7% of women reported being obese (11), and the prevalence of obesity in the population has been increasing (12). Maternal BMI status can significantly influence fetal growth and size, and also increases risks of adverse maternal and fetal and delivery-related events (13–16).

Rates of twin births are also increasing, with 3.3% of all births in Canada being multiple births in 2011, as compared to 2.1 % in 1991 (17). Growth trajectories in utero can vary in twins and higher order multiples as compared to singleton pregnancies (18,19). Twin and multiple births can be at increased risk of adverse events as compared to singleton births (20). Twin growth in utero is understudied, due to the increased statistical complexity required.

The effect of growth restriction due to multiple gestations, combined with the influence of maternal obesity on fetal growth presents an interesting intersection of potentially at-risk mothers and

infants to be studied. Infants born to obese mothers are at risk of different health outcomes than those born to mothers with 'normal' BMI, which are different from those born to mothers with underweight BMI. These risks can increase the further an infant deviates from their optimal growth (21,22), and increase further still in multiple gestations (23). While some studies have explored outcomes of obesity in twin births(24), few studies to date have explored the combination of these factors on fetal growth and size for gestational age.

It is unclear how infant size for gestational age is influenced by maternal obesity class and multiple births. Results from this study aim to explore the potential associations between maternal obesity and fetal size for gestational age in singleton and multiple pregnancies and have the potential to inform clinical practise.

1.5 Thesis Structure

This thesis is written in the monograph format following the Western University School of Graduate and Postdoctoral Studies guidelines.

Chapter 1 is an introduction to the thesis and discusses objectives, hypotheses and rationale. Chapter 2 presents the literature review discussing the three main topics; fetal growth, maternal obesity and multiple births. Chapter 3 outlines the various methods used in this thesis project, while Chapter 4 describes the results, by objective. Chapter 5 concludes the thesis, discussing the findings, as well as strengths, weaknesses and future directions of the project. Finally, appendices of topics relevant to this thesis are included at the end of this document.

2 Chapter 2 – Literature Review

2.1 Overview

This chapter presents the background information relevant to the thesis topic and identifies the gaps to be studied. Given the importance of the measures of fetal growth, section 2.2 presents the overarching framework whereby modern literature distinguishes between fetal size and fetal growth, the latter being one of two major contributors to the former. The remainder of the chapter is divided into 3 relevant sections; Section 2.3 discussing fetal growth, the key outcome focus of this study, and sections 2.4 and 2.5 discussing maternal obesity and twin birth, respectively, as the two key predictive factors of interest in this study.

2.2 Fetal Size at Birth is Reflective of Gestational Age and Fetal Growth Relative to Gestational Age

Historically, clinicians and researchers were interested in measuring fetal size at the time of birth as an important predictor of fetal health. Birth weight is amongst the strongest factors related to infant mortality and survival (4,22). Low birth weight is diagnosed at birth weights less than 2500g (5,25), owing to the increased risks of mortality and other adverse health outcomes occurring below this threshold (4), with a 2004 UNICEF publication reporting that the risk of death is increased 20 times in babies with birth weights below 2500g (5), as compared to babies with higher birthweights. Macrosomia, a term used to describe excess birth weight, has been defined as birth weight above 4000 grams, and more recently as above 4500g (26), as adverse health risks for both mother and child increase significantly at birth weights above 4500g (6,26). Therefore, a 'typical' birth weight is considered to be 2500g to 4000g. Risks of adverse health outcomes are generally lower within this birthweight range(8–10). However, neither macrosomia nor low birth weight account for gestational age at birth. Using birth weight alone does not allow clinicians to distinguish between unusual birth weight due to gestational age vs. due to an altered growth rate, and also has the potential to overlook or hide trends over time (27).

Gestational age is considered amongst the main determinants of birthweight (4,22,28). Term births occur between 37-40 weeks gestational age; Preterm births occur prior to 37 weeks; and post term births occur past 42 weeks gestational age (29). Gestational age at birth can be related to many adverse health outcomes in both mother and child (30,31).

The fetus' growth rate in utero and total duration of gestation are the two factors that combine to determine overall birth weight (4). Final birth weight may be suboptimal either due to insufficient time

spent in utero, insufficient growth rate in utero, or a combination of the two factors. At the other end of the birth weight spectrum, excess birth weight can be due to additional time spent in utero, a higher gestational growth rate, or a combination of the factors. Given a desire to differentiate these two factors, newer literature looks separately at gestational age and fetal growth as two independent constructs shaping fetal size at birth.

Modern literature therefore relies on measures of fetal growth have evolved which are based on birthweight for gestational age as compared to a standard distribution. Size for gestational age classifies birth weight for gestational age into three categories; small for gestational age (SGA) births are defined as those below the 10th percentile for the population, appropriate for gestational age (AGA) births are defined as those between the 10th to 90th percentiles, and large for gestational age (LGA) births are greater than the 90th percentile (32). These measures can be developed as population standards, which are based on normal pregnancies only, or as population references, which are based on both normal and obstetrically complex pregnancies(2), and are constantly updated to reflect changing trends in maternal health and subsequent fetal growth.

Some authors state that there is no such thing as a 'normal' preterm birth (33–35). Many studies have suggested a link between poor intrauterine growth and preterm birth (36–41).

2.3 Fetal Growth

2.3.1 Introduction

Fetal growth and size are significant determinants of health (2). Events that occur in the 9 months of gestation can go on to determine later life health as well (42–44). This section will outline key developmental stages of uterine growth, normal vs. abnormal fetal growth trajectories, the risk factors that can lead to abnormal fetal growth and following outcomes, and common measures and clinical diagnoses used to quantify fetal growth.

2.3.2 What is 'Normal' (Typical) Fetal Growth?

Fetal growth is influenced by genetic and environmental factors (44–46) with maternal, fetal, and placental health, all having an effect on growth potential (47). Abnormal fetal growth is any increase or decrease in fetal growth that veers from the optimal path and can also be traced back to interactions

between these main factors(2,21). Fetal developmental milestones such as those published by the US National Library of Medicine (48), provide estimates of fetal size by gestational age and can be used to determine whether a fetus is on the 'right track' for growth. It is important to note that these gestational milestones are not concrete; different fetuses of similar gestational age will not necessarily develop at exactly the same rate(49). The following section outlines key terms that can be used to describe normal and abnormal growth.

2.3.3 Fetal Development

Langman's Medical Embryology (50) provides an in depth overview of singleton fetal development. Following is a quick overview relevant to this thesis. 'Normal' fetal development begins with fertilization at day 0 with the combination of male and female haploid gametes. Once combined, both maternal and paternal chromosomes double and split, forming a two-celled mass called a zygote containing the typical diploid number of chromosomes. This two cell stage of the zygote forms approximately 30 hours after fertilization. Following this, the cells further divide, in a process known as cleavage. These cleaved cells are known as blastomeres. The four cell stage of the zygote forms at approximately 40 hours. Blastomeres form a loose 'clump' prior to the 8 cell stage, after which they join together in a process called compaction. By 3 days post-fertilization, the compacted zygote grows to develop a 12 to 16 cell sized morula. Fluid enters the morula causing the separation of the outer cell mass of trophoblast from the inner cell mass called the embryoblast. The amniotic cavity forms within the inner (epiblast) cell layer of the embryoblast. The outer cells of the morula will develop into the trophoblast. This occurs by the 8th day post fertilization. Following this, the zygote can begin implantation in the uterine wall. The chorionic cavity will form by the 11th or 12th day post fertilization from cells derived from the trophoblast. The chorionic cavity surrounds the amniotic cavity.

The third to eighth weeks are referred to as the embryonic period, where the ectodermal, mesodermal and endodermal germ layers continue further differentiating. During this period the fetus experiences rapid growth in both length and weight of the body, which can be measured as the crown-rump-length (CRL), as well as a slowing of growth of the head, relative to the rest of the body. Major organ structures will form during this period.

The fetal period occurs from the 8th week of development onwards. At this time, major organs and systems continue to develop. Fetal weight increases rapidly in the second half of gestation (i.e. month 5 onwards), with the majority of weight increase occurring in the last 2.5 months. Growth generally occurs at the rate of 5 centimeters per month. A fetus born in the 6th month of development is at great

difficulty of surviving, due to underdevelopment of the central nervous system and respiratory system, as well as lack of communication between the two essential systems. However, a fetus born in the 7th month of gestation will have an approximately 90% chance of survival. At this time, the fetus will have, on average, a 25 cm CRL, and can weigh around 1100g. By birth, the fetus will weigh anywhere from 2500-4000g and will have a CRL of approx. 36 cm and crown-heel-length (CHL) of approximately 50 cms (50).

Please refer to the US National Library of Medicine (48) for an overview of fetal development by week, and Williams Obstetrics 24th edition(49) , and Langmans' Medical Embryology 12th edition (50) for an in depth discussion on the topic.

2.3.4 Abnormal Fetal Growth

In contrast, abnormal fetal development can be defined as fetal growth that does not follow these common milestones. It is important to note that abnormal growth is not necessarily dangerous; many babies will be born slightly above or below the ideal range that are healthy (21). Abnormal development can be caused by a number of factors and can lead to multiple outcomes such as miscarriage, preterm birth, and congenital abnormalities -further outlined in sections 2.2.4 and 2.2.5.

2.3.5 Pathologically vs Constitutionally Determined Size

Not all abnormally grown babies will be at risk for further adverse health outcomes and not all will be so due to any underlying pathology (21). It is important to be able to distinguish between infants that are pathologically large, versus infants that are simply constitutionally large. Constitutionally large infants may have been born to larger parents, and may not necessarily have experienced overgrowth, when considered relative to their parents size (21,51). Pathologically large infants can go on to experience later life adverse events, possibly due to metabolic consequences that led to excess fetal growth in a poor uterine environment (52). A 1995 study determined that anthropometric measurements, such as a higher quadriceps skinfold thickness can be used to identify LGA infants at risk of adverse health events (53).

Likewise, infants can also be pathologically or constitutionally small(54,55). Using customized birthweight standards allows for more accurate identification of pathologically small infants (54,56), with one American birth population study determining that 17.4% of infants diagnosed as SGA were only constitutionally small, and were not at risk for any complications (57). These results have been replicated in French(58), Dutch (59), Swedish (60), and New Zealand (61) populations. Diagnoses such as IUGR

can be helpful in differentiating infants that are more likely to be pathologically small, however, not all SGA infants are so due to IUGR (21). An American study on 19 million singleton births suggested that in early preterm, SGA could be a proxy for growth restriction (i.e. more likely to be pathologically small), and that at term SGA babies were more likely to just be constitutionally small (62). Infants identified as SGA that have normal umbilical artery Doppler flow results were more likely to be constitutionally small, as compared to SGA infants with abnormal Doppler flow results in a 2000 study (63), and confirmed in another study (64). Lower quadriceps skinfold thickness can be used to detect pathologically SGA infants (53). Maternal placental functioning can also be key in identifying IUGR and pathologically small infants (47) and gestational age at birth can also play a role in determining whether infants' size is pathological. A 2009 study suggested that when SGA babies are born at term they were more likely to be constitutionally small, whereas when SGA babies are born preterm, they were more likely to be SGA due to IUGR (62).

2.3.6 Measures of Fetal Growth

There are many ways to measure fetal growth. Measures such as birth weight, crown rump length, bi-parietal diameter, femur length, head circumference, and abdominal circumference are simple measurements that have potential to reflect if a newborns size falls outside of a normal range. More complex measures, such as size for gestational age take into account fetal weight relative to gestational age at birth, and are better able to capture abnormal growth, and infants in need of special care (65).

2.3.6.1 Size for Gestational Age

Infant Size for Gestational Age, relative to a birth population, is a measure that incorporates infant size as well as their gestational age and sex.

Size for gestational age is a population-based measure that can be further refined to take into account essential variables such as maternal ethnicity and BMI to create more customized values (62). An infant is classified as small for gestational age (SGA) if they are below the 10^{th} percentile for their given gestational age; large for gestational age (LGA) infants will be greater than the 90^{th} percentile for the given gestational age and appropriate for gestational age (AGA) infants will fall between the 10^{th} and 90^{th} percentiles for the given gestational age. The term small for gestational age is often used as a proxy for discussing fetal growth restriction. Table 2.1 below outlines the 10^{th} and 90^{th} percentile cutoffs (in grams) at 37 weeks gestational age for the standard used in this study (Robertson, 2002), as well as other standards that were considered for use. The most recent comprehensive Canadian reference (Kramer,

2001) defines the 10th percentile cutoff at 37 weeks as 2452g for female infants, and 2552g for male infants. The 90th percentile cutoff is 3542g for female infants and 3665g for male infants born at 37 weeks gestation (32).

Table 2. 1 10th and 90th percentile cutoffs (in grams) at 37 weeks gestational age

	Singleton Female	Singleton Male	Twin Female	Twin Male
Robertson 2002				
10th	**2435**	**2540**	**2165**	**2225**
90th	**3530**	**3655**	**3039**	**3170**
Kramer 2001				
10th	2452	2552	*n/a**	*n/a**
90th	3542	3665		
Joseph 2009				
10th	2466	2570	2183	2268
90th	3572	3714	3085	3204
Ghi 2017		**		**
10th	*n/a*+*	2220	*n/a*+	1955
90th		3195		3063

**note that Kramer 2001 only assessed singletons*

+*Ghi 2017 did not stratify by sex*

***Ghi cutoffs are reported for 36 weeks (37th week and further were not assessed in that study)*

SGA and LGA are not diagnoses, rather, they are simply benchmarks that have the potential to alert to underlying conditions. SGA will capture babies that are below the 10th percentile that are still healthy, and can fail to capture a growth restricted baby that still classifies as average for gestational age relative to the population (21). Not all SGA babies will be growth restricted, and not all growth restricted babies will be classified as SGA(21,66). For example, growth restriction can cause a fetus to drop from the 70th percentile to the 50th percentile; while this could be due to growth restriction, the baby will not be classified as SGA (21,67), however, it could be argued that this baby is at increased risk of adverse health outcomes as compared to a baby that was consistently growing at the 7th percentile of birthweight for gestational age (68). Maternal and fetal genetic factors and their environmental interactions can account for up to 50% of the variation in birth weight for gestational age (46). A limitation of the low birth weight

value is the fact that it will include infants that are SGA, as well as preterm births, since it does not account for gestational age.

The 10th and 90th percentile cutoffs are not concrete; they are simply one set of 'tail ends', or extremes of the population distribution of size for gestational age at birth, however, these are the most commonly used values when defining adverse size for gestational age. Values such as the 5th and 95th or the 3rd and 97th percentiles cutoffs can also be used (69); the tighter cutoffs have the potential to capture the most extreme cases of abnormal growth. There is no consensus as to which cutoffs to use, however, rates of adverse health outcomes do increase at extremes of the birth weight for gestational age distribution (70,71). Mayer and Joseph (2), discuss that setting certain percentile points as cutoffs for SGA or LGA wrongly implies that the rate of growth restriction is constant across all gestational ages.

2.3.7 Excess Fetal Growth

Excess fetal growth is rapidly becoming a common clinical concern. Excess fetal growth can be defined as growth greater than 4000g – a birth weight of 4000g is equivalent to the 90th percentile at 40 weeks gestational age (72). Excess growth may also be diagnosed if a fetus is LGA; similar to the limitations of the SGA definition, the LGA measure has the potential to capture both fetuses at higher risk for adverse health outcomes related to increased size, as well as 'normal' fetuses not at increased risk (73). Excessively grown fetuses may not necessarily be categorized as LGA and not all LGA infants will be excessively grown. It is difficult to predict macrosomia with certainty in a routine checkup, therefore, knowing the determinants is essential for effective management. This section will cover determinants of excess fetal growth, as well as related post birth maternal and fetal outcomes. Excess fetal growth is a cause for concern because it leads to many adverse maternal and fetal outcomes requiring further clinical management.

2.3.7.1 Determinants of Excess Growth

Excess growth is usually determined by the gestational environment. Excess growth can be associated with multiple factors (74), which can be divided into constitutional, metabolic and placental factors. The main maternal factors related to fetal macrosomia are parity, pre pregnancy BMI, gestational weight gain, prior macrosomic or LGA births and ethnicity. Maternal metabolic factors include maternal pre-pregnancy diabetes, gestational diabetes, and fasting plasma glucose levels. A maternal placental factor affecting excess growth is arterial overgrowth, and a fetal factor is fetal sex.

Maternal Factors

Parity

Parity is a well-known factor in determining birth weight. Nulliparous women are at increased risk (OR: 1.41, 95%CI: 1.26-1.58) of giving birth to infants with lower birth weight, as well as increased risk (OR: 1.89, 95%CI: 1.82-1.96) of giving birth to SGA infants than multiparas (75,76). A 2008 study found that multiparous women were more likely to give birth to a high birth weight infant, with 71.2% of births greater than 5000g to multiparous mothers (77). In a study of consecutive pregnancies, an increase of 138g mean crude birthweight was measured from first to second pregnancies (78). The effect of parity on birthweight is thought to be non-linear, with the steepest increase in birthweight occurring from first to second pregnancies (76). Parity is closely tied to maternal age (4), obesity(79), and socioeconomic status (80).

Maternal Pre-pregnancy BMI

The role of maternal Body Mass Index is well known in predicting birth weight and size for gestational age. Studies have found a strong association between increasing maternal BMI, and increasing offspring birthweight (as well as increasing size for gestational age) (81–87). Pre-pregnancy BMI is a main variable in this study, and is described in further detail in section 2.3.

Gestational Weight Gain

Increasing gestational weight gain is associated with increasing birth weight (84,88,89). One study reported that late gestational weight gain has a stronger positive effect on birth weight than early gestational weight gain (90). Excess weight gain related risks of macrosomia are greater for obese mothers as compared to non-obese mothers (26). Excess gestational weight gain (seen in Table 2.2 below), defined by Institute of Medicine guidelines (91), was found to be a predictor of LGA births, independent of the effect of maternal pre-pregnancy BMI in a Canadian population. Overweight and obese women demonstrated higher rates of excess gestational weight gain (overweight: > 25lbs; obese: >20 lbs. total weight gain), and also demonstrated higher odds of giving birth to LGA infants; with overweight women having an odds ratio of 3.59 (95%CI: 2.60-4.95), and obese women having an odds ratio of 6.71 (95%CI: 4.83-9.31) as compared to women in the ‘normal’ BMI category that did not exceed gestational weight gain guidelines (86). A 2014 study in an Italian population also determined that the effect of gestational weight gain on fetal macrosomia is independent of maternal pre-pregnancy BMI (87).

In morbidly obese women, giving birth to an LGA infant was associated with gestational weight gain exceeding 25 lbs., and also found that insufficient gestational weight gain was not associated with lower birth weight (92). Lower income mothers are at increased risk for both insufficient and excess gestational weight gain (93,94).

Table 2. 2 Institute of Medicine 2009 Gestational Weight Gain Guidelines

BMI Category (kg/m^2)	Recommended Gestational Weight Gain Range (lb)
Underweight (<18.5)	28-40
Normal Weight (18.5-24.9)	25-35
Overweight (25.0 – 29.9)	15-25
Obese (≥30)	11-20

Previous LGA or Macrosomic Birth

A mothers' previous birth history is a non-modifiable risk factor (95) that can influence birthweight. Mothers with previous macrosomic births can be anywhere from 3 to 12 times more likely to go on to give birth to another macrosomic infant, as compared to women who give birth to normal weight infants (95–98). A 1980 study reported that mothers giving birth to macrosomic infants have higher rates of previous birth >4000g, as compared to mothers giving birth to 'normal weight' infants, with 33.4% of macrosomic infants having a macrosomic sibling, as compared to 3.2% of normal weight infants having a macrosomic older sibling (99). A Canadian case control study reported that prior history of macrosomic birth was a significant predictor of subsequent macrosomia, reporting an odds ratio of 9 (95%CI: 5.8-14.2) (97). This effect persists in infants of diabetic mothers; a 2005 study reported a significant correlation between macrosomic first born infants and subsequent macrosomia in the second born sibling born to diabetic mothers ($p<0.001$) (100). Maternal obesity is also linked to both macrosomia and history of macrosomic births (83).

Maternal Ethnicity

Maternal ethnicity has been found to play a role in determining birthweight (51,101–103) with a 2002 Norwegian birth registry study reporting higher average birthweights for Norwegian and North African mothers, and lower mean birthweights in infants of Vietnamese and Pakistani mothers (104). A 2013 study on a United States birth population found that Hispanic mothers in this study gave birth to the highest proportion of macrosomic infants, while mothers of Asian/Pacific Islander descent gave birth to

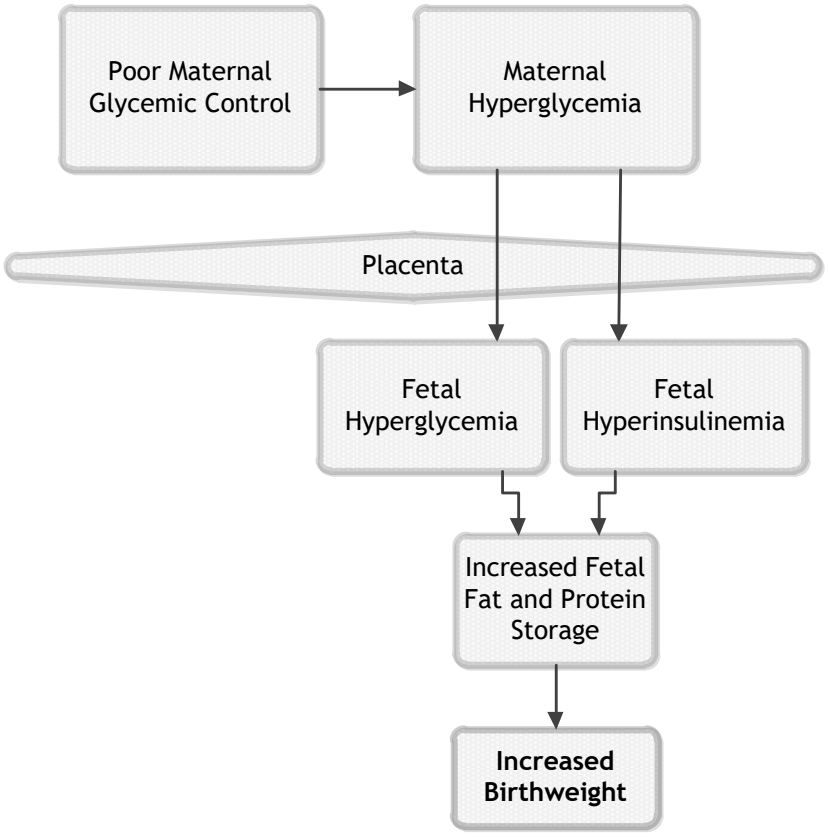
the highest proportion of infants born LGA (while also being least likely to have a high Prepregnancy BMI) (101). Rates of confounding factors (i.e. maternal BMI, diabetes) can vary significantly across ethnic groups (105–108). The role of ethnicity must be approached with caution, as ethnicity can be related to varying socioeconomic status, and access to care in certain countries and populations.

Metabolic Factors

Diabetes

Maternal diabetes leads to an excess of glucose and insulin to be passed on to the fetus. Fasting plasma glucose (FPG) levels are elevated in individuals with diabetes. When this exists in pregnant women, the increase in blood sugar is translated in excess to the growing fetus (109). The Pedersen hypothesis (Figure 2.1 below) was developed in 1954 to explain the biological basis of fetal macrosomia (110). In this model, poor maternal glycemic control, possibly caused by pre-existing, or gestational diabetes (111), causes increases in maternal blood glucose concentrations. This increased glucose can pass through the placenta through to fetal circulation (112), causing fetal hyperglycemia. Maternal insulin does not pass through the placenta, leaving the fetal pancreas responsible for the production of insulin, and thus hyperinsulinemia in response to the maternal hyperglycemia. The combined effect of fetal hyperglycemia and hyperinsulinemia leads to increases in fetal fat and protein storage, ultimately producing an increase in fetal size(113,114). Specifically, “insulin-sensitive tissues” such as muscle and adipose tissue as well as the liver and heart can be overgrown due to the hyperinsulinemia, leading to an overall increase in birth weight (115). These effects can increase significantly in the case of a combined diabetic and obese uterine environment (116).

Figure 2. 1 Conceptual model of the modified Pedersen hypothesis of fetal macrosomia



(adapted from MACFARLANE 1988 (106) & KAMANA et al. 2015(109))

Diabetes has been associated with higher birth weights in multiple studies (117–119). A 1990 study determined that the concentration of insulin found in amniotic fluid was a predictor of fetal macrosomia (120). Increasing blood glucose concentrations are associated with increasing birth weights in infants of diabetic mothers (109,121,122). A study of 553 pregnancies found an increased maternal fasting plasma glucose is associated with a 4.5 times increase for the risk of macrosomia (OR: 4.5, 95%CI: 1.7-12.5) (macrosomia defined as birth weight above 4200g) (123). This study also found that overweight and obese mothers who gave birth to macrosomic infants showed increased fasting plasma glucose levels at weeks 14-16 and weeks 30 -32 of pregnancy. 'Normal' sized, or non-macrosomic infants born to overweight women showed no similar change in FPG. In this study, maternal 30-32 week fasting plasma glucose level was found to be a predictor of fetal macrosomia independent of maternal BMI (123). Diabetes is more likely to be present in obese women (92,111,124,125), and is linked to lower socioeconomic status (126–128), and increasing maternal age (129). Evidence exists to suggest that twin and singleton pregnancies are differently affected by maternal diabetes (130). It is important to note that

maternal obesity, high gestational weight gain and diabetes are highly comorbid conditions (111,131–134).

Carbohydrate Disorders

Evidence exists to suggest that maternal carbohydrate disorders (separate from diabetic conditions) can contribute to excess fetal growth. A 1996 study on a Canadian population reported an incidence rate of 6.7% for gestational carbohydrate intolerance (135). Maternal carbohydrate intolerance has been found to lead to adverse infant health outcomes such as increased incidence of infant macrosomia, LGA, and hypoglycemia and hypocalcemia (136). Specifically, infant LGA and macrosomia were more likely in infants of mothers who had carbohydrate intolerance, but a negative gestational diabetes diagnosis. The 1995 Toronto Tri-Hospital Gestational Diabetes project also studied maternal fetal outcomes in mothers with carbohydrate intolerance and negative diagnosis for overt diabetes. They found that these pregnancies had increased rates of fetal macrosomia (137). A 2001 Danish study also found that maternal carbohydrate intolerance (as measured by a 2-hour oral glucose tolerance test) was associated with fetal macrosomia, as well as maternal hypertension. These studies emphasize that mild carbohydrate intolerance (below the levels of overt diabetes), can still lead to adverse maternal and fetal outcomes (138). Untreated gestational carbohydrate intolerance was found in one study to lead to increased rates of LGA in singletons (20%), as compared to mothers who received treatment(135). Literature on the topic of carbohydrate intolerance is difficult to interpret at times; some authors use the term carbohydrate intolerance to include diabetes, whereas other authors use the term carbohydrate intolerance to describe a condition not ‘strong’ enough to be diagnosed as overt diabetes.

Placental Factors

Placental factors, such as arterial overgrowth in the chorionic plate of obese mothers can contribute to increased energy and nutrient exposure for the fetus (139). Maternal arterial development (providing blood supply to the placenta) has been found in one 2015 study to determine fetal overgrowth (140). Women giving birth to babies over 4500g are more likely to also have higher placental weights, as compared to women giving birth to babies under 4500g (141). Increased rates of placental growth hormone (which is related to insulin-like growth factor and is involved in energy transfer to the growing fetus) during gestation have also been found to be associated with fetal growth(142).

2.3.7.2 Outcomes of Excess Growth

Adverse outcomes of excess growth can affect both mother and child. Adverse fetal outcomes include stillbirth, perinatal mortality, birth trauma related injuries, cerebral palsy and differential adiposity, as well as later life events such as increased risk of giving birth to an LGA infant. Adverse maternal outcomes include complications due to obstructed birth, and major blood loss. These risks generally increase with increasing size at birth. Asymmetric growth patterns can also occur due to excess growth. Other outcomes include low APGAR scores, shoulder dystocia, higher rates of caesarean sections, failed trials of labor, and Erb's Palsy (143).

Fetal Outcomes

Stillbirth

There is an association between increasing size at birth and stillbirth. A 2008 study reported that the odds ratio of stillbirth were 2.7 (5%CI: 2.2-3.4) in infants with birthweight 4500-4999g, and 13.2 (95% CI: 9.8 to 17.7) in infants with birthweight greater than 5000g, as compared to infants born at 3500-4499 g (77). A 2012 Canadian study (144) found that for infants above the 99th birthweight percentile (i.e. extremely LGA), the adjusted OR for stillbirth was 2.2 (95%CI:1.76-2.86), suggesting that extreme fetal overgrowth may be a contributing risk factor towards being stillborn. Similarly, an Australian study found that births in the 99th percentile of size for gestational age were at higher risk of perinatal mortality as compared to average for gestational age (50th -90th percentile) births (145).

Perinatal and neonatal mortality

High birthweight has also been linked to perinatal mortality; a 2017 study of over 1.9 million births in Norway found an "inverted –J pattern" between perinatal mortality and birthweight, with macrosomic infants (defined as z-standardized birth weight >+2 SD's above the mean birth weight) (146). A 2008 study found increased odds of early and late neonatal death in infants born greater than 5000g (OR: 6.4, 95%CI: 3.9-10.4) of early neonatal death in infants greater than 5000g; (OR: 5.2, 95%CI; 2.9-9.4) of late neonatal death in infants greater than 5000g, compared to infants born 3500-4499g (77).

Birth trauma

Birth trauma related injuries include clavicular fractures (26,147), and brachial plexus injuries (26,148); conditions which are an immediate result of larger fetal size at delivery. Clavicular fractures

were strongly associated with vacuum delivery, shorter maternal stature, and advanced age in a 2014 study (149), and infants with birthweights above 4500g were 10 times more likely to experience clavicular fractures (150). Increasing birth weight is associated with increased risk of brachial plexus injury during delivery in both diabetic and non-diabetic mothers (151). Erb's palsy and Duchenne's palsy are spinal injuries related to brachial plexus injury, and are found to be associated with increasing birth weight (152). Bryant et al, recently reported that birth weight is not a strong predictor of brachial plexus injury in a predominantly African American birth population (153). Neonatal brachial plexus palsy can also occur as a result of fetal macrosomia, and is strongly linked to shoulder dystocia, fetal birthweight greater than 5000g for mothers with diabetes, and fetal birthweight greater than 4500g for mothers without diabetes. (154).

Perinatal asphyxia is also associated with fetal macrosomia (155), as well as meconium aspiration, assisted ventilation (148), and facial nerve injuries (150). Infants who experience birth traumas are more likely to have lower 1- and 5-minute APGAR scores, as compared to non-injured infants (150). Bryant et al found that infants at risk for brachial plexus injury were also at higher risk of having low APGAR scores (153) and macrosomic infants with low 5 minute APGAR were at increased risk of an extended NICU stay (156). Mode of delivery can also play a role in birth injury incidence (157–160).

Cerebral palsy

Rates of cerebral palsy have also been found to be 1.5 to 3 fold higher in births above the 97th percentile for size for gestational age (2,161). A 2013 study found that cerebral palsy in larger infants may be due to delivery related factors (162).

Later Life Adverse Health

Fetal macrosomia can lead to later life poor health and obesity. Later life obesity in macrosomic infants is more likely, than in infants born at 'normal weight' (81). One 1990 study in a United States population suggested that fetuses exposed to excess gestational insulin were predisposed to later obesity by age 6 (120). Another study found a strong association between higher maternal BMI during gestation and higher offspring BMI at age 14 (109,163). Fetuses exposed to a diabetic intrauterine environment experience changes in pancreatic β-cell function, leading to lifelong changes in glucoregulation (109,120,164). One study found that mothers born LGA themselves were more likely to have an increased BMI in adulthood; when the mothers birth weight for gestational age was 2.0 standard deviations above the mean, the adjusted odds ratio for later life overweight status (BMI 25.0-29.9) was

1.50 (95%CI: 1.39-1.61), and the adjusted odds for later life class I obesity (BMI: 30.0-34.9) was 1.77 (95%CI: 1.59-1.98). These same mothers were also found to be more likely to go on to give birth to LGA infants; overweight mothers with a birth weight greater than 2.0 SD above mean have an odds ratio of 8.43 (95%CI: 6.00-11.85), and obese mothers with a birth weight greater than 2.0 SD above the mean have an odds ratio of 14.14 (95%CI: 9.59-20.83) of giving birth to an LGA infant compared to mothers born appropriate for gestational age (81). These results were replicated in a 2011 study in a Swedish birth population (81), and in a 2013 European population (165).

Asymmetric Growth in Macrosomic Infants

Asymmetric growth is another outcome of fetal macrosomia. Studies on macrosomic infants have found them to have a higher relative amount of adipose tissue as compared to normal weight or low birth weight fetuses (2). In mothers with poor glycemic control, there is an increased risk of giving birth to a macrosomic infant with increased volume of subcutaneous fat (155). A 2006 study (166) discovered a positive association between maternal fasting glucose levels in the third trimester and increased birth weight. Macrosomic infants of diabetic mothers grow differently than those of non-diabetic mothers. In diabetic mothers, macrosomic infants will have asymmetric growth of the abdominal circumference(AC) (120,155). These infants will also have higher amounts of muscle and fat in the abdominal and scapular areas compared to macrosomic infants of non-diabetic mothers. These features can contribute to an increased risk of shoulder dystocia during delivery (155). Asymmetric growth related to GDM is thought to occur due to differential sensitivities of fetal tissues to insulin. Fetal symmetry can be determined using the following formula: $Symmetry\ Index = \frac{observed\ weight}{median\ for\ age} / \frac{observed\ height}{median\ for\ age}$, further described in the methods section of Metzger 1990 (120). A value of 1.0 indicates symmetrical skeletal growth relative to adipose tissue, and higher values represent asymmetric growth. Some authors question the clinical utility of investigating fetal growth symmetry (167).

Birthweight over 5000g

A study of 182 infants with birthweight greater than 5000g reported many adverse fetal and maternal outcomes. Neonatal poor outcomes related to birthweight over 5000g include a significantly lower number of infants with APGAR scores greater than 7 (The APGAR score is a quick measure of newborn overall health at the 1st and 5th minutes after birth. Scored out of 10, it measures Appearance, Pulse, Grimace, Activity and Respiration (168)), shoulder dystocia, and clavicular fractures due to birth trauma (147).

Maternal Outcomes

Adverse maternal outcomes related to fetal overgrowth include complications due to obstructed birth, and major blood loss. Because macrosomia cannot be accurately diagnosed prior to birth (155), delivering an infant over 4000g will present significant and perhaps unexpected challenges during delivery. Obstructed labour is becoming increasingly common in the case of overgrown fetuses with smaller mothers (140). A study of infants weighing over 5000g at birth reported adverse maternal outcomes including increased rates of episiotomies, sphincter injuries, and blood loss over 1000mL (147). Maternal adverse outcomes related to operative deliveries due to fetal macrosomia include postpartum hemorrhage (157), postpartum infections and anal sphincter lacerations (148,159). Major blood loss has been found to be associated with higher birthweight as well (169–171). Mothers are at an increased risk of 3rd and 4th degree lacerations when delivering macrosomic infants (169). Mothers who undergo vaginal births after caesarean delivery are also at increased risk of 3rd and 4th degree lacerations (172). Anal sphincter tears were found to be more likely in nulliparous women delivering macrosomic infants (OR = 3.8, 95%CI: 2.4-6) (173).

Mothers are at increased risk of undergoing a caesarean delivery when delivering a macrosomic infant (26), as compared to a normal weight infant. However it is important to note that poor diagnostic accuracy of macrosomia prior to delivery are also related to adverse outcomes more so than actual infant birthweight (174–176).

2.3.8 Insufficient Fetal Growth

Insufficient fetal growth can occur due to a variety of factors. This section will discuss Intrauterine Growth Restriction (IUGR), and outline common determinants of insufficient growth, as well as related fetal outcomes. Insufficient growth is commonly linked to perinatal morbidity and mortality.

2.3.8.1 Intrauterine Growth Restriction and Insufficient Growth

Intrauterine Growth Restriction (IUGR) is a concerning sub-class of poor growth in fetuses. IUGR is a clinical diagnosis which is not simply based on the smallness of the fetus but on the pathological reasons for decreased fetal growth. At present, there is no consensus as to the exact definition of IUGR. It has been defined as “fetal growth less than normal for the population and growth potential of an infant” (177) and “a rate of growth that is less than normal for the growth potential of a

fetus" (178) whereas the American College of Obstetricians and Gynecologists define it as "fetuses with an estimated fetal weight that is less than the 10th percentile for gestational age" (179).

IUGR is estimated to occur in approximately 3 to 7% of all pregnancies (180). These infants are at risk for further complications (poor birth and survival outcomes) as compared to infants that are SGA without IUGR(181).

It is important to note that not all SGA babies will be classified as IUGR, and not all babies classified as IUGR will be SGA. The classification SGA can and does include healthy (but small) babies, whereas babies diagnosed as IUGR are not necessarily as healthy as possible.

Gardosi (2009) (182), identifies an interesting population of babies born relatively small to their larger mothers, who are considered SGA only when using customized population centiles. Babies that only are SGA by population standards, and are not considered SGA under customized centiles are not at higher risk for any adverse perinatal outcomes (OR:1.9, 95%CI: 0.3-13.9), and are most likely "small-normal" babies which have not experienced any pathological conditions in utero. Compared to babies that are SGA by population centiles (OR: 4.0, 95% CI: 2.3-7.1), babies that can only be identified as SGA on customized centiles are at higher risk (OR: 10.8, 95%CI: 5.6-20.8) of adverse outcomes.

Factors leading to IUGR can be similar to those leading to insufficient growth, and include (50): Poor maternal health – i.e. cardiac disease, hypertension, renal disease, low SES, smoking, drug and alcohol use, poor nutrition, placental insufficiency, multiple births (further discussed in section 2.3.4), mutations in IGF-I (insulin-like growth factor -I) gene, chromosomal abnormalities, congenital infections (i.e. cytomegalovirus, rubella, syphilis, toxoplasmosis) and teratogens (50). Placental insufficiency can lead to IUGR (155), directly and indirectly via pregnancy induced hypertension (183–186) which in turn leads to IUGR.

Symmetry vs. Asymmetry in IUGR

Similar to overgrown fetuses, undergrown fetuses can also exhibit either symmetrical or asymmetrical growth patterns. Symmetrical growth restriction occurs in the first and second trimesters of growth, and leads to the entire fetal body proportionally being growth restricted (global restriction) (187). Symmetric growth restriction occurs in approximately 20-30% of all IUGR infants (188). Asymmetrical growth restriction, on the other hand, is hypothesized to be protective towards head and brain growth (189), leading to the abdomen being smaller relative to the head. This pattern of growth occurs in the third trimester of pregnancy, and approximately 70- 80% of IUGR cases exhibit this type of growth restriction

pattern (187). A 1991 study (188) of growth restriction found that the timing of the risk factor (causing growth restriction) interacting with the fetus was more important in determining whether growth restriction would be symmetrical or asymmetrical, rather than the specific risk factor. A 1989 paper suggested that symmetric growth restriction is likely to be a consistent growth restriction, whereas asymmetric growth restriction is likely to occur as a result of slowing growth rates towards the end of the pregnancy (68). They also determined that symmetric growth restricted pregnancies resulted in more preterm deliveries than asymmetric ones, and that symmetrically growth restricted infants born at term had a lower mean birth weight than their asymmetric term counterparts. As with asymmetric growth in macrosomic infants, some authors question the clinical utility of investigating fetal growth symmetry (167) and studies have failed to show a difference in outcomes between symmetrically and asymmetrically grown infants (190–193).

2.3.8.2 Determinants of Insufficient Growth

There are many established risk factors known to influence fetal growth. These factors can be classified as maternal, fetal and placental factors (2). Maternal factors include: maternal age, low pre-pregnancy weight and BMI, low gestational weight gain, mother being SGA at birth, multiple gestation, parity, low interpregnancy interval, maternal illnesses such as: hypertension, diabetes, autoimmune disorders, drug and alcohol use, teratogen exposure and smoking. Fetal factors include: genetic conditions, congenital abnormalities and congenital infections contracted by the mother. Placental factors include: pre-eclampsia, placenta previa, vasa previa, velamentous cord insertion, and uterine and placental abnormalities.

Maternal Factors

Maternal Age

Maternal age plays a role in determining fetal growth, with teenage pregnancies at high risk of SGA births (194), however, this effect may be due to lower socioeconomic status within the age group (195). Maternal age is closely tied to maternal pre-pregnancy weight and BMI, especially in the case of adolescent mothers, who may still be growing. The factor of extremely young age is likely an indirect factor affecting birth weights (4). Likewise, older maternal age likely affects birth weight indirectly via age related risk factors. A 2016 Finnish population study found that being $\geq$ 40 years was associated with a 2.2 percent increase in the probability of giving birth to a low birth weight infant (196). Older maternal age has also been established as a risk factor for IUGR (197,198).

Low Pre-Pregnancy Weight/BMI

A 2011 systematic review and meta-analysis found that the risk of low birth weight (RR: 1.64, 95%CI: 1.38-1.94) was increased in mothers with underweight BMI. This effect holds in both developing, and developed countries. Underweight women are also at increased risk of giving birth to an infant with IUGR (RR: 1.54, 95%CI; 1.38-1.72) (199). Mothers' pre-pregnancy BMI has been found to be a strong predictor of low birth weight in Japanese populations, with underweight mothers at higher risk of delivering a low birth weight infant as compared to mothers with 'normal' BMI (OR: 1.86, 95%CI: 1.04-3.31) (200), and similar findings were reported in a 2010 study as well (201). Socioeconomic status may play a role in this association (4,202,203). Maternal pre-pregnancy BMI and gestational weight gain are highly related factors in determining infant birth weight and size for gestational age.

Maternal obesity has been linked to lower birth weight and small size for gestational age in numerous studies. One explanation for the phenomenon of low birth weight infants being born to mothers with higher BMIs is the increased rates of preterm birth with increasing maternal BMI. Factors such as increased risks of pre-eclampsia (204–206) with increasing maternal obesity contribute to increased rates of preterm births. Multiple studies have associated maternal obesity and low birth weight with increased rates of preterm births. A 2010 systematic review and meta-analysis suggested that the incidence of low birth weight (<2500g) in mothers with higher BMIs may be complicated by the effect of increased rates of pre-term birth in these mothers, finding that overweight and obese mothers had an increased risk of giving birth to a very low birth weight (<1500g, RR: 1.61, 95%CI: 1.42-1.82) or extremely low birth weight infant (<1000g, RR: 1.31, 95%CI: 1.08-1.59). They also found that risks of giving birth to an extremely low birth weight infant (<1000g) increased with increasing maternal BMI; with overweight mothers' RR: 1.18, (95%CI: 0.94-1.47), obese mothers' RR: 1.43, (95%CI: 1.05-1.95), and very obese women RR: 1.98, (95%CI: 1.36-2.89) (207). These authors suggest that higher maternal BMI is not a protective factor against low infant birth weight (207). A 2018 retrospective cohort study based in Hawaii found that the odds of preterm birth were increased with increased maternal BMI (BMI>30.0), as compared to normal weight women (aOR: 1.24, 95%CI: 1.06-1.45). These risks were increased in Native Hawaiian and Pacific Islander mothers as compared to white mothers. These authors speculate that increases in preterm deliveries can potentially contribute to increases in low birthweight (208). A 1992-2010 Swedish cohort study found that odds of extremely preterm deliveries increased with increasing maternal BMI (209), with BMI 25-30: (OR: 1.26, 95%CI: 1.15-1.37), BMI 30-35: (OR:1.58, 95%CI: 1.39-1.79), BMI 35-40: (OR: 2.01, 95%CI: 1.66-2.45), and BMI greater than 40: (OR: 2.99, 95%CI: 2.28-3.92) (209). Additionally, some studies have found a link between maternal obesity and growth restriction. A 2013 study in a Romanian birth population found that offspring of obese mothers

demonstrated a higher incidence of IUGR as compared to offspring of normal BMI mothers (210). Numerous other studies support this association (7-12).

Induced early births also contribute to the rates of low birth weight infants born to mothers with increased BMI. A 2010 systematic review found that the risk of an induced preterm birth increased with increased BMI, with overweight women having a relative risk of: 1.15, (95%CI:1.04-1.27), obese women having a relative risk of: 1.56, (95%CI: 1.42-1.71) and very obese women having a relative risk of: 1.71, (95%CI: 1.50-1.94) ((preterm defined as birth <37 weeks, 32-36 weeks) this effect was not present when looking at overall preterm births) (207). A 2015 study using data from the Prospective Observational Trial to Optimize Pediatric Health Study (PORTO) found that obese mothers were more likely to deliver early via both planned and emergency Caesarean delivery, leading to lower birth weights, as compared to mothers with normal BMI (212).The 2005 Preterm Prediction study found that pre-pregnancy obesity is associated with lower rates of spontaneous preterm births as compared to normal weight pre-pregnancy. Authors do note that increased rates of medically indicated preterm births in mothers with higher BMIs may be in part due to increased rates of pre-eclampsia (213).

Other factors likely to contribute to SGA and growth restricted births in mothers with higher BMI include differences in gestational weight gain (214–218), and bariatric surgeries (219–221). It is important to note that some studies have reported no association between increasing maternal BMI and insufficient fetal growth (222).

Low Gestational Weight Gain

Suboptimal maternal gestational weight gain has been linked to lower birth weight in infants (84,88). A 2009 systematic review of current gestational weight gain guidelines determined that strong evidence exists for the association between poor gestational weight gain, and lower birthweight (regardless of how gestational weight gain was measured –i.e. rate vs. total). The systematic review also determined that a strong association exists between gestational weight gain below the guidelines, and birthweights under 2500g, specifically in normal weight and underweight mothers. Being born SGA was also found to be associated with maternal gestational weight gain below Institute of Medicine guidelines. (89). Lower income mothers are at increased risk for both insufficient and excess gestational weight gain (93,94).

Mothers SGA at Birth

A mother that is born SGA herself is 2.5-2.7 times more likely to go on to give birth to a baby that is also SGA, as compared to a mother born AGA (181,223).

Multiple Gestation

Growth patterns in utero can vary when a mother is carrying multiples, as compared to a singleton pregnancy (224). This is discussed further in section 2.4 of this thesis.

Parity and Inter-Pregnancy Interval

High parity and short inter-pregnancy intervals can be linked to insufficient growth; these factors may be tied to low socioeconomic status (80) as well as age (4). A 2013 study found that nulliparous women younger than 18 years demonstrated the highest odds (pooled, adjusted OR: 1.80) of giving birth to a SGA infant as compared to mothers aged 18-35 that are multiparous (having parity 1-2) (225). A recently published Spanish birthweight for gestational age chart customized for parity and delivery type reported that birthweights were lower in primiparous mothers as compared to in multiparous women(226).

Hypertensive Disorders

Hypertensive disorders include gestational and chronic hypertension, pre-eclampsia, and eclampsia. Hypertensive disorders are estimated to affect 7% of all Canadian pregnancies (227,228).

Hypertension is hypothesized to contribute to insufficient growth by decreasing the rate of utero-placental blood flow (229–231). Both mild and severe forms of maternal hypertension has been found to be associated with lower birth weights (232).

Maternal hypertension has been found to vary across ethnicities (101,233–235). A 2006 study found that having chronic hypertension was associated with giving birth to a low birth weight infant in both Haitian (OR: 6.8, 95%CI: 4.3-10.6) and African American (OR: 2.9, 95%CI: 2.1-4.0) women (236). One study found that gestational hypertension can be associated with concurrent carbohydrate intolerance (237). Data from the Public Health Agency of Canada Perinatal Surveillance System data have also reported that rates of gestational hypertension can vary with maternal age- with older mothers experiencing increased rates of gestational hypertension (238). Factors increasing the risk of maternal hypertension include multiple gestation, and parity, whereas factors decreasing the risk of hypertension include smoking. (239).

Evidence exists to suggest that hypertension has different effects in singleton and twin pregnancies (240), with twin pregnancies experiencing higher rates of gestational hypertension(239,241).

A 2013 study reported that chronic hypertension was more likely to progress to pre-eclampsia/eclampsia in twin pregnancies, as compared to in singleton pregnancies. Twins of hypertensive pregnancies were also delivered at earlier gestational ages than singletons of hypertensive mothers (242). Authors of a 2015 study comparing hypertensive versus 'normotensive' twin pregnancies found that birth weights and frequencies of SGA births were comparable in the groups, suggesting that maternal gestational hypertension during a twin pregnancy may not necessarily detract from growth in utero (243).

Pre-eclampsia is related to low birth weight and SGA infants (244,245), and has also been associated with IUGR in singleton births (246). Pre-eclampsia was found in one Canadian population to have an association with babies born as severe (<3rd percentile size for gestational age) SGA at term (OR: 4.6, 95%CI: 1.6-13.2) (247). In pre-eclamptic pregnancies, babies born preterm are more likely to have experienced insufficient growth, and babies born at term exhibited similar growth to babies of mothers without pre-eclampsia. Authors of this study suggest that gestational age plays a key role in determining birth weight in pregnancies complicated by pre-eclampsia (231). Other studies support the role of gestational age in affecting the outcome of pre-eclamptic pregnancies (229,230). Evidence exists to suggest that pre-eclampsia is also more common in twin pregnancies than in singleton pregnancies (241,248,249). However, authors of a 2014 study suggested that pre-eclampsia and IUGR are not correlated in twin gestations (248).

Gestational Diabetes and Hypoglycemia

Maternal pre-existing and gestational diabetes can be linked to decreased fetal growth (250), in part by affecting normal placental function (251), as well as fetal and placental vascular development (252). The fetal insulin hypothesis can also explain the link between a diabetic uterine environment and low birth weight (253). In this theory, a genetically predisposed resistance to insulin in the fetus, along with other genetic factors, are thought to contribute to the decrease in 'insulin-mediated growth'. Changes in fetal or maternal insulin secretion, resistance, or glucose sensing can also contribute to altered growth(253).

Maternal hypoglycemia has been found to lead to low birth weights in infants, as compared to infants born to mothers with 'normal' serum glucose levels (254–256).

Smoking

Tobacco use is amongst one of the most well established risk factors for insufficient fetal growth (4). Smoking during pregnancy has been found to increase the risk of growth restriction by 2 to 3 times (4). Another study also found maternal smoking to be linked to an up to 250g discrepancy in birth weight (182,257). Maternal smoking was to have an association (OR: 5.3, 95%CI: 2.4-11.7) with being severely SGA (<3rd percentile size for gestational age) births at term in a Canadian population (247). Smoking more than half a pack of cigarettes per day was found to be associated with greater risks of premature delivery (OR:1.2, 95%CI: 1-1.44), IUGR (OR:2.02, 95%CI: 1.67-2.43) and low birth weight (OR: 2.00, 95%CI: 1.56-2.57) in a 2005 United States study (258). The association between tobacco exposure and decreased birth weight has been shown in numerous studies (4,259–264). Second hand smoking has also been found to have an effect on fetal birth weight(262,265–267). Furthermore, Gestational smoking has also been linked to preterm births in many studies (268–270).

Alcohol Use

Maternal alcohol use is associated with insufficient growth. The effect of alcohol will vary between early and late stages of pregnancy, with late stage alcohol consumption having stronger effects on birth weight(4). This does not, however, imply that early pregnancy drinking has no effect. Heavy alcohol use was also found to increase the risk of IUGR (OR: 1.35, 95%CI: 1.03 – 1.76) and low birth weight (OR: 1.57, 95%CI: 1.12-2.22) (258). The use of alcohol has been linked to concurrent use of tobacco (271). Concurrent alcohol and tobacco use was found to increase rates of preterm births in a 2006 study (270). Alcohol use has also been linked to socioeconomic status (272), and obesity(273).

Drug Use

A 2005 United States study found that cocaine use increased the risk of premature delivery (OR: 1.25, 95%CI: 1.01-1.55), IUGR (OR 2.24, 95%CI: 1.72-2.91), and low birth weight (OR: 3.59, 95%CI: 2.38-5.42)(258).

Mothers who use report drug use during pregnancy are more likely to be younger, have lower educational attainment, lower household income, and are more likely to have also used tobacco and alcohol (274). Maternal use of tobacco and cocaine are associated with decreased birth weight as compared to mothers who do not use any illicit drugs (275).

Marijuana exposure in utero has also been linked to insufficient growth. A 2015 study in a population with legalized access to marijuana found that mothers who self-reported marijuana use were 50% more likely to give birth to an infant with low birth weight (OR:1.5, 95%CI: 1.1-2.1; p=0.2), controlling for concurrent tobacco use, maternal age, race and ethnicity. Being born SGA was not associated with marijuana exposure (276). A 2016 Australian study found that marijuana use at 20 weeks gestation was linked to preterm birth (277). Numerous other studies have explored the effects of marijuana use on fetal growth related outcomes (278–281).

Prescription drug usage during pregnancy can also affect fetal growth. A 2012 meta-analysis found that maternal gestational antidepressant use is significantly associated with low birth weight (RR: 1.44, 95%CI: 1.21-1.70), and this association holds, regardless of type of antidepressant being used (282).

Kuczkowski (2007) has a comprehensive overview of how various illicit drugs interact with a pregnancy (283). Drug use during pregnancy is difficult to ascertain due to increased stigma, and fear of repercussions. Preterm birth can also confound the relationship between gestational drug use and decreased fetal growth (261,283).

Fetal Factors

Congenital Abnormalities

A majority of congenital defects have concurrent insufficient growth, usually diagnosed as IUGR. Khoury et al., in 1988 found that 22.3% of infants born with congenital abnormalities were also IUGR (relative risk of 2.6) (with IUGR classified in this study as birth weight below the 10th percentile for gestational age, race and sex). The relative risk of for infants with trisomy 18 of being IUGR was 46 (95%CI: 20.6-104.0), trisomy 13 has a relative risk of 9.5 (95%CI: 5.0-18.1), and a relative risk of 24.7 (95%CI: 18.2-33.6) was reported for infants with anencephaly being IUGR. The authors suggest three hypotheses explaining the association between congenital abnormalities and insufficient growth; a) insufficient growth predisposes the fetus to congenital abnormalities, b) congenital abnormalities are the cause of insufficient growth, or c) congenital abnormalities and growth restriction coexist due to some other factor(284). An Atlanta population based study found that there is a significant association between birth defects and insufficient growth, and that there is excess morbidity in the low birth weight population, in part attributable to birth defects (285). It is important to note that increased premature births in this population can also contribute to the observed increased rates of insufficient growth.

Congenital Infection

A wide variety of congenital infections such as cytomegalovirus, rubella, syphilis, hepatitis and toxoplasmosis can be contracted by the mother during pregnancy that have the potential to lead to insufficient fetal growth (286,287).

Premature Delivery

Insufficient growth is strongly linked to prematurity at birth. Premature births can be, but are not necessarily always due to a pathological concern. It is important to note that iatrogenic premature births have increased, due to increased rates of obstetric interventions such as caesarean delivery, and induction of labour, in what Louis and Platt (2011) (288) call the 'paradox of modern obstetrics'. This has gone on to cause a "left shift" in the population distribution of gestational age at birth (289). Despite this, evidence does exist to suggest that preterm births are associated with decreased growth, amongst other adverse outcomes. Threatened preterm labour was found to be associated (OR: 3.9, 95%CI: 1.3-11.4) with severe SGA births in a Canadian population (247). Preterm birth has been found to be linked to fetal growth restriction in numerous studies (37–39). Previous preterm birth has also been associated with subsequent preterm birth and low birth weight infants (91,290). Using the size for gestational age measure, which incorporates both weight and gestational age at birth allows for a better assessment of the role of premature delivery on insufficient growth (291).

Placental Factors

Placental factors include: pre-eclampsia, placenta previa, and vasa previa. Other placental factors include velamentous cord insertion, and uterine and placental abnormalities. Poor maternal arterial development (leading to decreased placental blood flow) has also been found to lead to insufficient fetal growth (140). Decreased rates of placental growth factor and insulin-like growth factor have been associated with insufficient fetal growth (142,292,293). Note that some of these factors have also been found to have an influence on multiple births as well (further explored in section 2.3.4).

Placenta Previa and Vasa Previa

Both placenta and vasa praevias and placenta accreta may contribute to the effect of low birth weight by way of preterm birth –infants affected by these conditions may be more likely to be born early by scheduled Cesarean delivery, before their full growth potential is reached (294–298). A 2001 study

found that mothers diagnosed with placenta previa were at increased odds of having a preterm delivery from 20- 23 weeks (OR: 1.81, 95%CI: 1.24-2.63), from 24-27 weeks (OR: 2.90, 95%CI: 2.46-3.42) and subsequent smaller sized infants (OR: 1.24, 95%CI: 1.17-1.32) (297). However, a 1991 hospital based study concluded that placenta previa does not contribute to SGA, with authors suggesting that conservative clinical management may have played a role in this (299). A 2010 retrospective cohort study found no association between placenta previa and decreased size for gestational age, however, this study did not explore preterm delivery (300). Lastly, a 2015 systematic review and meta-analysis paper found that increased risks of preterm delivery exist for women diagnosed with placenta previa (RR: 5.32, 95%CI: 4.39-6.45), vasa previa (RR:3.36, 95%CI: 2.76-4.09) and velamentous cord insertions (RR: 1.95, 95%CI: 1.67-2.28) (301).

2.3.8.3 Outcomes of Insufficient Growth

IUGR and overall insufficient growth lead to increased risks of immediate and later life adverse events (302). 'Immediate' events include congenital abnormalities, neurological problems, hypocalcemia, hypoglycemia, meconium aspiration, respiratory distress syndrome (303), cerebral palsy, polycythemia and hyperbilirubinemia (2). Later life (long term) events caused by IUGR are primarily metabolic, and include later life obesity, cardiovascular disease, type 2 diabetes, hypertension and hypercholesterolemia (303).

Fetal Short Term Outcomes

Short term outcomes of insufficient fetal growth include congenital abnormalities, neurodevelopmental problems, differential body composition, hypocalcemia and hypoglycemia. Respiratory distress syndrome, perinatal asphyxia, polycythemia, polyhydramnios and hyperbilirubinemia are other acute outcomes of insufficient growth. Stillbirth is another cause of concern associated with insufficient growth (62,144). It is important to note that these outcomes are also strongly associated with preterm birth.

Neurological problems

Low birth weight infants have higher rates of neurological problems. This may be due to clinical management practices (i.e. resuscitation, steroid therapies, surfactant therapies) meant to increase overall

survival of these infants. (304,305). Perinatal infections such as necrotizing enterocolitis and meningitis, have also been linked to poor neurodevelopmental outcomes in low birth weight and extremely low birth weight infants (306). Rates of cerebral palsy have been found to be 4 to 6 times higher (in live births from 32-42 weeks gestation) in babies below the 10^{th} percentile for size for gestational age (compared to births between the 25^{th} to 75^{th} percentiles) (2,161,307). A 2013 paper also reported that higher rates of spastic unilateral cerebral palsy was associated with insufficient intrauterine growth, and low birth weights, length, and head circumference (162). Increased rates of premature births in this population also contributes to this association (308).

Body Composition and Hormonal Status

Fetal body composition can be compromised by suboptimal growth. Growth restriction occurs due to the fetus undergoing "adaptive changes in metabolism" as a developmental response to poor uterine conditions (309). This leads to decreases in body fat percentage, total fat composition and lean mass in the growth restricted infant, as compared to an average grown infant. These changes are associated with decreased cord insulin and IGF-1 (insulin-like growth factor 1) levels, factors which can be affected by available maternal nutrient supply.

Hypocalcaemia

Hypocalcaemia and hypoglycemia are associated with insufficient growth in infants. Hypocalcaemia has been linked to low birth weight infants, however, this outcome may be linked to prematurity at birth as well (177,310). SGA infants experience higher rates of hypoglycemia as compared to matched average for gestational age infants (311). Hypoglycemia due to IUGR has also been linked to poor neurodevelopmental outcomes (312).

Fetal Long Term Outcomes

Long term outcomes of insufficient growth include type 2 diabetes, decreased adult functionality, hypertension, hypercholesterolemia, diabetes mellitus, blood pressure abnormalities, cardiovascular disease and coronary heart disease (313–319).

Type 2 Diabetes

Type 2 diabetes may have early life origins due to insufficient growth conditions. Insulin resistance developing as a result of insufficient growth and suboptimal growth environment can contribute to the development of later life type 2 diabetes (309). This association has been shown in multiple studies (320–323).

Maternal Long Term Outcomes

Maternal long term outcomes also exist, and include later life coronary heart disease, increased risk of subsequent SGA pregnancies, later life obesity, and cardiovascular disease. One long term outcome affecting mothers who give birth to undergrown fetuses is an increased risk of later coronary heart disease (2,324,325). Mothers who give birth to low birth weight infants can also be at increased risk of developing later life obesity or later life cardiovascular disease, however, this is likely due to underlying conditions (i.e. socioeconomic status) contributing to the adverse health outcomes of both mother and child (2). Mothers who give birth to SGA singletons were found to be at increased risk of SGA in subsequent twin pregnancies (326).

2.3.9 Trends Over Time

SGA births have been decreasing, and LGA births have been increasing (2). This trend has been observed in Sweden(327), Canada (32), the United States (148), China (328), Germany (329), Scotland(330), and Denmark (331). The LGA increase can be attributed in part to increases in maternal pre-pregnancy weight and BMI, increased gestational weight gain and decreased maternal smoking. The SGA decrease can be attributed to increasing maternal age, and increased rates of diabetes and hypertension; trends recently studied in the Canadian and American populations(332). It is important to note, however, that increases in caesarean deliveries and labour induction (2,21) have led to earlier deliveries, leading to an impact on population level size for gestational age measurements. As discussed earlier, iatrogenic premature births have increased, due to increased rates of obstetric interventions such as caesarean delivery, and induction of labour, in what Louis and Platt (2011) (288) call the ‘paradox of modern obstetrics’, causing a recent “left shift” in the population distribution of gestational age at birth (289).

2.3.10 Fetal Growth – Gaps in Knowledge

Most studies focus on the outcomes of being SGA or having low birth weight. Only recently have studies begun to focus on the excessively grown babies, as they are able to survive, however, they are still at risk of later life adverse outcomes. Babies born small relative to their larger mothers (182) are an understudied population, as it is difficult to determine the cause of smaller size at birth than anticipated. There is no consensus on how to determine optimal fetal growth trajectories, whether an optimal growth trajectory even exists, or if it is clinically necessary (45). At present, because fetal growth in utero is highly inaccessible, it is difficult to know with certainty which factor comes first (i.e. does insufficient growth cause an abnormality, or does the abnormality lead to insufficient growth?), making it difficult to determine causality.

Fetal growth is well studied in singletons, however, less research is available for multiples. The accurate study of fetal growth is further complicated by the fact that the fetus is highly inaccessible in utero. Methods such as ultrasound can have poor accuracy in determining anthropometric measurements and estimated weights (176,333,334).

2.3.11 Fetal Growth – Conclusions

Understanding normal fetal growth allows us to better understand patterns of abnormal fetal growth. Overgrown and undergrown fetuses are both at increased risk of perinatal morbidities and mortality as compared to ‘optimally’ grown babies.

2.4 Maternal Obesity

2.4.1 Introduction

Maternal obesity is a rapidly increasing cause for clinical concern. Increasing maternal BMI leads to increases in adverse outcomes for both mother and child, some of which are long-lasting. Rates of obesity in adult Canadian women have increased from 14.5% in 2003 to 18.7% in 2014(335). The combined rate of overweight and obesity in women was 46.2%, or approximately 6.1 million women in Canada in 2014(335). According to the Public Health Agency of Canada Maternity Experiences Survey (2006), 13.3% of women of reproductive age were obese pre-pregnancy, and 48.8% of women had excess levels of gestational weight gain (336,337).

Fetal growth is determined by 4 key factors: maternal, fetal, and placental health, and their effect on predestined growth potential (47). Maternal lifestyle can play a key role in affecting fetal size (338).

Looking at infant size for gestational age, the number of infants being born SGA has decreased, and the number of infants born LGA has increased, due in part to societal changes in maternal BMI and behavior(2). This section will outline how maternal obesity affects the pregnancy and fetal growth.

2.4.2 Maternal Obesity and Adverse Events in Singletons

Increases in obesity, and maternal obesity, bring with them increases in the risk of maternal obesity related adverse events. The Pedersen Hypothesis, shown in Figure 2.1 outlines one biological mechanism by which increased energy transfer from mother to child can lead to excess fetal growth. Numerous studies have established the detrimental effects of maternal obesity on maternal-fetal health(13–16). Additionally, maternal obesity can lead to later life adverse events for infants (339). These adverse events can be categorized into maternal, fetal, and delivery events.

2.4.2.1 Adverse Maternal Events

Adverse maternal events include gestational hypertension, gestational diabetes, preeclampsia, as well as postpartum complications, such as hemorrhage, thrombosis, infection, and placenta previa (14). A 2004 study of over 16,000 births concluded that obese women (BMI 30-34.9) were 2.5 times more likely (95%CI: 2.1-3.0) to develop gestational hypertension, and 1.6 times more likely to develop pre-eclampsia (95%CI:1.1-2.2) and that morbidly obese women (BMI>35) are 3.2 times more likely (95%CI: 2.6-4.0) to develop gestational hypertension, and 3.3 times more likely (95%CI: 2.4-4.5) to develop preeclampsia as compared to women with a normal BMI (340). The same study found that obese women had an odds ratio of 2.6 (95%CI: 2.1-3.4) of developing gestational diabetes, and this OR increases to 4.0 (95%CI; 3.1-5.2) in morbidly obese women. (340). These results of increasing likelihood of maternal complications with increasing BMI have been replicated in numerous studies (13,16,341–343).

2.4.2.2 Adverse Fetal Events

Adverse fetal/neonatal events include stillbirth**,** intrauterine growth restriction, birth traumas, fetal macrosomia, and fetal malformations/congenital anomalies such as neural tube defects, spina bifida, cardiovascular anomalies, cleft lip and palate**,** low APGAR scores, anorectal atresia and hydrocephaly (344)**.** A 2007 meta-analysis looking at the risk of stillbirth found that for obese women, the odds ratio of

a stillbirth is 2.07 (95%CI:1.59-2.74) as compared to women with normal BMI (345), and further studies have confirmed an effect of increasing risk of stillbirth with increasing maternal obesity (346,347). In morbidly obese women (BMI >40), one study found the adjusted odds ratio of stillbirth to be 2.79 (1.94-4.02) (14). One study found that obese women are 1.7 times more likely (95%CI: 1.4-2.0) to deliver a macrosomic infant (birth weight >4000g), and this likelihood increases to 2.0 times more (95%CI: 1.5-2.3) for morbidly obese women, as compared to a control of women with normal BMI. The odds of delivering a macrosomic infant weighing greater than 4500g is further increased; obese women are 2.0 times more likely (95%CI:1.4-3.0) and morbidly obese women are 2.4 times more likely (95%CI: 1.5-3.8) as compared to women with normal BMI (340). Morbidly obese women are also at greater risk of delivering an LGA infant with an odds ratio of 3.82 (95%CI: 3.50-4.16) (14). A 2008 meta-analysis studying neural tube defects (NTD) found that obese women have an odds ratio of 1.70 (95%CI: 1.34-2.15) of NTDs and severely obese women demonstrate an odds ratio of 3.11 (95%CI: 1.75-5.46) of giving birth to an infant with a neural tube defect, as compared to women with normal BMI (348). Lastly, a comprehensive systematic review and meta analysis from 2009 concluded the following odds ratios for the risk of congenital anomalies in infants born to obese mothers: neural tube defects 1.87 (95%CI: 1.62-2.15); spina bifida 2.24 (95%CI: 1.86-2.69); cardiovascular anomalies 1.30 (95%CI: 1.12-1.51); cleft lip and palate 1.20 (95%CI:1.03-1.40); anorectal atresia 1.48 (95%CI: 1.12-1.97); and hydrocephaly 1.68 (95%CI: 1.19-2.36) (349). Infants of mothers with higher BMIs are at significant risk of many adverse health outcomes.

2.4.2.3 Adverse Birth and Delivery Events

Adverse birth and delivery events include shoulder dystocia, increased rates of caesarean birth, preterm delivery, and other birth traumas **(**such as operative vaginal delivery which can lead to increased risk of maternal and fetal mortality (344)**.** A 2004 study by Weiss et al. found that morbidly obese women (BMI>35) had an odds ratio of 1.5 (95%CI 1.1-2.1) of giving birth to a preterm infant, as compared to women with normal BMI; (obese women demonstrated a similar propensity towards preterm birth as normal BMI women) (340). Other studies have also replicated this effect of increased rates of preterm births in morbidly obese women (213). A 2008 meta-analysis of pregnancy outcomes found the risk of shoulder dystocia to be 1.04 (95%CI: 0.97 – 1.13) for obese women, as compared to women with normal BMI (350). In morbidly obese women (BMI >40), the risk of shoulder dystocia (increases to) was 3.14 (95% CI: 1.86-5.31) compared to women with normal weight (BMI 19.8-26). (14). A multicenter prospective study found that rates of caesarean delivery increased with increasing maternal BMI. The odds ratio of caesarean delivery for obese women (BMI 30-34.9) was 1.7 (95%CI: 1.4-2.2), and increases

to 3.0 (95%CI: 2.2-4.0) for morbidly obese women (BMI >40), as compared to women with normal BMI (BMI < 30). Caesarean rates were 20.7% for normal BMI women (3752 patients, BMI < 30), 33.8% in obese women (1473 patients, BMI 30-34.9) and 47.4% in morbidly obese women (877 patients, BMI >35) (340). In morbidly obese women (BMI>40), one study found that the risk of a Caesarean delivery increased to 2.69 (2.49-2.90) as compared to women with normal weight (BMI 19.8-26) (14).

This section has explored the increasing risks of the aforementioned adverse events for both mother and child with maternal obesity. These effects are well studied in singleton, nulliparous, low risk births. Research is still lacking that describes how these adverse events translate to a twin pregnancy. The next section will outline what is known about adverse events specifically in twin pregnancies further complicated by maternal obesity.

2.4.3 Maternal Obesity and Adverse Events in Twins

Adverse events in singletons of obese mothers are well studied. Relevant studies exploring the aforementioned outcomes in twins born to obese mothers are not as well explored. The literature on this topic is divided; some studies have found evidence of an effect of obesity as a risk factor for adverse events in twin pregnancies, whereas others have not. Again, these adverse events can be categorized into maternal, fetal and delivery events. Risks for the following outcomes are generally increased for twins, as compared to singletons.

2.4.3.1 Adverse Maternal Events

Maternal adverse events include gestational hypertension, preeclampsia and gestational diabetes. A 2013 study comparing adverse outcomes in twin pregnancies across maternal BMI categories determined that obesity was associated with increases in maternal adverse events (351) . This study found that obese (BMI>30) mothers of twins are 2.37 times (95%CI: 1.20 – 4.68, p=0.011) more likely than normal weight (BMI: 18.5-24.99) mothers of twins to develop gestational hypertension, 2.23 times (95%CI: 1.07-4.62, p=0.028) more likely to develop preeclampsia, and 5.82 times (95%CI: 2.46 – 13.81, p<0.001) more likely to develop gestational diabetes. These results were replicated in a 2013 study in a Canadian population (352), as well as in a 2014 Slovenian matched case-control study (353).

2.4.3.2 Adverse Fetal Events

Fetal adverse events include intrauterine growth restriction, fetal macrosomia, small size for gestational age and stillbirth. A 2011 study of 313 twin births in New York found that maternal obesity (BMI>30) was not a contributing risk factor to intrauterine growth restriction in twins (354). This study defined IUGR as either twin with birth weight below the 10th percentile for gestational age. A 2013 study of adverse events in twin pregnancies reported only one case of fetal macrosomia out of 514 included births (351). Maternal pre-gravid BMI was found to be an insignificant risk factor towards SGA designation in twins in a 2010 Japanese study of dichorionic twins (355). In twin pregnancies, obesity was found to lead to a 31% greater chance of stillbirth as compared to mothers with normal BMI (OR: 1.31, 95%CI: 1.02 -1.68). This effect was only found to be significant for class I obese mothers (356).

2.4.3.3 Adverse Delivery Events

Delivery events include caesarian delivery, preterm delivery and shoulder dystocia. A 2014 study in a Canadian population reported that increased maternal obesity was associated with an increased risk of Caesarian delivery (OR: 2.2, 95%CI: 1.2-4.1)(357). A 2008 study from Missouri determined that obese women (BMI>30) delivering twins were at a lower risk (OR: 0.68, 95%CI: 0.62-0.75) of spontaneous preterm birth, as compared to obese women delivering singletons. This association was seen in mothers who gained between 0.23 and 0.69 kg per week. When looking at medically indicated preterm births of twins, obese women were at greater risk (OR: 1.37, 95%CI: 1.24-1.52) than non-obese women. This risk increases with increasing BMI, with women of class III BMI at greater risk (OR: 1.64; 95%CI: 1.35-2.01)(358).

2.4.4 Maternal Obesity – Gaps in Knowledge

While it may be intuitive to assume that the effects of maternal obesity leading to adverse events in singleton pregnancies would also translate to the same adverse events in twin pregnancies affected by maternal obesity, many prior studies do not verify this effect. The mechanisms leading to adverse events in twin pregnancies may not necessarily be the same mechanisms leading to adverse events in singleton pregnancies. A 2000 study of dichorionic twin pregnancies found no association between increased maternal BMI and increasing pre-eclampsia in twins, however the association between BMI and pre-eclampsia was present in singletons (359). A 2005 study of twin and singleton pregnancies in a high socioeconomic level population confirmed this; finding that maternal BMI was associated with increased fetal BMI, weight and length, and this association was not confirmed in twins (360). These highly

differing results may be due to differences in populations studied. Recently, a 2017 study found that maternal height (short (<159 cm) vs 'normal' (>160 cm)) may not be associated with gestational age or birth weight in twin pregnancies(361).

Few data exist on mothers with extremely high BMI levels (i.e. >50). No data currently exists exploring an association between maternal obesity and birth trauma in twins. The majority of studies exploring twin pregnancies and maternal obesity have focused on maternal outcomes- few studies have attempted to determine the combined effect of maternal obesity and multiple births. It is unsure whether this gap exists due to a lack of an association, due to restrictions in sample size or is simply due to coincidence. Twin pregnancy is associated with higher risk of maternal complications (353) however, the contribution of maternal obesity to this risk in twin pregnancies is still unknown.

2.4.5 Maternal Obesity – Conclusions

Maternal obesity is increasingly becoming a cause for concern- due to the increased risks to both mother and child. These risks are further complicated in the case of multiple gestations. Further research is necessary to match the growing burden of obesity.

2.5 Twin Births

2.5.1 Introduction

Twins and higher order multiple births require special obstetric consideration, because they are more complicated than the average singleton birth. These considerations usually lead to twins and other higher order multiple births being treated as exclusions in research. This section will outline the epidemiology of twin births, pathophysiology of the twin development process, and the different types of twins that can arise, and will explore how despite the added complications of studying twins, they are a relevant population for prenatal studies.

2.5.2 Prevalence of Twins

In 2011, 3.3% of all births in Canada were multiple births, a rate which has risen from 2.1% in 1991(17). This increase can be attributed in part to the increasing usage of artificial reproductive technologies (such as in vitro fertilization, frozen embryo transfer, and intracytoplasmic sperm injections) to aid conception (362,363), as well as increasing maternal age (364,365). Other factors include parity,

race, nutrition, and fecundity. Influence of these risk factors varies for monozygotic versus dizygotic pregnancies (366), and across different ethnic populations (367–371).

In Canada, the multiple gestation rate was 20 per 1000 live births in 1991, 28.3 per 1000 live births in 2004, and rose to 31.4 per 1000 as of 2009 (372). A similar change in rate of twin births can be observed in the United States; 23.1 per 1000 live births in 1991, 32.2 per 1000 live births in 2004, and 33.2 per 1000 live births in 2009 (1). The same study also concluded that, based on data from 1991 to 2009, the rate of twin births is increasing in North America This trend can be attributed to increasing artificial reproductive technology usage, combined with increasing maternal age, and this trend seems to hold across multiple developed countries (i.e. England, Germany, France and South Korea) (367).

A comprehensive global study of twin birth rates published the following 'natural' twin birth rates: less than 8 twin births per 1000 births (low) in East Asia and Oceania; 9-16 twin births per 1000 births (intermediate) in Europe, India and the United States, and greater than 17 twin births per 1000 births (high) across Central Africa(373) . Past studies have found that the rate of identical (monozygotic) twin births is globally constant at approximately 4 per 1000 births (367) and that variations in twin birth rates are largely attributable to the differential birth rates of fraternal (dizygotic) twins across populations(366,370).

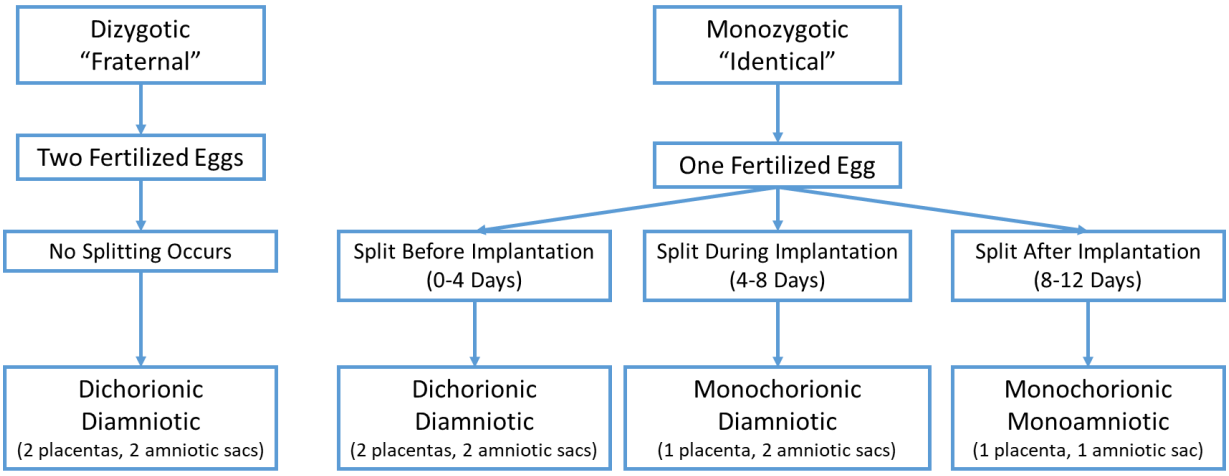
2.5.3 Types of Twins

Differences in cell division within the first two weeks of development (see section 2.2.2) are crucial in determining whether a singleton or multiple pregnancy will occur. Figure 2.2 below outlines how twin types occur. If, at conception, two oocytes are fertilized, the resultant embryos will develop into dizygotic (DZ) or fraternal twins (374). Each twin will independently undergo the aforementioned cell division stages, developing their own amniotic sac and placenta. This is referred to as a diamniotic dichorionic (DA/DC) **(**2 placentas) pregnancy. Dizygotic twins share approximately 50% of their genes, on average (equivalent to pairs of singleton siblings)(370). Dizygotic twins are always dichorionic.

Monozygotic (MZ) twins are derived from fertilization of a single oocyte that splits, resulting in (genetically) identical twins. Depending on when during development the split occurs, different forms of monozygotic twins can arise. If this split occurs before the 3rd day of fertilization, the resultant twins will be dichorionic (DC) and diamniotic (DA), meaning that they develop 2 distinct placentas and 2 distinct amniotic sacs. If the split occurs after the 3rd day post fertilization, when the morula has separated, the resultant twins will develop in 1 placenta and 2 separate amniotic sacs, called monochorionic and diamniotic. If the embryonic split occurs past 9 days past fertilization, the twins are monochorionic (MC)

and monoamniotic (MA), meaning that they develop within the same placenta and amniotic sac (362). Because of their increased proximity, MA/MC twins are at greatest risk of obstetric complications.

Figure 2. 2 Development of Monozygotic and Dizygotic Twins



2.5.4 Determinants of Twin Births

Many factors have been hypothesized to be determinants of multiple births. These include: maternal BMI/obesity, hereditary factors, ethnicity, increasing maternal age, artificial reproductive technology use, smoking, seasonal variations and folic acid supplementation. (301,305–312).

2.5.5 Twin Births and Fetal Growth

Many authors and clinicians have suggested that twins may grow differently than singletons (224,353,386–389). But, being a small twin does not necessarily mean the baby is unhealthy compared to singletons. Therefore, it follows that twins should not necessarily be assessed by singleton standards.

However, when comparing the total "fetal mass" of a singleton and twin pregnancy, a total twin pregnancy will have a higher overall mass than a singleton pregnancy, leading many to consider a multiple gestation to be growth promoted in comparison (390,391).The utero-placental system is able to supply 50-75% more in a multiple gestation compared to a singleton one; an effect which holds true even in birth-weight discordant twins (390). This suggests that twin pregnancies are not inherently *doomed,* rather, their growth trajectories are different from those of singleton pregnancies (389,392). It is important

to note that the smaller size of multiples is not necessarily pathological in origin, and rather just a consequence of sharing a uterine environment.

Growth trajectories are different between twins and singletons. Numerous studies have determined that the growth trajectories of twins and singletons are similar until 28 weeks gestation; after which, twin growth slows down (18,28,393,394). (This means that until 28 weeks, twins and singletons exhibit similar weights, after this, singletons go on to gain more weight until birth as compared to their twin counterparts).

Several possible mechanistic explanations have been proposed for these distinct growth trajectories, such as crowding in the uterus, (393,395) or placental dysfunction causing hypoxia (396).

Twins with 'typical' growth are not the same thing as growth restricted singletons; as different factors can contribute to the reduced growth. A recent review suggests that the origins of reduced growth in twins are distinct from those of reduced growth in singletons (397), and may thus lead to different outcomes in the long term. Studies on fetal reductions have found that singletons resulting from fetal reductions will still have a birth weight less than that of natural singletons (398). Monochorionic twin pairs more commonly experience fetal growth restriction and growth discordancy as compared to dichorionic pairs (49). A 1998 study exploring the role of chorionicity found that, on average, MC twins weighed 66.1g ($p<0.05$) less than DC twins that are age-matched (390,399). One study found that for same sex twins, male twins will demonstrate a greater median birth weight than female twins across all gestational ages(18), attributable to the presence of androgens (400). In sex-discordant twins, the effect of sharing the uterine environment with an opposite sex sibling leads to longer gestation for the male twin, on average by 2.1 days (compared to male-male twins), and an increased birthweight for the female twin, on average by 102g (compared to female-female twins) (400).

2.5.6 Twins – Gaps in Knowledge

Twins require special consideration due to increased obstetric complications that may arise from a multiple pregnancy, such as lower birth weight, higher rates of preterm births, fetal and infant mortality and long term developmental disabilities(401). Furthermore, twin specific complications can also arise depending on the type of twin (i.e. MA/MZ/DZ) (362), and can range from fetal weight discordance to Twin to Twin Transfusion Syndrome, or even fetal loss (fetal reduction). There is a differential obstetric risk between MC and DC twins, where there are increased complications in MC twins, due to placental sharing, and connected vascular systems (374). For instance, MC DA twins are at a 10-15% increased risk of twin to twin transfusion syndrome (402).

Owing to these aforementioned complications, twins are generally excluded from fetal studies. Maternal complications are also more prevalent in twin and multiple births. For instance, maternal heart rate, stroke volume and cardiac output are increased in twin births, as compared to singletons. Blood plasma volume in a twin pregnancy can be increased by 10 to 20% more as compared to in a singleton pregnancy (362). Other maternal complications specific to twin and multiple births include increased nausea and vomiting, increased obstetric and intrahepatic cholestasis, urinary tract changes leading to increased risk of urinary tract infections, higher rates of gestational hypertension and pre-eclampsia. Additionally, in twin pregnancies, pre-eclampsia can be more severe, and can have an earlier onset (403).

Twin growth is poorly studied as compared to singleton growth. This is due to the increase in statistical complexity necessary to account for the non-independence of twin pairs.

It is still unknown whether the factors leading to smaller size in twins are the same factors that lead to smaller sized (IUGR) singletons. However, the pathological conditions that would cause a singleton to be growth restricted are not more common in twin pregnancies; therefore smaller sizes at growth are not necessarily caused by the same factors(397).

2.5.7 Twins – Conclusions

Twins are an understudied population. They grow in different conditions compared to singletons, and therefore need to be studied separately to twins. It is important to compare and contrast growth patterns of twins and singletons to determine the best method of clinical management, especially to determine twin pairs at risk, compared to healthy twins.

3 Chapter 3 – Methods

3.1 Introduction

This chapter describes the methodologies used to carry out the objectives outlined in section 1.2.

3.2 Study Design

This was a retrospective longitudinal study, using observational prospectively entered data from the St. Josephs Health Care/London Health Sciences Centre Perinatal Database.

3.3 Data Source

Data for this study were extracted from a citywide database of birth records from the Women's Care Program based in the London Health Sciences Centre (LHSC) and Victoria Hospital in London, Ontario, which are used for clinical quality audits as well as research activity (404). Entries in this perinatal clinical database are prospectively extracted from obstetrical and medical records (405), and entered since 1995, and contain demographic, pregnancy, delivery and birth data from mothers and their newborns. An estimated 61,000 deliveries are currently in the database.

3.4 Population of Interest

Database intake and relevant study population was based out of two major birth centers serving London Ontario and the surrounding area. High risk transfers from the southwest Ontario region were also included. Approximately 4700 live births occurred in the Middlesex-London Health Unit each year (406), and there were approximately 56000 live births in the region from 2006 to 2017. This project used data from both mothers and their newborn singletons and twins.

3.4.1 Inclusion and Exclusion Criteria

Targets for inclusion in this study were all eligible singleton and twin newborns born at London Health Sciences Centre and Victoria Hospital in the database from June 1st, 2006 to August 31st, 2018, born to mothers aged 18-45 with complete pre-pregnancy BMI data. Inclusion and exclusion criteria were applied by the Decision Support Office at Victoria Hospital.

These years were chosen due to consistency of definitions of variables from 2006 to 2018, as well as addition of new variables collected in the database. For instance, gestational age was only recorded in the database as completed weeks starting Nov 1, 1995 and smoking was only included if the mother smoked over 1 pack of cigarettes per day, which was changed to any smoking starting Dec 1, 1998. Other variables with changing definitions include: drug use, multiple birth status, diabetes, and gestational hypertension. Mothers' age range of 18-45 was chosen to reflect changing definitions and changing clinical management of "low risk" pregnancies.

Exclusion criteria varied for mothers and newborns. Fetal exclusion criteria included congenital and/or chromosomal abnormalities, stillbirths, and significant missing exposure or outcome data. Lastly, values from the Robertson (1) standard for birthweight for gestational age were applied to further exclude individuals ineligible for further analyses. Figure 4.1 outlines how the final sample size for this study was achieved.

3.5 Variables of interest

The following section outlines the variables available in the perinatal database that were used to address the objectives of this thesis. Following a review of the literature, these variables available in the perinatal database were chosen to be included as covariates in the analyses.

Table 3. 1 Variables Chart

Original Variable in Coding Manual	New Variable Name in Dataset	Description	Original Coding	Recoding for Analysis
Pre-Pregnancy Maternal Variables				
Maternal Pre-pregnancy BMI HEIGHT HGHTINCH PPWEIGHT PPWTLB BMI	*newbmi*	Two original variables are required to derive the BMI variable; maternal height and maternal weight. Maternal BMI was provided in the dataset as a calculated variable based on maternal pre-pregnancy height and weight data. To calculate BMI, the following formula was used: $BMI = \frac{weight\ in\ kg}{(height\ in\ m)^2}$,	Continuous Range: (-3.70 to 268.46)	Categorical (6): Underweight BMI (16.0 - 18.49 kg/m^2) **Normal BMI *ref (18.5-24.99 kg/m^2)** Overweight (25.0-29.99 kg/m^2)

		used commonly by Health Canada (407) as well as the World Health Organization (408). For the purposes of this study, BMI was treated as a categorical value following commonly used clinical values. The lower limit of 16.0 kg/m^2 was set based on limits of human chronic energy deficiency, as described by Henry (2001) (409). *Note that extremely implausible values (i.e. negative values or 268.46) are likely due to measurement errors (i.e. reporting a weight in lbs incorrectly as kgs)		Obese Class I (30.0-34.99 kg/m^2) Obese Class II (35.0-39.99 kg/m^2) Obese Class III (40.0-60.0 kg/m^2)
Maternal Age MAGE	*matagebirth*	Maternal age values are calculated in the dataset using the following formula:$maternal\ age = infant\ date\ of\ birth - maternal\ date\ of\ birth.$ Age responses are provided in whole years in the dataset. Study inclusion criteria pre-specified a range of 18-45. Original coding of the variable is maintained.	Continuous: 18-45	Continuous: 18-45
Parity Prevtermdeliv Prevpretermdeliv Livebirths	*parity*	Three variables in the dataset were assessed to determine maternal parity; number of previous term deliveries, number of previous preterm deliveries, and number of livebirths at time of data collection. Mothers are coded as multiparous if any of the above variables are ≥1, and nulliparous if all of the above variables are 0.	Continuous:	Binary: **Nulliparous *ref** Multiparous
Pregnancy Related Variables				
Smoking SMOKE	*Smoking2*	Smoking is specified in the dataset as "any smoking during pregnancy" and is a binary variable for data entries after December 1st 1998. This variable is only collected from June 2006 onwards in the provincial minimal database. Null entries in the database are treated as missing values in analyses.	Binary: No smoking Any smoking NULL	Binary: **No smoking *ref** Any smoking (Missing)
Alcohol Use ALC	*Alcohol1*	Alcohol use data is collected for women who have more than 4 drinks per week during the pregnancy. In cases where a physician is concerned about alcohol consumption during the pregnancy, the variable is also coded.	Categorical (3): No Yes Partial	Binary: **Non- Drinking *ref** Any Drinking

		Response options 'yes' and 'partial' are combined to represent any drinking during the pregnancy.		
Any Drug Use DRUGS	*drugs*	Drug use at any time during the pregnancy is collected as a binary variable in the dataset. The dataset defines drug use as "street drugs or drugs noted as having high risk for adverse events". Original coding of the variable is maintained and null entries in the database are treated as missing values in analyses.	Binary: No drug use Any drug use	Binary: **No drug use *ref** Any drug use
Cocaine Use MHCOCAINE	*Cocaine1*	Cocaine use is coded if used at any time during the pregnancy (if/when disclosed). This variable is only collected from June 2006 onwards in the provincial minimal database. Original coding of the variable is maintained. Null entries in the database are treated as missing values in analyses.	Categorical: No Yes NULL	Binary: **No *ref** Yes (Missing)
Marijuana Use MHMARIJUANA	*Marijuana*	Any marijuana use is coded if used at any time during the pregnancy (if/when disclosed). This variable is only collected from June 2006 onwards in the provincial minimal database. Original coding of the variable is maintained. Null entries in the database are treated as missing values in analyses.	Categorical: No Yes NULL	Binary: **No *ref** Yes (missing)
Prescription Medication Use MHPRESCRIPTIONDRUGS	*prescdrugs*	Prescription drug use is coded if used at any time during the pregnancy. This variable is only collected from June 2006 onwards in the provincial minimal database. Original coding of the variable is maintained. Null entries in the database are treated as missing values in analyses.	Categorical: No Yes NULL	Binary: **No *ref** Yes (Missing)
Current (pre-existing) Diabetes MHDIABINSDEP MHDIABNONINS	*Diabfeb5*	This variable is coded as a combination of two separate diabetes variables: insulin dependent diabetes, non-insulin dependent diabetes, and the category "overt diabetes" from the variable carbohydrate disorders. All diabetes variables used for analysis code for diabetes that is pre-existing and persists into the current pregnancy, or develops within the current pregnancy.	Categorical: Insulin dependent diabetes: No Yes NULL Categorical:	Binary: **No *ref** Yes (Missing)

		These variables are only present in the dataset from June 2006 onwards. Null entries in the database are treated as missing values in analyses.	Non-insulin dependent diabetes: No Yes NULL Categorical: Carbohydrate intolerance Gestational onset Overt Diabetes No NULL	
Carbohydrate Disorders DIAB	*Carbdisfeb 5*	The carbohydrate disorders variable collects information on maternal carbohydrate related health concerns during the current pregnancy. Carbohydrate intolerance was diagnosed when there was an abnormal reading during a 75-gram oral glucose tolerance test (GTT). **Note that in the original dataset, the carbohydrate disorders variable included response options for levels of maternal carbohydrate disorders, as well as overt diabetes. The diabetes response option was dropped from this variable and incorporated into the aggregate diabetes variable* Null entries in the database are treated as missing values in analyses. **Response options are derived from Creasy-Resnick, Maternal Fetal Medicine, 4th edition**	Categorical: Carbohydrate intolerance Gestational onset Overt Diabetes No NULL	Binary: **No *ref** Yes (missing)
Hypertensive Disorders	*hypdis*	The hypertensive disorders variable was created as an aggregate of gestational hypertension, chronic hypertension and eclampsia/pre-eclampsia by combining response options from the variables *currentchronhtx, and gesthtx* and *eclampsia. (Note that in the original dataset, one variable coded for both gestational hypertension, and levels of eclampsia/pre-eclampsia – and this*	Current chronic hypertension: Binary: No Yes Gest. Hypertension and	Binary: **No *ref** Yes

		original variable was used here). Unknown and NULL values were coded as a "no". **Response options are derived from Creasy-Resnick, Maternal Fetal Medicine, 4th edition*	eclampsia/pre-eclampsia: Categorical: Eclampsia Mild pre-eclampsia Severe pre-eclampsia Gestational hypertension No Unknown NULL	
Chronic Hypertension – Current Pregnancy HTX	*currentchronhtx*	Codes for chronic hypertension. Null entries in the database are treated as missing values in analyses.	Binary: No Yes	Binary: **No *ref** Yes
Gestational Hypertension PIH	*gesthtx*	The provided variable codes for gestational hypertension and pre-eclampsia /eclampsia in one variable. The variable responses were separated to assess these options separately in analyses. Coding manual specifies *"For any case with pre-eclampsia superimposed on chronic hypertension, enter code 1 for chronic hypertension, and enter the appropriate code (2,3 or 4) in pre-eclampsia/eclampsia".* Null entries in the database are treated as missing values in analyses.	Categorical: Eclampsia Mild pre-eclampsia Severe pre-eclampsia Gestational hypertension No Unknown NULL	Binary: **No *ref** Yes (Missing)
Birth and Delivery Related Variables				
Placenta Previa PREVIA	*Placprev*	Codes placental placement relative to the cervix (defined as *'Implantation of the placenta low in the uterus either overlying or reaching the vicinity of the cervical os'* in the coding manual) Response options 'marginal', 'partial', and 'complete' are combined into an 'any placenta previa noted' variable.	Categorical: No Marginal Partial Complete NULL	Binary: **No *ref** Any (Missing)

		Null entries in the database are treated as missing values in analyses.		
Infant variables				
Infant Size for Gestational Age BIRTHWT GESTWK GESTDAY	*Bwtnew* *Gestage1* *Singrobsga* *Singroblga* *Twinrobsga* *Twinroblga*	Infant birth weight for gestational age is derived from two variables found in the perinatal database; birth weight, and gestational age at birth Birthweights are recorded into the database in grams in a birth outcomes form. No upper limit was set for birthweight. A lower limit was set based on the lowest published value available in the chosen standards. Gestational age is recorded in the dataset as completed weeks and completed days. Days 1-3 will be rounded down to the nearest week, and days 4-7 will be rounded up to the nearest completed week. Gestational age is measured in the perinatal database using the best obstetric estimate, defined as a combination of a first trimester ultrasound scan and mothers last menstrual period. (404). For singletons and twins, size for gestational age percentiles will be derived from Robertson (2002) which includes separate sex-specific published values for both singletons and twins. **Please see Appendix Section E for a discussion of infant size for gestational age, and appendix section F for a chart outlining current size for gestational age standards and references – these 10th and 90th percentile cutoffs were used to create the various size for gestational age variables*	Birthweight: Continuous: (-8 to 6160) Gestational Age: Continuous 18 weeks and 3 days to 43 weeks and 2 days)	Birthweight: Continuous: (110-6160g) Gestational Age: Continuous (18-43 weeks) **Size for Gestational Age:** SGA: (<10th percentile of birthweight for gestational age) AGA**:** (10th to 90th percentiles of birthweight for gestational age) LGA: (>90th percentile birthweight for gestational age)
Multiple Gestations DELORDER MULTGEST DELIVNM	*twin*	The variable "DELORDER" allows for distinguishing between singletons and twins, and is coded as birth order/#born (i.e. a singleton would be entered as 1/1, and a set of twins would be entered as 1/2 and 2/2). Study inclusion criteria pre-specify	Binary: Singleton Twin	Binary: Singleton Twin

		that only twins and singletons will be studied.		
Fetal Sex SEX	*Fetsex1*	Sex at birth is recorded when available. Ambiguous, unknown and null entries in the database are treated as missing values in analyses.	Categorical (5): Female Male Ambiguous Unknown NULL	Binary: Male Female (Missing)
Preterm (Premature) Delivery GESTWK GESTDAY Gestage1	*Preterm*	Preterm or premature delivery is defined for this study as births prior to 37 weeks gestational age – following World Health Organization definitions (29). Variable Gestage1 (derived from GESTWK and GESTDAY) was used to derive the binary premature variable.	Continuous: 18-43 weeks	Binary: **Term ≥37 weeks *ref** Preterm <37 weeks

3.6 Data Cleaning Methods

Variables of interest were assessed for outliers, or implausible values, based on known biological ranges. Maternal BMI values were trimmed at values less than 16 and greater than 60, following clinical categorization of BMI. A lower limit for birthweight was set (110g) based on the lowest published value available in the chosen standards. Newborn gestational age was recorded as *'x weeks and y days'*, which was converted to a numeric value for analysis. The raw data provided had many "NULL" response options, which could potentially represent 'no response recorded', 'other', or 'unknown'. Any "NULL" entries in the database were treated as missing values in analyses.

3.7 Data Analysis

All analyses were carried out using SAS 9.4 (SAS Institute Inc., Cary, NC) software. Analyses were stratified by multiple gestations. Wald based hypothesis tests were two sided with a 5% type I error rate. Estimated crude and adjusted odds ratios, 95% Wald-based confidence intervals, and associated p-values were reported for all regression models.

3.7.1 Descriptive Statistics

Descriptive analyses were completed to determine pre-pregnancy, during pregnancy, birth and delivery related variables, and infant characteristics for mothers of singletons and mothers of twins. Analyses were carried out for the entire study sample, as well as categorized by multiple gestations, and

maternal BMI category. Means and standard deviations were reported for continuous variables. Counts and percentages (frequencies and proportions) were reported for levels of categorical variables. To assess differences between demographics of singletons and twins, the two sample t-test was used for continuous variables, and a two proportion z-test for categorical variables. To assess demographic differences between maternal BMI categories, one-way analysis of variance was used for continuous variables, and the chi squared test was used for categorical variables. Fisher's exact test was used when the chi-squared test was deemed inappropriate by the software.

3.7.2 Creation of the Outcome Variable – Size for Gestational Age

We required externally published values to create our outcome variable. Using the Robertson (2002) (1) Canadian birthweight for gestational age standard, we categorized singletons and twins into SGA, AGA, and LGA categories for further analyses.

The Robertson standard we used in our analyses consisted of approximately 556,000 singletons, and approximately 12,000 twin Albertan livebirths from 1985 to 1998. Similar exclusion criteria were applied in both studies, increasing our confidence in using these external values. Authors created a sex-specific birthweight for gestational age standard using the best clinical estimate of gestational age from 21 to 44 weeks based on early 2nd trimester ultrasounds. Curves were not smoothed with the rationale that both birthweight and gestational age data were highly accurate. Our choice of standard is further explored in the discussion and appendix sections.

3.7.3 Regression Analysis

Two different regression techniques were used to determine whether the association between maternal BMI and infant size for gestational age exists in the population of interest. A logistic regression model was used to analyze singleton birth data, and the Generalized Estimating Equations extension of logistic regression was used to analyze data from twin births, to account for the paired nature of twin data.

Within the singleton and twin groups, two distinct logistic or GEE regression models were carried out, comparing SGA infants to AGA infants, and comparing LGA infants to AGA infants. The reference categories for all regressions were the infants born to mothers with 'Normal' BMI.

These comparisons were made separately in both the singleton and twin groups. Both crude and adjusted analyses controlling for various maternal factors known to be associated with fetal growth and size related outcomes (based on the variables discussed in the Literature Review Chapter and reported in

table 3.1) were carried out. Variables such as inter-pregnancy interval, and plasma glucose levels (that were discussed in the literature review) were not included in analyses, as they were not present in the dataset. Section D in the appendix compares the ideal variables for this study to the actual variables available for analysis. The regression modelled the effect of maternal pre-pregnancy BMI category on infant size for gestational age, controlling for variables found in the literature review found to be potential confounders related to the current pregnancy only (parity, current diabetes, smoking, carbohydrate disorders, hypertensive disorders and preterm birth). Confounding variables were assessed for model fit following the guidelines in Vittinghof 2012 (410,411).

3.7.3.1 Generalized Estimating Equations Extension of Logistic Regression

Outcomes from twins tend to be correlated. To account for this correlation, the Generalized Estimating Equations (GEE) extension of Logistic Regression was used. The GEE method allows for a model to be fit to correlated outcomes data using a robust variance estimator to account for dependencies between twins (412,413).

3.7.4 Interaction Analysis

To assess whether multiple births modify the association between maternal pre-pregnancy BMI and infant size for gestational age, two separate models were run, assessing how multiple births modifies the odds of SGA, and the odds of LGA in the sample. Since singletons and twins were combined for this analysis, the GEE logistic regression extension will be used to account for correlated twin outcomes. The interaction term “BMI*twin” was included to assess whether an interaction was present. Underweight mothers were not included in this analysis as we did not have any underweight mothers that gave birth to LGA twins (and these “zero cells” prevented overall model convergence).

4 Chapter 4 – Results

4.1 Study Sample

We requested births recorded in the LHSC/SJHC Perinatal Database from June 1st 2006 to August 31st 2018. Births were excluded from provided data for failing to meet the following inclusion criteria: maternal age <18y or >45y at birth, higher order births (i.e. triplets and higher multiples), stillbirths, congenital or chromosomal abnormalities, and significant missing outcome or exposure data, for either mother or infant. These criteria were applied externally by the Decision Support office located at Victoria Hospital where the data are housed. A total of 32,144 infants (30,686 singleton infants and 729 pairs of twins) with full maternal pre-pregnancy BMI and infant birthweight for gestational age data were provided for inclusion in the study. An additional 34 pairs of twins (68 infants) were excluded due to a matched twin having missing data, leaving 695 pairs of twins or 1390 infants for further analyses, and a new study sample size of 32076 infants. Lastly after applying the Robertson standard to the study population, and removing individuals with omitted maternal BMI values, 30396 singletons and 1346 twin infants, for a total of 31742 infants, were available for analysis. The Robertson standard only reported percentiles for the 21st to 44th weeks of gestational age, whereas births in the study population ranged from the 19th to 43rd weeks of gestational age. A flow chart is provided (figure 4.7 below) outlining how the final sample size for this study was achieved.

4.2 Description of Mothers in the Study Population

Maternal variables are reported in table 4.1 below. The distribution of pre-pregnancy BMI classes was similar between mothers of singletons and twins. Maternal pre-pregnancy 'Normal' and 'Overweight' BMI were similar between mothers of singletons and twins (50% had 'Normal' BMI, and 23% had 'Overweight' BMI). Twenty percent of mothers of singletons were 'obese', whereas approximately 24% of mothers of twins were 'obese' pre-pregnancy. Mothers in the study sample were on average aged 30 (singletons) and 31 (twins). Greater than 55% of mothers were multiparous.

Fourteen percent of mothers reported smoking, and about 10% reported any drug use during the current pregnancy. Less than 2% of all mothers in the study population had diabetes in the current pregnancy. Maternal carbohydrate disorders were more prevalent (almost doubled) in twin pregnancies (9.6%) as compared to in singleton pregnancies (5.6%). Maternal hypertensive disorders (chronic

hypertension, gestational hypertension, eclampsia, and pre-eclampsia) were also more prevalent in twin pregnancies (17.7%) as compared to singleton pregnancies (7.2%). It is important to note that these data are based on patient self-reports and may be subject to inaccurate recall or bias.

4.3 Birth and Delivery, and Infant Variables

Birth and delivery and infant variables are presented in table 4.2 below. Singletons had higher birthweights than twins in this study population. Males had higher birthweights than females in both singletons and twins. Consistent with the literature, twins were, on average, born 4 weeks earlier than singletons, (414). About 50% of twins were born preterm.

4.4 Outcome Variable: Birthweight for Gestational Age

Infant birthweight for gestational age was assigned using Robertson (2002) published values and assessed separately in singleton and twin populations. Table 4.3 below reports size for gestational age distributions by fetal sex in singletons and twins. When size for gestational age was assigned using Robertson (2002) values, 30396 singletons met conditions (i.e. fell within the reported gestational ages (21-44w) available in the Robertson published standard, and were born to mothers with BMI values within the specified range) to be classified; of these, 10.0% (3052) of singletons were categorized as SGA, 79.6% (24193) of singletons were AGA, and 10.4% (3151) of singletons were LGA. In twins, 1346 infants met the criteria to be classified; of these, 11.4% (154) were categorized as SGA, 79.1% (1064) were AGA, and 9.5% (128) were LGA. By definition, approximately 10% of infants should be SGA, 80% AGA and 10% LGA. The Robertson singleton and twin standards very closely approximate the theoretical distribution of size for gestational age categories.

Table 4.4 below reports size for gestational age distributions by maternal obesity category in singletons and twins, stratified by sex. When stratified by sex, the size for gestational age measure retains, on average, the 10-80-10 distribution described earlier, which was as expected, due to the Robertson distribution being sex-specific.

4.5 Associations Between Maternal BMI and Infant Size for Gestational Age

4.5.1 Overall Findings

The unadjusted relationship between maternal pre-pregnancy BMI and the risks of SGA and LGA, as estimated by univariable regression, are presented in table 4.5, and these relationships adjusted for covariates, as estimated by multivariable regression, are presented in table 4.6, and in appendix G. Odds of infants being born small or large for gestational age vary by both level of maternal pre-pregnancy obesity, and by multiple pregnancy. Adjustment for chosen covariates (parity, current diabetes, smoking, hypertensive disorders, carbohydrate disorders, and preterm birth) did not alter the overall pattern of odds of being small or large for gestational age.

There may be evidence of a dose response relationship between increasing maternal pre-pregnancy BMI and increasing odds of LGA. This relationship does persist both before and after adjustment for relevant covariates, for both singleton and twin populations. As this was not a main focus of this thesis, we did not explore this further.

4.5.2 Small for Gestational Age

Overall, increased maternal pre-pregnancy BMI is associated with decreased odds of giving birth to an SGA infant, with this association achieving statistical significance for singleton pregnancies only.

4.5.3 Large for Gestational Age

Overall, increased maternal pre-pregnancy BMI is associated with increased odds of giving birth to a large for gestational age infant, and this association achieved statistical significance for both singleton and twin pregnancies. The twin findings for both small and large for gestational age appear to be in the same direction as for the singletons, although sample sizes preclude estimating the relationships with precision.

4.5.4 Predictor Variables

The full multivariable regression model results are presented in appendix G. The final multivariable model comprised of variables explored in the literature review for which there were sufficient sample sizes (i.e. no "zero cells") across each category of maternal pre-pregnancy BMI for both singletons and twins. Additionally, only variables related to the current pregnancy were considered in these analyses. Overall, the effects of predictor variables on infant odds of SGA or LGA appeared to vary between singleton and twin pregnancies. The variables smoking, hypertensive disorders and preterm birth overall contributed to infant SGA and the variables parity, diabetes and carbohydrate disorders overall contributed to infant LGA. Given that the main purpose of inclusion of these variables was to control for potential confounding, the individual variables' relationships to SGA and LGA are not discussed further below, but are presented in Appendix G.

4.5.5 Adjusted models – Singletons

Table 4.6 below reports odds of being small or large for gestational age, for singletons and twins, adjusted for variables discussed in the literature review and methods chapters. Adjustment for chosen variables did not change the overall relationship between maternal pre-pregnancy BMI and infant SGA or LGA. In singletons, increased maternal pre-pregnancy BMI is associated with decreased odds of being born SGA both before and after adjustment for covariates. Underweight mothers had the highest odds, and Obese Class II mothers had the lowest odds of giving birth to SGA singletons. Increased maternal pre-pregnancy BMI is associated with increased odds of being born LGA both before and after adjustment for covariates. Obese Class III mothers had the highest odds and Underweight mothers had the lowest odds of giving birth to an LGA singleton.

4.5.6 Adjusted Models – Twins

In twins, there was generally no statistically significant association between increased maternal pre-pregnancy BMI and decreased odds of being born SGA, before or after adjustment for relevant confounders. Obese class III mothers had the lowest odds of giving birth to an SGA twin. In twins, as maternal pre-pregnancy BMI increased, odds of being born LGA also increased, both before and after adjustment for relevant confounders, and the overall association was found to be statistically significant.

Obese Class III mothers had the highest odds of giving birth to an LGA twin. Significance was not reached for many of the twin comparisons, potentially due to the small sample size available for analysis.

4.6 Influence of Multiple Births on the Association of Pre-pregnancy BMI and Infant Size for Gestational Age

Further analyses were carried out to determine whether a statistical interaction was present in our population. Overall, we did not find evidence to suggest that multiple births modified the association between pre-pregnancy BMI and infant size for gestational age. Adjustment for chosen variables (parity, current diabetes, smoking, hypertensive disorders, carbohydrate disorders, and preterm birth) did not change this relationship.

Multiple births did not modify the association between pre-pregnancy BMI and odds of infant SGA in this population *(crude: p=0.29; adjusted: p=0.41).* Multiple births also did not modify the association between pre-pregnancy BMI and infant LGA in this population *(crude: p=0.07; adjusted: p=0.26).*

Table 4. 1 Maternal Variables Stratified by Singleton and Twin

	Singleton N= 30686	**Twin N=1390**	**P-value***
Pre-Pregnancy Related Variables			
Pre-Pregnancy BMI (kg/m^2) *n (%)*			
Underweight: (16.0 -18.49)	1471(4.79%)	35 (2.52%)	<0.0001
Normal: (18.5-24.99)	15614 (50.9%)	692 (49.8%)	
Overweight: (25.0 -29.99)	7182 (23.4%)	320 (23.0%)	
Obese Class I: (30.0 -34.99)	3502 (11.4%)	195 (14.0%)	
Obese Class II: (35.0-39.99)	1580 (5.15%)	89 (6.40%)	
Obese Class III: (40.0-60.0)	1139 (3.71%)	56 (4.03%)	
'Omitted' values:(16.0> BMI <60.0)	198 (0.65%)	3 (0.22%)	
Maternal Age (years) *mean (SD)*	30.2 (5.2)	31.2 (5.1)	<0.0001
Parity *n (%)*			0.16
≥1	17587 (57.3%)	770 (55.4%)	
Pregnancy Related Variables			
Any Smoking During Pregnancy			0.03
Yes	4402 (14.3%)	193 (13.8%)	
No	26154 (85.3%)	1187 (85.5%)	
Missing	130 (0.42%)	10 (0.72%)	
Any Alcohol During Pregnancy			0.002
Yes	812 (2.65%)	19 (1.4%)	
No	29874 (97.4%)	1371 (98.6%)	
Any Drug Use During Pregnancy			0.41
Yes	3088 (10.1%)	149 (10.7%)	
No	27598 (89.9%)	1241 (89.3%)	
Cocaine Use During Pregnancy			0.46
Yes	96 (0.31%)	6 (0.43%)	
No	30584 (99.7%)	1384 (99.6%)	
Missing	6 (0.02%)	0 (0.0%)	
Marijuana Use During Pregnancy			0.008
Yes	777 (2.53%)	20 (1.44%)	
No	29903 (97.5%)	1370 (98.6%)	
Missing	6 (0.02%)	0 (0.0%)	
Prescription Drug Use During Pregnancy			<0.0001
Yes	11047 (36.0%)	672 (48.4%)	
No	19633(63.9%)	718 (51.7 %)	
Missing	6 (0.02%)	0 (0.0%)	
Current (pre-existing) Diabetes			0.34
Yes	355 (1.16%)	20 (1.44%)	
No	30325 (98.8%)	1370 (98.6%)	

Missing	6 (0.02%)	0 (0.0%)	
Carbohydrate Disorders			
Yes	1706 (5.56%)	134 (9.64%)	<0.0001
No	28977 (94.4%)	1256 (90.4%)	
Missing	3 (0.01%)	0 (0.0%)	
Hypertensive Disorders			
Yes	2199 (7.2%)	246 (17.7%)	<0.0001
No	28251 (92.1%)	1108 (79.7%)	
Missing	236 (0.8)	36 (2.6%)	

**Two tailed Students t-test, Fishers exact test (2-group comparisons) or Pearson chi square (categorical comparisons) p-values are reported*

***Maternal BMI values >16.0 and <60.0 kg/m^2 were omitted from regression analyses due to low sample size*

Note: Column percentages are reported

Note: 'missing' values are reported when available- variables without any 'missing' are assumed to have no "missingness"

Table 4. 2 Birth, Delivery and Infant Variables Stratified by Singleton and Twin

	Singleton N= 30686	Twin N=1390	Total N=32076	P-value *
Birth and Delivery Related Variables				
Placenta Previa *Yes* *No* *Missing*	 116 (0.38%) 30263 (98.6%) 307 (1.0%)	 2 (0.14%) 1368 (98.4%) 20 (1.44%)	 118 (0.37%) 31631 (98.6%) 327 (1.02%)	0.16
Infant Variables				
Sex *n (%)* *Female* *Male* *Unknown* *Ambiguous* *Missing*	 15006 (48.9%) 15619 (50.9%) 10 (0.03%) 2 (0.01%) 49 (0.15%)	 662 (47.6%) 725 (52.1%) 0 (0.0%) 0 (0.0%) 3 (0.21%)	 15668 (48.8%) 16344 (50.9%) 10 (0.03%) 2 (0.0%) 52 (0.16%)	0.37
Birthweight (g) *mean (SD)* *Female* *Male* *n= 32027*	 3332 (572) 3449 (594)	 2302 (601) 2387 (634)	 3288 (610) 3401 (635)	<0.0001
Gestational Age (weeks) *mean (SD)*	 39.3 (2.1)	 35.4 (3.1)	 39.1 (2.2)	<0.0001
Preterm *n (%)* *<37 weeks* *≥37 weeks*	 1756 (5.72%) 28930 (94.3%)	 705 (50.7%) 685 (49.3%)	 2461 (7.7%) 29615 (92.3%)	<0.0001

**Two tailed Students' T test (2 group means), Fishers exact Test (binary) and Pearson Chi-square test (categorical) derived p-values are reported*

Note: Column percentages are reported

Note: 'missing' values are reported when available- variables without any 'missing' are assumed to have no 'missingness'

Note: variation in sample size for birthweight is due to removal of implausible values – see methods (chapter 3)

Table 4. 3 Size for Gestational Age Category for Singletons and Twins – Stratified by Fetal Sex using the Robertson (2002) Standard *n (%)*

	Singleton N= 30396	**Twin N=1346**
Size for gestational age -Female		
SGA	1513 (10.2)	73 (11.4)
AGA	11772 (79.0)	496 (77.9)
LGA	1607 (10.8)	68 (10.7)
Size for gestational age – Male		
SGA	1539 (9.9)	81 (11.4)
AGA	12421 (80.1)	568 (80.1)
LGA	1544 (10.0)	60 (8.5)
Size for Gestational age – Total		
SGA	3052 (10.0)	154 (11.4)
AGA	24193 (79.6)	1064 (79.1)
LGA	3151 (10.4)	128 (9.5)

Note: Column percentages are reported

Table 4. 4 Singleton and Twin Infant Size for Gestational Age by Maternal Pre-Pregnancy BMI category for Females and Males using the Robertson (2002) Standard *n (%)*

Maternal Pre-Pregnancy BMI Category	Size for Gestational Age	Singleton N= 30396	Singleton Female n=14892	Singleton Male n=15504	Twin N=1346	Twin Female n=637	Twin Male n=709
	Underweight *SGA* *AGA* *LGA*	294 (20.0) 1138 (77.5) 36 (2.5)	153 (20.7) 567 (76.7) 20 (2.7)	141 (19.4) 571 (78.4) 16 (2.2)	*n/a**	*n/a**	*n/a**
	Normal *SGA* *AGA* *LGA*	1718 (11.0) 12704 (81.6) 1154 (7.4)	872 (11.5) 6153 (80.9) 576 (7.6)	846 (10.6) 6551 (82.1) 578(7.3)	87 (12.7) 547 (79.5) 54 (7.85)	44 (13.4) 255 (77.7) 29 (8.8)	43 (11.9) 292 (81.1) 25 (6.9)
	Overweight *SGA* *AGA* *LGA*	588 (8.2) 5707 (79.7) 870 (12.1)	281(8.0) 2782(79.3) 444 (12.7)	307 (8.4) 2925 (79.9) 426 (11.7)	31 (9.69) 258 (80.6) 31 (9.69)	18 (11.8) 117 (76.5) 18 (11.8)	13 (7.8) 140 (84.3) 13 (7.8)
	Obese Class I *SGA* *AGA* *LGA*	258(7.4) 2692 (77.4) 530 (15.2)	107 (6.3) 1311(77.4) 277(16.3)	151 (8.5) 1381 (77.4) 253 (14.2)	22 (11.3) 157 (80.5) 16 (8.21)	7 (8.24) 71 (83.5) 7 (8.24)	15(13.6) 86 (78.2) 9 (8.2)
	Obese Class II *SGA* *AGA* *LGA*	105 (6.7) 1155 (73.3) 315 (20.0)	60 (7.4) 585 (72.5) 162 (20.1)	45 (5.9) 570 (74.2) 153 (19.9)	12 (13.6) 65 (73.9) 11 (12.5)	3 (7.69) 32 (82.1) 4 (10.3)	9 (18.4) 33 (67.3) 7 (14.3)
	Obese Class III *SGA* *AGA* *LGA*	89 (7.9) 797 (70.4) 246 (21.7)	40 (7.4) 374 (69.0) 128 (23.6)	49 (8.3) 423 (71.7) 118 (20.0)	2 (3.57) 38 (67.9) 16 (28.6)	1 (3.13) 21 (65.6) 10 (31.3)	1 (4.17) 17 (70.8) 6 (25.0)

**Note that Underweight mothers were omitted from analyses due to zero cells impeding model fit*

Table 4. 5 Unadjusted (Crude) Odds of Being Small or Large for Gestational Age by Maternal Pre-Pregnancy BMI Category in Singletons and Twins (Female and Male Combined) Using the Robertson (2002) Standard

		Singleton		Twin	
		OR *(95%CI)*	**P value**	**OR** *(95%CI)*	**P value**
Maternal BMI Category	**Small For Gestational Age**				
	Underweight	1.91(1.67-2.19)	<0.0001	n/a*	n/a*
	Normal	*Ref*	-	*Ref*	-
	Overweight	0.76 (0.69-0.84)	<0.0001	0.76 (0.49-1.17)	0.21
	Obese Class I	0.71 (0.62-0.81)	<0.0001	0.89 (0.52-1.51)	0.66
	Obese Class II	0.67 (0.55-0.83)	0.0002	1.16 (0.59-2.28)	0.66
	Obese Class III	0.83 (0.66-1.03)	0.09	0.32 (0.08-1.30)	0.11
	Large for Gestational Age				
	Underweight	0.35 (0.25-0.49)	<0.0001	n/a*	n/a*
	Normal	*Ref*	-	*Ref*	-
	Overweight	1.68 (1.53-1.84)	<0.0001	1.23 (0.72-2.12)	0.45
	Obese Class I	2.17 (1.94-2.42)	<0.0001	1.07 (0.58-1.97)	0.83
	Obese Class II	3.00 (2.61-3.45)	<0.0001	1.67 (0.77-3.65)	0.20
	Obese Class III	3.40 (2.91-3.97)	<0.0001	4.29 (2.25-8.19)	<0.0001

Two tailed Wald test derived p-values and confidence intervals are reported

**Note that Underweight mothers were omitted from analyses due to zero cells impeding model fit*

Wald chi-square p value: singletons (df=5) <0.0001 (SGA), <0.0001 (LGA); twins (df=4) 0.36 (SGA), 0.0003(LGA)

Table 4. 6 Adjusted Odds of Being Small or Large for Gestational Age by Maternal Pre-Pregnancy BMI Category in Singletons and Twins (Female and Male Combined) Using the Robertson (2002) Standard

		Singleton		Twin	
		OR *(95%CI)*	**P value**	**OR** *(95%CI)*	**P value**
Maternal BMI Category	**Small For Gestational Age**				
	Underweight	1.70 (1.47-1.96)	<0.0001	n/a*	n/a*
	Normal	*Ref*	-	*Ref*	-
	Overweight	0.76 (0.69-0.85)	<0.0001	0.78 (0.50-1.21)	0.26
	Obese Class I	0.65 (0.56-0.74)	<0.0001	0.91 (0.52-1.60)	0.75
	Obese Class II	0.62 (0.50-0.76)	<0.0001	1.12 (0.53-2.34)	0.77
	Obese Class III	0.67 (0.53-0.85)	0.001	0.38 (0.10-1.47)	0.16
	Large for Gestational Age				
	Underweight	0.37 (0.26-0.52)	<0.0001	n/a*	n/a*
	Normal	*Ref*	-	*Ref*	-
	Overweight	1.60 (1.46-1.76)	<0.0001	1.27 (0.73-2.21)	0.40
	Obese Class I	1.97 (1.76-2.21)	<0.0001	1.19 (0.64-2.20)	0.59
	Obese Class II	2.72 (2.35-3.14)	<0.0001	1.80 (0.84-3.87)	0.13
	Obese Class III	2.85 (2.42-3.36)	<0.0001	4.51 (2.29-8.86)	<0.0001

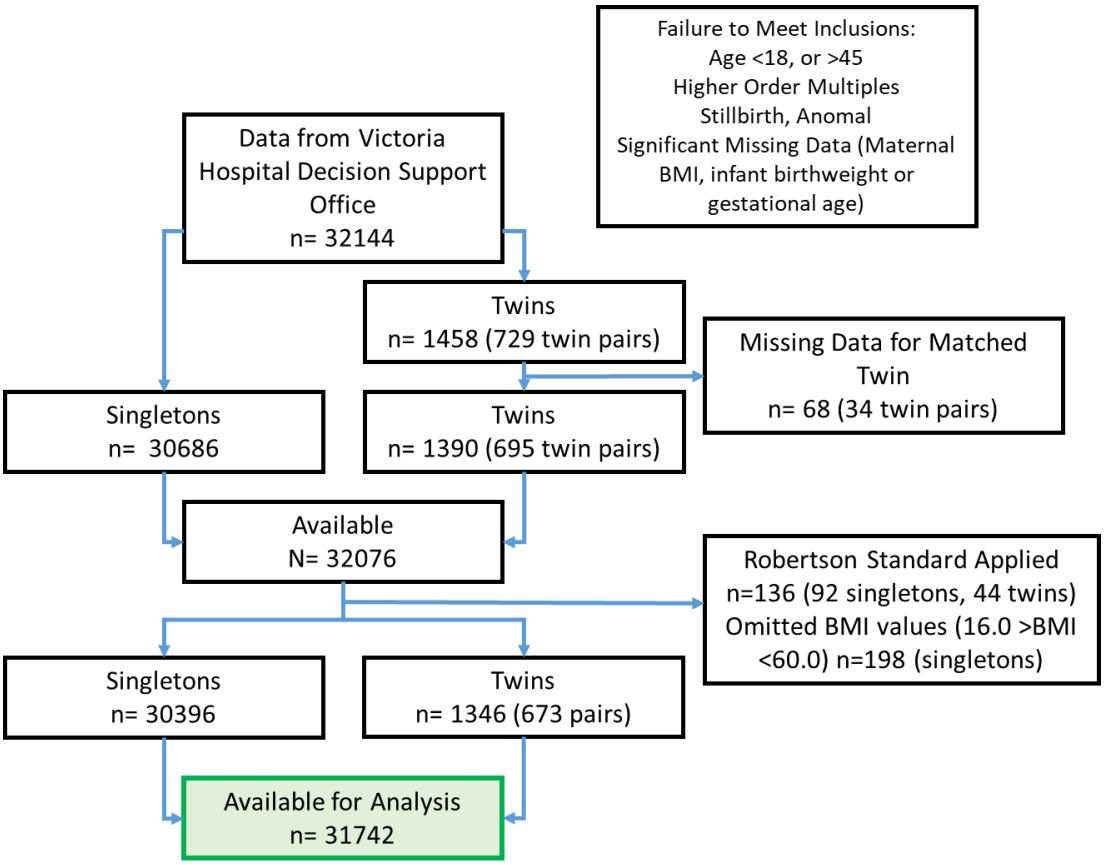
Two tailed Wald test derived p-values and confidence intervals are reported

Models are adjusted for mothers' parity, current diabetes, smoking, hypertensive disorders, carbohydrate disorders and preterm birth. A discussion of these variables can be found in the methods chapter

**Note that Underweight mothers were omitted from analyses due to zero cells impeding model fit*

Wald chi-square p value: singletons (df=5) <0.0001 (SGA), <0.0001 (LGA); twins (df=4) 0.50 (SGA), 0.0004(LGA)

Figure 4. 1 Study Sample Flow Diagram



5 Chapter 5 – Discussion

5.1 Overview

This study examined the relationship between maternal obesity and size for gestational age in twins in comparison to the well-established relationship in singletons in the London Ontario population. Although many studies to date have explored the role of maternal pre-pregnancy obesity on fetal growth, few studies have focussed specifically on the outcome of size for gestational age, and fewer still have extended focus to twin pregnancies. Our study adds updated and relevant information regarding the association of maternal BMI and twin growth. A strength of the study was the use of data from a common source population in London Ontario. These results contribute to the available body of literature by confirming what is already known about singleton growth, as well as adding to the growing body of knowledge on twin growth. Results also contribute to studies on Canadian birth populations, and emphasize the need for further Canadian-focused, and twin-focused work.

With this study, we aimed to determine the potential associations between maternal obesity and fetal size for gestational age in singleton and twin pregnancies. Specifically, we aimed to compare the odds of infant small or large for gestational age across clinical categories of maternal pre-pregnancy BMI, and to compare these odds in singleton and twin gestations.

We had initially hypothesized that an association would be found to be present between maternal BMI and infant size for gestational age. It was hypothesized that decreasing maternal BMI would be associated with decreasing size for gestational age, and increasing maternal BMI was hypothesized to be associated with increasing size for gestational age, and this association was expected to be stronger in singletons than in twins.

5.2 Interpretation of Findings

Overall, increased maternal BMI was found to be statistically significantly associated with decreased odds of giving birth to an SGA infant, for singleton pregnancies only. Although there was no significant association found for twins, it should be noted that sample sizes were small and confidence intervals around the estimates were large. We had expected to see evidence of an association between

increased maternal BMI and decreased odds of infant SGA and increased odds of infant LGA, in both singleton and twin groups. Since none of the twin associations were statistically significant, it is not possible to validly compare the strength of the associations between singletons and twins.

It was found that increased maternal BMI was associated with increased odds of giving birth to an LGA infant, for both singleton and twin pregnancies; this association did not attenuate appreciably after control for maternal diabetes or hypertensive disorders, suggesting a biologically independent effect remained that was not mediated through these pathways. For twins, associations did not reach statistical significance, with the exception of twins born to Obese Class III mothers. It should be noted that the twin findings do appear to be in the same direction as those for singletons, however, sample sizes preclude estimating the relationships with precision and also preclude valid comparison of the strengths of the associations in twins and singletons.

We had initially expected that singletons would have stronger associations than twins in part due to their growth in utero occurring in a 'simpler' environment. Twins have to share maternal energy resources in utero, and the mechanisms by which this occurs, as well as how factors such as chorionicity and amnionicity affect twin growth, are still being studied in humans (415). We were unable to compare singletons and twins due to the lack of statistical significance for most relationships estimated in twins. It is possible that the lack of an association in twins was due to large variation in the strength of the association (i.e. the explanation was not as simple as a 'weaker' association) due to the complicated nature by which placental nutrient transfer occurs in a multiple gestation. However, the main explanation is likely the substantially smaller sample size for twins as compared to singletons (we only had data on 1390 twins born over a 12-year period).

Visually, odds of LGA differed substantially between singletons and twins in our population when stratified by maternal obesity category. We conducted further analyses to determine whether multiple births were modifying this association between maternal pre-pregnancy BMI and infant size for gestational age. While the overall tests for interaction were not statistically significant, *(crude: BMI*twin: p= 0.29 (SGA), 0.07 (LGA); adjusted: BMI*twin: p= 0.41 (SGA), 0.26 (LGA))* odds of LGA in Obese Class I mothers were significant *(p=0.03)*. This did not persist after adjustment for chosen covariates *(p=0.1)*. As above, it is possible that the decreased twin sample size relative to singleton sample size (twins comprised about 4% of our total sample) may have contributed to this. Other explanations as to why we did not see evidence of a statistical interaction may be that the mechanisms that govern how

maternal pre-pregnancy BMI and size for gestational age are associated do not differ substantially between singleton and multiple gestations. To date, no studies have explored the role of multiple births in modifying the association between maternal pre-pregnancy BMI and infant size for gestational age. As such, it is difficult to make comparisons, or place these results relative to other literature in the field.

We considered the idea of maternal obesity being a 'protective factor' against the 'smallness' present in twins. As increasing maternal obesity contributes to fetal growth, it would lead to a right shift of the population birthweight curve (i.e. shift favouring increased birthweights), whereas the factor of multiple pregnancy would shift the population birthweight curve to the left (i.e. shift favouring decreased birthweights). However, because a twin-specific birthweight distribution was used to classify SGA and LGA in twins, the latter effect was accounted for in the study design. Therefore, we expected our results to reflect the effect of maternal BMI with control for the covariates available. Shifts in birthweight curves have also been described in relation to maternal smoking (416). Evidence does exist to suggest that gestational weight gain plays a strong role in determining size for gestational age in both singletons and twins. We suspect that having gestational weight gain data would have refined our results.

Our results are consistent with current literature (351,417–419) exploring the role of maternal BMI in relation to fetal growth in singletons. Few have explored this association in twins, and fewer studies still have compared both singletons and twins in one study. One such study, Hinkle et al. (2016) (420), aimed to determine the association between infant size for gestational age and mothers' pre-pregnancy BMI, and how this affected perinatal mortality in singletons. Similar to our study, Hinkle et al. determined that risk of SGA was decreased in mothers with increased BMI, and this was replicated using three different measures of infant size for gestational age (a population based reference, an estimated fetal weight based reference, and a customized reference based on maternal characteristics and fetal sex). Another study, Gaillard et al. (2013) (417), focused on both maternal pre-pregnancy obesity and gestational weight gain, as well as their risk factors, and reported that increased maternal obesity was associated with increased odds of giving birth to an LGA (singleton) infant (OR:2.97, 95%CI:2.16-4.08).

Fox et al. (2013) (23) explored the effects of maternal obesity on adverse outcomes in twin gestations only, however, this study did not focus on growth-related outcomes. Colletto et al. (2005) did study the effect of maternal BMI on twin anthropometric measures (360). Authors found no significant correlation between maternal pre-pregnancy BMI and newborn weight or BMI. Gestational weight gain, however, was found to be positively correlated with infant weight.

Lucovnik et al. (2014) (353) is one of the few studies that did compare singletons and twins within the same study, finding that maternal obesity increased risk of preterm births in both groups. However, no fetal growth related outcomes were explored. A recent study that was very similar to ours used the BORN Ontario database to assess the role of gestational diabetes on singleton and twin pregnancies (421). This study used the 2001 Kramer (singleton only) reference to assess size for gestational age in both singletons and twins in their study population. Authors used a modified Poisson regression with robust error variance to determine risk ratios for their outcome of interest, and similarly to our methods, the GEE method was used to account for twin non-independence. They hypothesized that gestational diabetes would have a protective effect against adverse pregnancy outcomes in twins, as compared to singletons. Authors found that gestational diabetes was associated with increased birthweight (>90th percentile) in both groups, with twins having 2 times higher risk than singletons. Due to their use of a singleton standard to assess twins, it is difficult to compare to our study.

Study Validity

Due to the theoretical 10-80-10 distribution of the size for gestational age measure used in our study, we were able to assess the suitability of the standard used to classify our outcomes. In particular, we would anticipate that approximately 10% of our population would be SGA and 10% LGA if the standard chosen was appropriate. This expectation was very closely approximated, across singletons and twins, and this distribution persisted when stratified by fetal sex. This indicates that the Robertson (2002) standard was a reliable external standard to use in our study.

Selection of this standard was done a-priori and based on the following criteria: Reporting birthweight in grams per gestational age in weeks, providing separate values for female and male infants, inclusion of live births only, and no estimated fetal weight values (i.e. no ultrasound values). Section F of the Appendix outlines the main standards reviewed and considered for this project. Based on our literature review, 5 studies (Robertson 2002, Kramer 2001, Joseph 2009, Arbuckle 1993, and Ghi 2017 (1,19,32,422,423)) were chosen for consideration. We decided to remove the Arbuckle study from consideration as the Kramer standard represents its updated version. However, the Kramer standard was deemed unsuitable for a different reason: it only reported singleton birthweight for gestational age percentiles. Our literature review determined that there was a need for separate singleton and twin standards. Ultimately, we decided to only use the Robertson (2002) standard because it incorporated the widest ranges of birthweights and gestational ages in their percentiles. Robertson (2002) reported values for singletons and twins, female and male, for 21-44 weeks gestational age. Joseph (2009) reported values for 36-42 weeks gestational age only, which would have decreased our sample size. The Joseph paper

also had maternal ethnicity based exclusion criteria, and were based on an American birth population, whereas the Robertson standard was Canadian (Alberta), and established inclusion and exclusion criteria similar to the ones in this study. Lastly, the Ghi (2017) study only reported 16-36 weeks gestational age, (the majority of births in the London cohort were ≥37 weeks) and while they specified twin chorionicity for their standards, they were not divided by fetal sex. As discussed elsewhere in this chapter, our ability to replicate the '10-80-10 distribution' of size for gestational age for both singletons and twins using an external standard solidifies the legitimacy of our decision to use this standard.

Hiersch et al. (2019) (421) used the Kramer 2001 Canadian standards to assess SGA and LGA in singletons and twins in their study, despite the fact that the Kramer standards were developed based on singletons. Their data demonstrate that this standard does not apply well to twins: singletons in the study approximated the '10-80-10' distribution for size for gestational age (SGA: 9.0 % (GDM group), 9.2% (non-GDM); LGA: 13.1% (GDM), 9.1 %(non-GDM)), whereas twins did not (SGA: 23.4% (GDM), 26.3% (non-GDM); LGA: 3.2% (GDM), 1.3% (non-GDM)). Authors make no comment on their use of a singleton standard to assess both singletons and twins.

Singleton standards have previously been used to assess multiple pregnancies (424), however, this method tends to result in a greater number of healthy twins being classified as SGA or growth restricted, especially at later gestational ages (425). Evidence exists to suggest that singleton anthropometric measurement charts may be more applicable to assess uncomplicated twin pregnancies (224,426) as compared to size for gestational age charts. Visual assessment of Robertson singleton percentile values and London population twin values suggests that a majority of twin births would be incorrectly classified, had we used a singleton size for gestational age measure to assess twins.

Our mean birthweights were within 5% of the mean birthweights recorded in the Robertson standard, which was based on a much larger population (singleton n=556,775; twin n=12125). However, since the differences were within 5%, it may confirm that selecting the Robertson standard was a valid approach to analysing this study population.

Hinkle 2016 (420) used an external standard to assess size for gestational age in their population (Hadlock et al. (1991) In utero analysis of fetal growth: A Sonographic Weight Standard (427)). They reported SGA rates ranging from 9.6 to 15.2% varying by the method used to calculate SGA (methods

used were a population based reference, an estimated fetal weight based reference, and a customized reference based on maternal characteristics and fetal sex). This paper analysed first born singletons only.

Studies such as Callaghan et al. (2010) and Dietz et al. (2009) (428,429) explored how different methods of calculating gestational age can affect the size for gestational age measure. Callaghan (2010) compared clinical, obstetric, last-menstrual-period (LMP) based, and 'gold-standard' (clinical or obstetric and LMP based estimates agree) based estimates, and suggested that size for gestational age can further vary depending on how gestational age in the measure is calculated. Authors suggested that LMP-based estimates were the most different, and may need to be revisited, especially when used in size for gestational age calculations. This may suggest that use of external standards is validated when the method of obtaining the gestational age is similar between source and analysis populations. Both our study and the Robertson study used a 'best estimate' based on a combination of ultrasound scan and last menstrual period to derive a gestational age.

It is important to note the conceptual limitations of using maternal BMI as our measure of maternal obesity. BMI, while useful, fails to detect subtle nuances in natural variations in human size. Specifically, BMI is a measure of relative weight, not body fat distribution, and therefore is unable to differentiate between varying body compositions (430,431). There is a subset of 'healthy obese' individuals who are likely being misrepresented as having high risk pregnancies. More 'direct' measures of obesity, such as bioelectrical impedance testing (432) were not available for use in this analysis.

5.3 Study Strengths

Strengths of this study include the use of retrospective cohort data from a large, single-population database. This allowed for a large singleton sample size, and comparatively large twin sample size.

We used an external outcome measure that was specific for singletons and twins – which allowed us to validly evaluate singleton and twin size for gestational age.

We also incorporated a unique statistical method to account for twin non-independence, the Generalized Estimating Equations (GEE) extension of logistic regression. Countless studies on twin pregnancies make no mention of accounting for the matched nature (non-independence) of twin data (433–438). Carlin et al. (2005) (413) recently published a review outlining various ways regression models can be applied to twin studies; GEE is one of the methods identified, which allows for a more

valid estimation of standard errors around the regression coefficients as compared to a basic logistic regression.

Another strength of our study was the comparison of singleton and twins from the same population in one study; while some studies do compare the two groups, the majority of studies tend to focus exclusively on singletons or exclusively on twins. As seen above, studies that do assess twin outcomes do not always use the best available statistical methods. Incorporating both groups into one study and using the appropriate statistical methods to analyze them allows for more valid findings.

5.4 Study Limitations

There were a few limitations we encountered during this project. This was a prospective study design but used retrospective data. Prospective data collection, while infeasible for a Masters Thesis project, would have allowed for greater control over variable measurement and collection, and would have allowed for greater diligence on prevention of missing values.

There were many important variables we did not have available to incorporate into our analyses due to limitations of the database. These included gestational weight gain, socio-economic status related variables, multiple children from one mother (presence of siblings), and types of twins (zygosity). Gestational weight gain is a particularly important missing variable. While the database does have a code for gestational weight gain, it does have data reflecting insufficient weight gain (coded as "weight gain less than 10 lbs)" and excess weight gain (coded as "weight gain greater than 20 kgs") and would not have contributed as meaningfully to analyses as a continuous variable would have. The medical records underlying the data entered into the database captured inadequate and excess weight gain separately, as two different "risk factors" and inconsistent measures (lbs and kgs) exist in the primary medical record. Numerous studies support the role of gestational weight gain as an important determinant of infant size for gestational age, in both singleton and twin pregnancies, perhaps even more so than pre-pregnancy BMI (439).

Other particularly important missing variables are measures of socio-economic status and/or maternal demographic characteristics. Evidence does exist to suggest that factors such as maternal race, and educational attainment can have some effect on fetal growth (19,440). We were unable to account for indicators of socioeconomic status, as many variables commonly used as proxies for SES were not collected in the SJHC/LHSC Perinatal database. Two potential SES proxy variables were collected in the dataset: marital status and mothers educational attainment. It was decided not to include marital status

based on suggestions that it may be a poor proxy for SES in modern times and is no longer the robust predictor of fetal health and growth that it was once considered to be. Numerous studies have explored the role of marital status on fetal growth related outcomes (441), finding that infants born to mothers in common law partnerships have similar outcomes to those born to married mothers. The other potential SES proxy, mothers' educational attainment, has very poor completion rates in the data source, and th missing data rate would prevent us from making valid conclusions about the entire maternal population studied.

We were unable to account for potential siblings in the dataset. As our data span 12 years and contains over 30,000 infants it is highly likely that siblings from other pregnancies to a shared mother exist in our analyses. This is an important factor to consider, as, just like twins, siblings represent a non-independent cluster of data.

Another factor we were unable to identify in our dataset was the specific type of twin (i.e.MC/DC, MA/DA, MZ/DZ (or, identical v. fraternal)). As explored in the literature review chapter, differences between twin types are significant enough to warrant stratifying them in our analyses. In fact, the Ghi (2017) standard published values stratified by chorionicity.

The self-reported nature of variables such as pre-pregnancy weight, smoking, alcohol use and drug use likely resulted in under-reporting. In some instances, self-report is the only available means of data collection. This has been documented in numerous studies(442–446).

In terms of conceptual limitations, it is important to note that accurate assessment of birth weight, size, or growth happens after birth. While ultrasound measurements can be taken, they are only estimates – ultrasound values were not available for this study. This limited our ability to use common formulas in the field, specifically, the Hadlock formulas for estimated fetal weight (427).

We discussed earlier in the literature review chapter how the size for gestational age measure can be useful in diagnosing at risk newborns. Ultimately, we were unable to make any statements about whether SGA/LGA individuals in our dataset were healthy, or whether their size was associated with adverse health effects. While the size for gestational age measure is interesting, its (clinical) utility lies in its ability to identify infants at risk for further adverse health outcomes. This, however, could be explored in future studies by incorporating adverse health outcomes.

5.5 Future Work and Conclusions

There are many potential avenues for future studies inspired by the work done in this thesis.

Changing trends in parental obesity (increasing obesity over time) and increasing birthweights and how these factors affect odds of infant SGA or LGA is another potential avenue to explore. A year to year comparison of changing odds of SGA/ LGA would have been interesting to explore, and would have been highly relevant to the ongoing 'obesity epidemic'. While this would have been possible in the singleton population, we likely did not have the sample size to accurately study this in twins.

There were many variables of interest unavailable for analysis in the current dataset. These include many measures of socioeconomic status, such as ethnicity, or income level. which may be useful to identify mothers who may be at higher risk of adverse birth/delivery related outcomes. Other missing variables that are of interest to the research question include gestational weight gain. Ideally the current dataset would start collecting more comprehensive information on gestational weight gain (i.e. actual amount of weight gained), however, this variable was not collected reliably in the records from which data were extracted for the database throughout the duration of the study period.

As discussed earlier, we did not have the means to identify potential siblings in the dataset. As the available data ranged from 2006-2018, it is very possible that one mother would have multiple birth events recorded in our dataset. Statistically, these siblings are non-independent, and would need to be analyzed using a method that accounts for this (such as the GEE approach used for twins). Understanding how fetal growth is affected by maternal body mass index in siblings would add to these results.

In conclusion, evidence from this study suggests that maternal BMI influences the growth of both singletons and twins. While the magnitude of the effect may differ for singletons and twins, we were unable to draw this conclusion. Although the study of twins increases the complexity of a study, tools do exist to make valid study of twins possible and our study is an example of this. Our study fills an important gap in knowledge not met by current literature, and adds to the growing body of knowledge on singleton and twin growth as affected by maternal obesity and factors comorbid with obesity. Overall, these results reiterate the idea that singletons and twins are different (from a statistical or methodological perspective), and should be treated as such. Studies continuing to compare these differences should be encouraged.

Appendices

A: Research Ethics Board Approval

B: Directed Acyclic Graphs

C: Sample Size Calculations

D: Ideal and Available Variables for Analysis

E: Considerations for Infant Size for Gestational Age

F: Current Infant Size for Gestational Age References and Standards

G: Predictors in the Multivariable Model

H: Interaction between Hypertensive Disorders and Maternal Pre-Pregnancy BMI

A: Research Ethics Board Approval

Western Research

Date: 12 July 2018

To: Barbra DeVrijer

Project ID: 111852

Study Title: The Association Between Maternal Obesity and Fetal Size for Gestational Age in Singletons and Twins

Application Type: HSREB Amendment Form

Review Type: Delegated

Meeting Date / Full Board Reporting Date: 07/Aug/2018

Date Approval Issued: 12/Jul/2018

REB Approval Expiry Date: 07/May/2019

Dear Barbra DeVrijer ,

The Western University Health Sciences Research Ethics Board (HSREB) has reviewed and approved the WREM application form for the amendment, as of the date noted above.

Documents Approved:

Document Name	Document Type	Document Date
111852_Data collection_July 5, 2018	Other Data Collection Instruments	05/Jul/2018

Documents Acknowledged:

Document Name	Document Type	Document Date
111852_Summary of Changes_July 5, 2018	Summary of Changes	05/Jul/2018

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Patricia Sargeant, Ethics Officer (ext. 85990) on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Western Research

Date: 21 September 2018

To: Barbra DeVrijer

Project ID: 111852

Study Title: The Association Between Maternal Obesity and Fetal Size for Gestational Age in Singletons and Twins

Application Type: HSREB Amendment Form

Review Type: Delegated

Meeting Date / Full Board Reporting Date: 02/Oct/2018

Date Approval Issued: 21/Sep/2018

REB Approval Expiry Date: 07/May/2019

Dear Barbra DeVrijer ,

The Western University Health Sciences Research Ethics Board (HSREB) has reviewed and approved the WREM application form for the amendment, as of the date noted above.

Documents Acknowledged:

Document Name	Document Type	Document Date
111852_Summary of Changes_Sept 10, 2018	Summary of Changes	10/Sep/2018

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

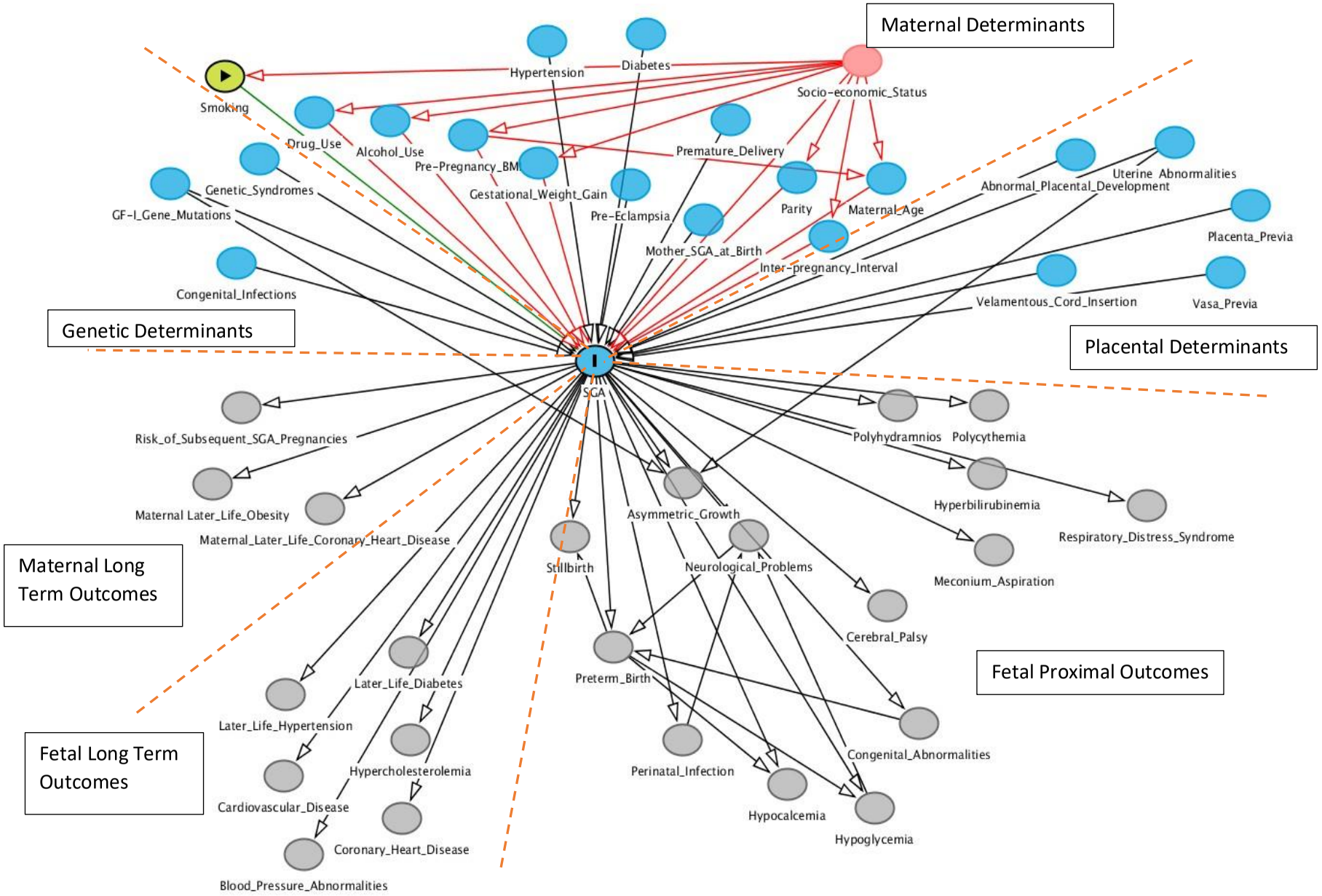
Please do not hesitate to contact us if you have any questions.

Sincerely,

Patricia Sargeant, Ethics Officer (ext. 85990) on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

B: Directed Acyclic Graphs


Maternal Determinants
Hypertension
Diabetes
Smoking
Socio-economic_Status
Drug_Use
Alcohol_Use
Pre-Pregnancy_BMI
Premature_Delivery
Gestational_Weight_Gain
Pre-Eclampsia
Parity
Maternal_Age
Genetic_Syndromes
GF-I_Gene_Mutations
Abnormal_Placental_Development
Uterine_Abnormalities
Placenta_Previa
Mother_SGA_at_Birth
Inter-pregnancy_Interval
Congenital_Infections
Velamentous_Cord_Insertion
Vasa_Previa
Genetic Determinants
Placental Determinants
SGA
Risk_of_Subsequent_SGA_Pregnancies
Polyhydramnios
Polycythemia
Maternal Later_Life_Obesity
Asymmetric_Growth
Hyperbilirubinemia
Maternal_Later_Life_Coronary_Heart_Disease
Respiratory_Distress_Syndrome
Maternal Long Term Outcomes
Stillbirth
Neurological_Problems
Meconium_Aspiration
Cerebral_Palsy
Later_Life_Diabetes
Preterm_Birth
Fetal Proximal Outcomes
Later_Life_Hypertension
Congenital_Abnormalities
Hypercholesterolemia
Perinatal_Infection
Fetal Long Term Outcomes
Cardiovascular_Disease
Hypocalcemia
Hypoglycemia
Coronary_Heart_Disease
Blood_Pressure_Abnormalities

C: Sample Size Calculations

Sample size (*n*) for logistic regression modelling the predictor variable maternal obese body mass index (BMI) vs 'normal' BMI on the prevalence (*p*) of infant small for gestational age (SGA) vs average for gestational age (AGA) in singletons was determined using the following formula from Vittinghoff (410):

$$\boldsymbol{n = \frac{(z_{1-\frac{\alpha}{2}} + z_{\gamma})^2}{\beta^2 * f(1-f) * p(1-p)}}$$

Sample size was estimated for the first objective with two tailed alpha value ($z_{1-\frac{\alpha}{2}}$) set at 0.05, and 80% power (z_{γ}). Sample size calculations are limited to a range of odds ratios (e^{β}**)** based on published data of SGA vs AGA in mothers with obese vs normal BMI (447). Prevalence of maternal obesity ranges from 10 to 20% in published data (448–450), while the prevalence of SGA ranges from 3 to 16% in published data (449–451). This comparison is anticipated to have the lowest sample size, therefore, the study will be sufficiently powered to examine other comparisons of maternal BMI on infant size for gestational age.

Sample Size for Singletons

For singletons, a minimum sample size of 18 to 1537 is determined based on the aforementioned range of conditions.

Prior studies using this dataset reported that the dataset contains approximately 41000 singleton births from 2001 to 2011(452).

Sample size for **singletons** modelling maternal BMI (exposure) comparing obese vs normal BMI, on the study outcome of infant size for gestational age comparing small vs average for gestational age:

Z-Alpha	Z- Power	Odds Ratio (e^{β})	F (prevalence of obesity)	P (marginal prevalence of SGA)	Sample size
1.96	0.84	0.25	0.106	0.164	368
1.96	0.84	0.25	0.106	0.115	496
1.96	0.84	0.25	0.106	0.034	1537
1.96	0.84	0.25	0.16	0.164	260
1.96	0.84	0.25	0.16	0.115	350
1.96	0.84	0.25	0.16	0.034	1084
1.96	0.84	0.25	0.2	0.164	218
1.96	0.84	0.25	0.2	0.115	294
1.96	0.84	0.25	0.2	0.034	911
1.96	0.84	0.595	0.106	0.164	184
1.96	0.84	0.595	0.106	0.115	248
1.96	0.84	0.595	0.106	0.034	769
1.96	0.84	0.595	0.16	0.164	130
1.96	0.84	0.595	0.16	0.115	175
1.96	0.84	0.595	0.16	0.034	542
1.96	0.84	0.595	0.2	0.164	109
1.96	0.84	0.595	0.2	0.115	147
1.96	0.84	0.595	0.2	0.034	455

1.96	0.84	0.86	0.106	0.164	108
1.96	0.84	0.86	0.106	0.115	146
1.96	0.84	0.86	0.106	0.034	452
1.96	0.84	0.86	0.16	0.164	76
1.96	0.84	0.86	0.16	0.115	103
1.96	0.84	0.86	0.16	0.034	319
1.96	0.84	0.86	0.2	0.164	64
1.96	0.84	0.86	0.2	0.115	86
1.96	0.84	0.86	0.2	0.034	268

Sample Size for Twins

For twins in objective one, the sample size (*n*) for a logistic regression modelling the predictor variable (*f*) maternal 'normal' body mass index (BMI) vs obese BMI on the prevalence of outcome (*p*) infant small for gestational age (SGA) vs average for gestational age (AGA) was determined using the following formula, derived from Vittinghoff (410). A design effect factor $(1 + (\mathrm{m}_0 - 1)$ and intraclass correlation coefficient *(ICC)* are included in the calculation to account for clustering of twin pairs, and the correlated nature of twin data.

$$\boldsymbol{n = (\frac{(z_{1-\frac{\alpha}{2}} + z_{\gamma})^2}{\beta^2 * f(1-f) * (p(1-p)}})(1 + (m_0 - 1)(ICC))$$

Mean cluster size is set at 2; clustering in this study is based on individual twin pairs. A range of estimated ICC values are tested. All other values are held consistent with calculations for singleton sample size.

For twins, a minimum sample size ranging from 80 to 3075 is required.

Sample size for **twins** modelling maternal BMI (exposure) comparing obese vs normal BMI, on the study outcome of infant size for gestational age comparing small vs average for gestational age:

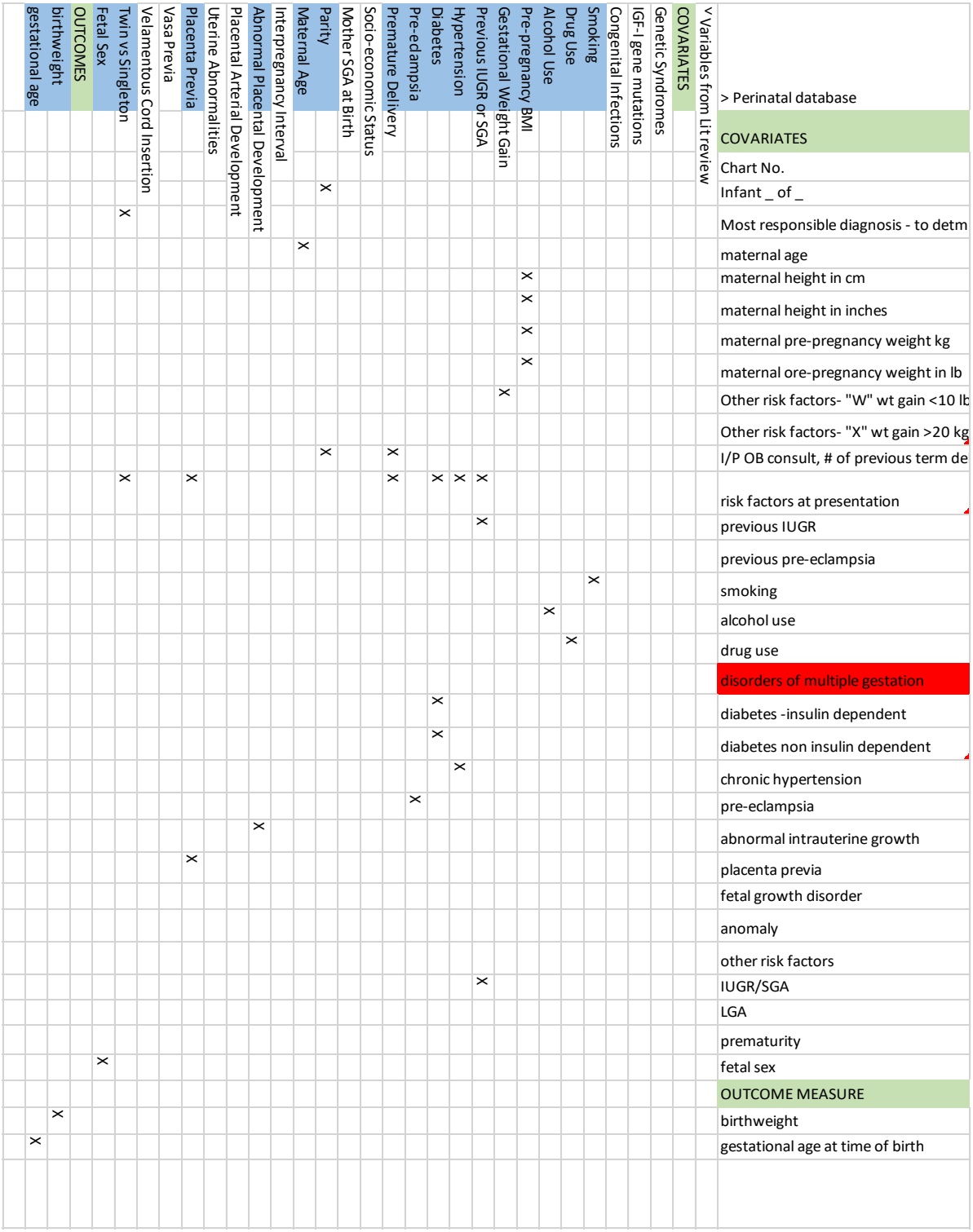
Alpha	**Power**	**Odds Ratio (beta)**	**F (prevalence of predictor)**	**P (marginal prevalence)**	**m_0 (Mean cluster size)**	**Estimated ICC**	**Sample Size**
1.96	0.84	0.25	0.106	0.164	2	0.25	460
1.96	0.84	0.25	0.106	0.115	2	0.25	620
1.96	0.84	0.25	0.106	0.034	2	0.25	1922
1.96	0.84	0.25	0.16	0.164	2	0.25	325
1.96	0.84	0.25	0.16	0.115	2	0.25	437
1.96	0.84	0.25	0.16	0.034	2	0.25	1355
1.96	0.84	0.25	0.2	0.164	2	0.25	273
1.96	0.84	0.25	0.2	0.115	2	0.25	367
1.96	0.84	0.25	0.2	0.034	2	0.25	1821
1.96	0.84	0.595	0.106	0.164	2	0.25	230
1.96	0.84	0.595	0.106	0.115	2	0.25	310
1.96	0.84	0.595	0.106	0.034	2	0.25	961
1.96	0.84	0.595	0.16	0.164	2	0.25	162
1.96	0.84	0.595	0.16	0.115	2	0.25	219

1.96	0.84	0.595	0.16	0.034	2	0.25	678
1.96	0.84	0.595	0.2	0.164	2	0.25	136
1.96	0.84	0.595	0.2	0.115	2	0.25	184
1.96	0.84	0.595	0.2	0.034	2	0.25	569
1.96	0.84	0.86	0.106	0.164	2	0.25	135
1.96	0.84	0.86	0.106	0.115	2	0.25	182
1.96	0.84	0.86	0.106	0.034	2	0.25	565
1.96	0.84	0.86	0.16	0.164	2	0.25	95
1.96	0.84	0.86	0.16	0.115	2	0.25	129
1.96	0.84	0.86	0.16	0.034	2	0.25	399
1.96	0.84	0.86	0.2	0.164	2	0.25	80
1.96	0.84	0.86	0.2	0.115	2	0.25	108
1.96	0.84	0.86	0.2	0.034	2	0.25	335
1.96	0.84	0.25	0.106	0.164	2	0.5	552
1.96	0.84	0.25	0.106	0.115	2	0.5	744
1.96	0.84	0.25	0.106	0.034	2	0.5	2306
1.96	0.84	0.25	0.16	0.164	2	0.5	390
1.96	0.84	0.25	0.16	0.115	2	0.5	525
1.96	0.84	0.25	0.16	0.034	2	0.5	1626
1.96	0.84	0.25	0.2	0.164	2	0.5	327
1.96	0.84	0.25	0.2	0.115	2	0.5	441
1.96	0.84	0.25	0.2	0.034	2	0.5	1366
1.96	0.84	0.595	0.106	0.164	2	0.5	276
1.96	0.84	0.595	0.106	0.115	2	0.5	372
1.96	0.84	0.595	0.106	0.034	2	0.5	1153
1.96	0.84	0.595	0.16	0.164	2	0.5	195
1.96	0.84	0.595	0.16	0.115	2	0.5	262
1.96	0.84	0.595	0.16	0.034	2	0.5	813
1.96	0.84	0.595	0.2	0.164	2	0.5	164
1.96	0.84	0.595	0.2	0.115	2	0.5	220
1.96	0.84	0.595	0.2	0.034	2	0.5	683
1.96	0.84	0.86	0.106	0.164	2	0.5	163
1.96	0.84	0.86	0.106	0.115	2	0.5	219
1.96	0.84	0.86	0.106	0.034	2	0.5	678
1.96	0.84	0.86	0.16	0.164	2	0.5	115
1.96	0.84	0.86	0.16	0.115	2	0.5	154
1.96	0.84	0.86	0.16	0.034	2	0.5	478
1.96	0.84	0.86	0.2	0.164	2	0.5	96
1.96	0.84	0.86	0.2	0.115	2	0.5	130
1.96	0.84	0.86	0.2	0.034	2	0.5	402
1.96	0.84	0.25	0.106	0.164	2	0.75	645
1.96	0.84	0.25	0.106	0.115	2	0.75	868
1.96	0.84	0.25	0.106	0.034	2	0.75	2690
1.96	0.84	0.25	0.16	0.164	2	0.75	454
1.96	0.84	0.25	0.16	0.115	2	0.75	612
1.96	0.84	0.25	0.16	0.034	2	0.75	1897
1.96	0.84	0.25	0.2	0.164	2	0.75	382
1.96	0.84	0.25	0.2	0.115	2	0.75	514
1.96	0.84	0.25	0.2	0.034	2	0.75	1594

1.96	0.84	0.595	0.106	0.164	2	0.75	322
1.96	0.84	0.595	0.106	0.115	2	0.75	434
1.96	0.84	0.595	0.106	0.034	2	0.75	1346
1.96	0.84	0.595	0.16	0.164	2	0.75	227
1.96	0.84	0.595	0.16	0.115	2	0.75	206
1.96	0.84	0.595	0.16	0.034	2	0.75	949
1.96	0.84	0.595	0.2	0.164	2	0.75	191
1.96	0.84	0.595	0.2	0.115	2	0.75	257
1.96	0.84	0.595	0.2	0.034	2	0.75	797
1.96	0.84	0.86	0.106	0.164	2	0.75	190
1.96	0.84	0.86	0.106	0.115	2	0.75	255
1.96	0.84	0.86	0.106	0.034	2	0.75	791
1.96	0.84	0.86	0.16	0.164	2	0.75	134
1.96	0.84	0.86	0.16	0.115	2	0.75	180
1.96	0.84	0.86	0.16	0.034	2	0.75	558
1.96	0.84	0.86	0.2	0.164	2	0.75	112
1.96	0.84	0.86	0.2	0.115	2	0.75	151
1.96	0.84	0.86	0.2	0.034	2	0.75	469
1.96	0.84	0.25	0.106	0.164	2	2.0	737
1.96	0.84	0.25	0.106	0.115	2	2.0	992
1.96	0.84	0.25	0.106	0.034	2	2.0	3075
1.96	0.84	0.25	0.16	0.164	2	2.0	519
1.96	0.84	0.25	0.16	0.115	2	2.0	700
1.96	0.84	0.25	0.16	0.034	2	2.0	2168
1.96	0.84	0.25	0.2	0.164	2	2.0	436
1.96	0.84	0.25	0.2	0.115	2	2.0	588
1.96	0.84	0.25	0.2	0.034	2	2.0	1821
1.96	0.84	0.595	0.106	0.164	2	2.0	368
1.96	0.84	0.595	0.106	0.115	2	2.0	496
1.96	0.84	0.595	0.106	0.034	2	2.0	1538
1.96	0.84	0.595	0.16	0.164	2	2.0	260
1.96	0.84	0.595	0.16	0.115	2	2.0	350
1.96	0.84	0.595	0.16	0.034	2	2.0	1084
1.96	0.84	0.595	0.2	0.164	2	2.0	218
1.96	0.84	0.595	0.2	0.115	2	2.0	294
1.96	0.84	0.595	0.2	0.034	2	2.0	911
1.96	0.84	0.86	0.106	0.164	2	2.0	217
1.96	0.84	0.86	0.106	0.115	2	2.0	292
1.96	0.84	0.86	0.106	0.034	2	2.0	905
1.96	0.84	0.86	0.16	0.164	2	2.0	153
1.96	0.84	0.86	0.16	0.115	2	2.0	206
1.96	0.84	0.86	0.16	0.034	2	2.0	638
1.96	0.84	0.86	0.2	0.164	2	2.0	128
1.96	0.84	0.86	0.2	0.115	2	2.0	173
1.96	0.84	0.86	0.2	0.034	2	2.0	536

D: Ideal and Available Variables for Analysis

Figure 6.6: Ideal Variables based on the literature review, vs variables available for analysis in the LHSC/SJHC perinatal database



E: Considerations for Infant Size for Gestational Age

Separate measures exist for singleton and twin births. These measures can either be standards or references; a population based standard only includes low risk "optimal" births, whereas a reference aims to include all births (i.e. abnormal birth outcomes are included in the development of the reference) (21). Standards and references have different utilities; a standard is useful in diagnosing abnormally grown infants, whereas a reference allows one to place the growth of the infant relative to the population from which the reference was derived (21). Authors of this paper suggest that greater clinical utility exists in growth standards, as compared to growth references.

Hutcheon and Platt (2007) recommend that birth weight for gestational age references and standards be developed using term births only – to account for the issue of missing birth weight data at extreme gestational ages, as well as the idea that infants born preterm may not necessarily be 'normal' pregnancies (33).

For this study, two options were considered to address/determine the fetal size for gestational age 'cut points'. One option is to use values from an already existing standard. Table 6.8a below outlines recent standards for singleton and twin populations. These values are commonly used by other studies, and using these values will allow for these results to be directly comparable to those in this study and others using this methodology. The second option was to determine 'internal' 10^{th} and 90^{th} percentile values for each gestational age for male and female infants, for singletons and for twins. These values would only apply internally and may allow for a good comparison of London population percentiles to the population level percentiles. However, this would be based on a smaller sample size (approx. 40 thousand) compared to the approximately 1 million infants used in the Kramer (32) standards.

Singleton standards have previously been used to assess multiple pregnancies (424), however, this method tends to result in a greater amount of healthy twins being classified as small for gestational age or growth restricted, especially at later gestational ages (425). Evidence exists to suggest that singleton anthropometric measurement charts may be more applicable to assess uncomplicated twin pregnancies (224,426) as compared to size for gestational age charts.

Customized vs. General standards/references

Standards and references can be customized to account for factors such as, but not limited to: maternal age, height, ethnicity, parity, pre-pregnancy BMI, and fetal sex. It is important to note that there is no

"best" way to develop a standard, however, there will be certain standards/references that will be better suited to the analyses being carried out in this thesis. The exclusion/inclusion criteria outlined below aim to address this. Studies such as the INTERGROWTH-21 project (453) have attempted to create an all encompassing, global reference, using ultrasound based measurements across 8 populations. Authors of this study suggest that a general standard is useful because less than 3.5% of growth variability can be explained by population-level differences (454). However drawbacks exist when using just one standard/reference for such a heterogeneous population (290), such as misclassification of infants at risk. Gardosi (2005) suggests that using an inappropriate standard has the potential to cause more harm to incorrectly identified babies (167). Hutcheon et al. used an interesting approach, using the concept of growth potential to create a simulated cohort of 'healthy' and 'growth restricted' newborns (where growth restriction was reproduced in the simulation by decreasing birthweights of 5% of the cohort from their 'optimal' value). They suggest that customized percentile charts offer minimal value over general ones, when identifying infants with IUGR(455) . Global references are not recommended by some authors (456).

Customization has the potential to allow for better diagnosis of infants that are small or large for gestational age due to a pathological condition (54,290), and many customized standards and references have been published recently. A 2001 Swedish birth study found that customized standards are better able to detect individuals at increased risk of adverse health outcomes such as stillbirth and neonatal death, as compared to a population based standard (60). Other studies have also replicated these findings (59,457,458). Growth curves customized for maternal factors (i.e. height, weight, parity, ethnicity and smoking status) have also proved beneficial in identifying large for gestational age births (459). Additionally, customization of growth standards can lead to a reduction in the rate of false positive diagnoses of growth restriction (458). One 2008 study, however, found that standards customized to maternal characteristics are no different from non-customized standards when using them to predict morbidity and mortality in the perinatal period (460). The NICHD Fetal Growth study found that significant differences in fetal growth exist across ethnicities in the United States, and thus support the need for customized standards and references (102). These findings have been replicated in global studies as well. Authors of the 2017 World Health Organization fetal growth charts argue that current standards and references are "of uncertain general applicability" due to source populations being mainly from high-income countries (461), and thus created a new reference including a variety of populations from 10 countries. The charts demonstrate high variability in birth weight across the populations studied and found evidence to suggest that parity, maternal age, height and weight and fetal sex can partially explain these differences in birthweight. The authors do suggest that adjustment of the charts to the local populations can improve applicability in terms of diagnostic and predictive ability (461). All of these

studies selected women with low risk pregnancies, without any health or environmental concerns or socioeconomic constraints. A 2006 French study sought to compare customized and general birth weight standards in their ability to determine infants at risk of being growth restricted. Using customised standards allowed for the identification of 2.7% of average for gestational age births that were reclassified to be small for gestational age. These reclassified small for gestational age infants were born to mothers with higher weight, height and parity, as compared to infants that were not reclassified (58). Numerous other studies support the use of customized charts to assess fetal growth (59,60,458,462). Customized charts have been shown to be effective in identifying at risk twins as well (463).

Criteria for using an external standard

For this study, certain criteria were set to choose the best possible standard/reference. These include: Reporting birthweight in grams per gestational age in weeks (i.e. no graphics), providing separate values for female and male infants, based on live births, no estimated fetal weights (i.e. no ultrasound values), needs to report twin values if possible, and needs the largest possible range of gestational ages (in weeks). Section 6.5 of the Appendix outlines the main studies considered for this project. Initially, studies 1-5 (Robertson 2002, Kramer 2001, Joseph 2009, Arbuckle 1993, and Ghi 2017) were considered for further analysis. As the project progressed, we decided to remove the Arbuckle study, due to the Kramer study being an updated version of it. Later, we also removed the Kramer study because it only reported singleton birthweight for gestational age percentiles. We had considered using the Kramer standard to assess both singletons and twins, however, our literature review determined that there was a need for separate singleton and twin standards, due to singleton standards being unable to accurately assess size for gestational age in twins (*this is discussed in the literature review chapter)*. Ultimately, we decided to only use the Robertson 2002 standard because it incorporated the widest ranges of birthweights and gestational ages in their percentiles. Robertson (2002) reported values for singletons and twins, female and male, for 21-44 weeks gestational age. Joseph (2009) reported values for 36-42 weeks gestational age only, which would have decreased our sample size. The Joseph paper also had maternal ethnicity based exclusion criteria, and were based on an American birth population, whereas the Robertson standard was Canadian (based in Alberta), and established inclusion and exclusion criteria highly similar to the ones in this study. Lastly, the Ghi (2017) study only reported 16-36 weeks gestational age, (the majority of births in the London cohort were ≥37 weeks) and while they specified twin chorionicity for their standards, they were not divided by fetal sex. As discussed in the results and discussion chapters, the fact that we were able to obtain the '10-80-10 distribution' of size for gestational age for both singletons and twins using an external standard solidifies the validity of our decision to use this standard.

F: Current Infant Size for Gestational Age References and Standards

	REFERENCE	POPULATION	METHODS	OUTCOMES
1	Robertson CMT, Svenson LW, Kyle JM. Birth weight by gestational age for Albertan liveborn infants, 1985 through 1998. J Obstet Gynaecol Can. 2002;24(2): 138–48.	Albertan live births from 1985 to 1998 -556,775 live born singletons -12,125 live born twins - data are from (from computerized livebirth and still birth registries from Alberta Registries- vital statistics- province of Alberta) <u>Exclusions:</u> -triplets and higher order gestations -individuals with missing birthweight or gestational age - gest age outside of range (22-44) GESTATIONAL AGE RANGE: 21-44 weeks TWINS INCLUDED?: Singletons and twins	-curves were not smoothed -Gestational age measured in completed weeks -Best estimate based on early second trimester ultrasound when possible, or first day of last menstrual period (LMP) otherwise. - Birth weight measured using a calibrated beam scale with non detachable weights – baby is nude for weighing -Weight is measured within 1 hr of birth	-Authors report 1st, 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th and 99th percentiles of birth weight for gestational ages for singletons, twins, males, females Authors provide separate references for singletons and twins but make no comment on the utility of separating births by twin status
2	Kramer MS, Platt RW, Joseph KS. A New and Improved Population-Based Canadian Reference for Birth Weight for Gestational Age. Pediatrics. 2001;108(613):5995.	All births in Canada from Jan 1 1994 through to Dec 31 1996 (excluding Ontario due to data quality) -data retrieved from "Canadian national linked live birth-infant death file" (linked file was chosen over the Canadian Birth Database because it allowed for identification and removal of duplicates) -Singletons only - no race data available -N= 347,570 males, 329,035 females GESTATIONAL AGE RANGE: 22-43 weeks TWINS INCLUDED?: Singleton only	-gestational age derived from early ultrasound based estimates, and was measured in completed weeks -gestational age errors and implausible values for gestational age corrected using a mixture distribution method Maximum likelihood estimates derived using estimation maximization algorithm to determine mean and SD to confirm recorded gestational ages -birthweight percentiles per gestational age created using a smoothing spline with 7 degrees of freedom -"bumps" in birthweight distribution (most likely due to misclassified data) were smoothed	-3rd, 5th, 10th, 50th, 90th, 95th, and 97th percentile birth weight for gestational age are reported for male and female singletons -"smooth monotonic curves with biologically sensible distributions at all gestational ages". -Authors recommend twins are treated under separate growth standards from singletons, due to different birthweight specific morbidities and mortality in twins and singletons -Percentile curves follow a sigmoid shape -LGA cutoff at low gestational age is lower than currently existing standards
3	Joseph KS, Fahey J, Platt RW, Liston RM,	All singleton and twin births at 36-42 weeks' gestational age in United States from 1995-2002 N= 17,811,922	-gestational age based on clinical estimate	-3rd, 10th, 90th and 97th percentiles are reported for females and males, singletons and twins.

	Lee SK, Sauve R, et al. An outcome-based approach for the creation of fetal growth standards: Do singletons and twins need separate standards? Am J Epidemiol. 2009;169(5):616–24.	Singletons : 17,554,934 Twins: 256,988 <u>Exclusions:</u> -non white, non black mothers -unknown sex, birthweight or gestational age -improbable birthweight for gestational age combinations -congenital anomaly (or birth in a state that does not report anomalies) -births ending in neonatal (<28 days) death -missing information -serious neonatal morbidity -all California births > (do not report clinical estimate of gestational age) GESTATIONAL AGE RANGE: 36-42 weeks TWINS INCLUDED?: Singleton and twin	-maximum likelihood methods to determine cutpoints (related to a separate objective) + slope -no smoothing techniques used	-authors also report upper and lower bounds of optimal birth weights (estimate and 95%CI) per gestational age, for males and females, singletons and twins. This outcomes based approach supports the need for separate standards for singletons and twins -authors **do not** recommend separating standards by race, education, parity, smoking, and maternal age
4	Arbuckle T, Wilkins R, Sherman G. Birth Weight Percentiles by Gestational Age in Canada. Obstet Gynecol. 1993;81(1): 39–48.	Over 1 million live births (singleton and twin) in Canada from 1986-1988 - N= 1,119,440 -data from computerized birth files (official vital statistics registrations of live births) - live births to Canadian residents only -data on congenital anomalies was not available. - no patient racial/ethnic background data available GESTATIONAL AGE RANGE: 22-44 weeks TWINS INCLUDED?: Singleton and twin	-self-reported gestational age in completed weeks was used (in Quebec, gestational age was physician reported) -Birth weights were rounded to the nearest 10 g - outliers were determined using birthweight relative to gestational age -percentiles calculated in SAS using the empirical distribution function with averaging	-1st, 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th, 99th percentiles of birthweight were reported for 22-44 weeks gestational age -percentiles are reported for male and female, singleton and twin -percentiles are provided in chart form – exact birth weights per gestational age are not reported (Authors did provide a table of birthweight per gestational age values via email request) -Authors report separate standards for singletons and twins -Authors suggest that references are updated every 5-10 years
5	Ghi T, Prefumo F, Fichera A, Lanna M, Periti E, Persico N, et al.	-1781 uncomplicated twin pregnancies sourced from 19 Italian birth centres - births from January 2010 to December 2015 1289 dichorionic (DC) twins + 492 monochorionic (MC) twins	-gestational age calculated using crown –rump length of larger twin using the Robinson and Fleming equation -chorionicity determined based on sonography results	-5th, 10th, 50th, 90th, 95th percentiles of birthweight for gestational age reported for singletons, dichorionic twins, and monochorionic,

	Development of customized fetal growth charts in twins. Am J Obstet Gynecol. 2017;216(5):514.e1-514.e17.	<u>Inclusions:</u> -uncomplicated twin pregnancy + known chorionicity -first trimester dating via crown-rump length -delivery ≥ 36 weeks <u>Exclusions:</u> -use of assisted reproductive technologies -structural or chromosomal anomalies -unknown/uncertain chorionicity -monoamniotic (MA) twins -fetal reduction -maternal smoking/drug use -maternal (pre-existing) hypertension, diabetes, renal disorders, autoimmune disorders -development of gestational diabetes or pre-eclampsia -twin pairs where one twin has a birth weight below the bottom fifth percentile GESTATIONAL AGE RANGE: 16-36 weeks TWINS INCLUDED?: Singleton and twin	-logarithmic transform of gestational age for model fitting	diamniotic twins. Only male values are reported -separate growth curves for DC and MC twins, and singletons were created for biparietal diameter, head circumference, abdominal circumference and estimated fetal weight -authors report different growth patterns between singletons and twins -differences were more significant in MC twins -authors support the use of customized charts, especially when diagnosing growth restricted infants -also support the use of charts customized by chorionicity when dealing with twins
6	Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States National Reference for Fetal Growth. Obstet Gynecol. 1996;87(2):163–8.	Singleton live births to American mothers in 1991 N= 3,134,879 GESTATIONAL AGE RANGE: 20-44 weeks TWINS INCLUDED?: Singleton only	Smoothing techniques (resistant non-linear technique – "4325H") used across gestational age categories -imputed gestational age when last day of menses is missing -implausible birth weight for gestational age combinations were trimmed using gestational age specific cutpoints	-authors report 5, 10, 50, 90, and 95th percentiles for 20-44 weeks (not-stratified by fetal sex)

10th and 90th birthweight for gestational age percentile values for singletons and twins, males and females

Reference 1: *Kramer MS, Platt RW, Joseph KS. A New and Improved Population-Based Canadian Reference for Birth Weight for Gestational Age. Pediatrics. 2001;108(613):5995*

Reference 2: *Robertson CMT, Svenson LW, Kyle JM. Birth weight by gestational age for Albertan liveborn infants, 1985 through 1998. J Obstet Gynaecol Can. 2002;24(2):138–48.*

Reference 3: *Joseph KS, Fahey J, Platt RW, Liston RM, Lee SK, Sauve R, et al. An outcome-based approach for the creation of fetal growth standards: Do singletons and twins need separate standards? Am J Epidemiol. 2009;169(5):616–24.*

Reference 4: *Ghi T, Prefumo F, Fichera A, Lanna M, Periti E, Persico N, et al. Development of customized fetal growth charts in twins. Am J Obstet Gynecol. 2017;216(5):514.e1-514.e17.*

Reference 5: *Arbuckle T, Wilkins R, Sherman G. Birth Weight Percentiles by Gestational Age in Canada. Obstet Gynecol. 1993;81(1):39–48.*

Table F.1: Singleton females 10th percentile

GEST AGE	Kramer(2001)	Robertson (2002)	Joseph (2009)	Ghi (2017)	Arbuckle (1993)
20	n/a	n/a	n/a	n/a	n/a
21	n/a	320	n/a	n/a	n/a
22	385	403	n/a	n/a	360
23	450	468	n/a	n/a	450
24	513	500	n/a	n/a	505
25	578	540	n/a	n/a	600
26	645	640	n/a	n/a	650
27	717	680	n/a	n/a	750
28	802	800	n/a	n/a	800
29	903	963	n/a	n/a	910
30	1022	1040	n/a	n/a	1030
31	1168	1177	n/a	n/a	1180
32	1346	1400	n/a	n/a	1350
33	1548	1542	n/a	n/a	1560
34	1768	1820	n/a	n/a	1770
35	1998	2000	n/a	n/a	1970
36	2227	2225	2255	n/a	2210
37	2452	2435	2466	n/a	2430
38	2658	2644	2665	n/a	2640
39	2825	2800	2835	n/a	2790
40	2955	2920	2930	n/a	2910
41	3051	3015	3040	n/a	3010
42	3114	3045	3062	n/a	3070
43	3159	2944	n/a	n/a	3070
44	n/a	2990	n/a	n/a	2960

Table F.2: Singleton females 90th percentile

GEST AGE	Kramer(2001)	Robertson (2002)	Joseph (2009)	Ghi (2017)	Arbuckle (1993)
20	n/a	n/a	n/a	n/a	n/a
21	n/a	500	n/a	n/a	n/a
22	552	616	n/a	n/a	600
23	669	720	n/a	n/a	700
24	790	790	n/a	n/a	855
25	918	950	n/a	n/a	920
26	1060	1051	n/a	n/a	1070
27	1218	1222	n/a	n/a	1220
28	1390	1453	n/a	n/a	1420
29	1578	1637	n/a	n/a	1560
30	1783	2045	n/a	n/a	1800
31	2004	2030	n/a	n/a	1980
32	2242	2375	n/a	n/a	2330
33	2494	2480	n/a	n/a	2550
34	2761	2820	n/a	n/a	2790
35	3037	3037	n/a	n/a	3030
36	3307	3340	3345	n/a	3360
37	3543	3530	3572	n/a	3520
38	3738	3720	3771	n/a	3710
39	3895	3860	3912	n/a	3860
40	4034	4000	4025	n/a	4000
41	4154	4115	4139	n/a	4130
42	4251	4190	4224	n/a	4200
43	4333	4276	n/a	n/a	4280
44	n/a	4291	n/a	n/a	4120

Table F.3: Singleton male 10th percentile

GEST AGE	Kramer(2001)	Robertson (2002)	Joseph (2009)	Ghi (2017)	Arbuckle (1993)
16	n/a	n/a	n/a	110	n/a
17	n/a	n/a	n/a	145	n/a
18	n/a	n/a	n/a	187	n/a
19	n/a	n/a	n/a	236	n/a
20	n/a	n/a	n/a	292	n/a
21	n/a	347	n/a	356	n/a
22	401	431	n/a	427	420
23	475	475	n/a	507	500
24	547	539	n/a	595	530

25	617	599	n/a	690	620
26	686	680	n/a	794	710
27	763	765	n/a	905	790
28	853	900	n/a	1024	880
29	964	996	n/a	1151	1000
30	1099	1214	n/a	1284	1150
31	1259	1219	n/a	1425	1250
32	1444	1469	n/a	1572	1460
33	1648	1690	n/a	1725	1630
34	1866	1874	n/a	1885	1850
35	2091	2100	n/a	2050	2070
36	2321	2310	2353	2220	2300
37	2552	2540	2570	n/a	2530
38	2766	2760	2778	n/a	2750
39	2942	2920	2948	n/a	2910
40	3079	3040	3033	n/a	3030
41	3179	3150	3175	n/a	3150
42	3222	3170	3202	n/a	3200
43	3249	3178	n/a	n/a	3220
44	n/a	3229	n/a	n/a	3150

Table F.4: Singleton male 90th percentile

GEST AGE	Kramer(2001)	Robertson (2002)	Joseph (2009)	Ghi (2017)	Arbuckle (1993)
16	n/a	n/a	n/a	155	n/a
17	n/a	n/a	n/a	206	n/a
18	n/a	n/a	n/a	267	n/a
19	n/a	n/a	n/a	338	n/a
20	n/a	n/a	n/a	421	n/a
21	n/a	612	n/a	515	n/a
22	587	630	n/a	620	630
23	714	733	n/a	738	770
24	844	881	n/a	866	850
25	981	970	n/a	1007	950
26	1125	1153	n/a	1159	1110
27	1278	1290	n/a	1321	1250
28	1445	1545	n/a	1495	1480
29	1629	1661	n/a	1678	1610
30	1837	1860	n/a	1871	1880
31	2069	2082	n/a	2073	2070
32	2319	2373	n/a	2283	2355

33	2580	2622	n/a	2501	2600
34	2851	2855	n/a	2726	2860
35	3132	3140	n/a	2957	3130
36	3411	3413	3463	3195	3450
37	3665	3655	3714	n/a	3640
38	3877	3865	3912	n/a	3860
39	4049	4012	4054	n/a	4010
40	4200	4174	4167	n/a	4170
41	4328	4300	4309	n/a	4310
42	4433	4370	4394	n/a	4420
43	4528	4476	n/a	n/a	4480
44	n/a	4392	n/a	n/a	4500

Table F.5: Twin female 10th percentile

GEST AGE	Kramer(2001)	Robertson (2002)	Joseph (2009)	Ghi (2017)	Arbuckle (1993)
20	n/a	n/a	n/a	n/a	n/a
21	n/a	n/a	n/a	n/a	n/a
22	n/a	267	n/a	n/a	n/a
23	n/a	358	n/a	n/a	n/a
24	n/a	495	n/a	n/a	n/a
25	n/a	592	n/a	n/a	n/a
26	n/a	580	n/a	n/a	n/a
27	n/a	673	n/a	n/a	n/a
28	n/a	442	n/a	n/a	930
29	n/a	972	n/a	n/a	850
30	n/a	1080	n/a	n/a	1050
31	n/a	1233	n/a	n/a	1230
32	n/a	1320	n/a	n/a	1370
33	n/a	1450	n/a	n/a	1560
34	n/a	1645	n/a	n/a	1610
35	n/a	1770	n/a	n/a	1810
36	n/a	1958	2040	n/a	1920
37	n/a	2165	2183	n/a	2120
38	n/a	2215	2296	n/a	2210
39	n/a	2327	2353	n/a	2330
40	n/a	2400	2325	n/a	2360
41	n/a	2340	n/a	n/a	2500
42	n/a	n/a	n/a	n/a	n/a
43	n/a	n/a	n/a	n/a	n/a
44	n/a	n/a	n/a	n/a	n/a

Table F.6: Twin female 90th percentile

GEST AGE	Kramer(2001)	Robertson (2002)	Joseph (2009)	Ghi (2017)	Arbuckle (1993)
20	n/a	n/a	n/a	n/a	n/a
21	n/a	n/a	n/a	n/a	n/a
22	n/a	677	n/a	n/a	n/a
23	n/a	605	n/a	n/a	n/a
24	n/a	863	n/a	n/a	n/a
25	n/a	878	n/a	n/a	n/a
26	n/a	970	n/a	n/a	n/a
27	n/a	1130	n/a	n/a	n/a
28	n/a	1200	n/a	n/a	1340
29	n/a	1497	n/a	n/a	1500
30	n/a	1631	n/a	n/a	1710
31	n/a	1833	n/a	n/a	1830
32	n/a	2079	n/a	n/a	2060
33	n/a	2179	n/a	n/a	2250
34	n/a	2430	n/a	n/a	2410
35	n/a	2620	n/a	n/a	2630
36	n/a	2865	2920	n/a	2820
37	n/a	3039	3085	n/a	3010
38	n/a	3200	3232	n/a	3230
39	n/a	3353	3290	n/a	3330
40	n/a	3532	3345	n/a	3490
41	n/a	3485	n/a	n/a	3460
42	n/a	n/a	n/a	n/a	n/a
43	n/a	n/a	n/a	n/a	n/a
44	n/a	n/a	n/a	n/a	n/a

Table F.7: Twin male 10th percentile

GEST AGE	Kramer(2001)	Robertson (2002)	Joseph (2009)	Ghi (2017)	Arbuckle (1993)
16	n/a	n/a	n/a	104	n/a
17	n/a	n/a	n/a	137	n/a
18	n/a	n/a	n/a	176	n/a
19	n/a	n/a	n/a	222	n/a
20	n/a	n/a	n/a	275	n/a
21	n/a		n/a	334	n/a
22	n/a	364	n/a	401	n/a
23	n/a	388	n/a	475	n/a

24	n/a	500	n/a	555	n/a
25	n/a	588	n/a	642	n/a
26	n/a	500	n/a	736	n/a
27	n/a	590	n/a	835	n/a
28	n/a	780	n/a	942	850
29	n/a	932	n/a	1053	1060
30	n/a	1126	n/a	1170	1180
31	n/a	1242	n/a	1291	1310
32	n/a	1403	n/a	1417	1440
33	n/a	1578	n/a	1547	1580
34	n/a	1710	n/a	1680	1730
35	n/a	1930	n/a	1816	1900
36	n/a	2065	2126	1955	2050
37	n/a	2225	2268	n/a	2180
38	n/a	2400	2381	n/a	2320
39	n/a	2440	2448	n/a	2390
40	n/a	2450	2466	n/a	2390
41	n/a	2528	n/a	n/a	2500
42	n/a	n/a	n/a	n/a	n/a
43	n/a	n/a	n/a	n/a	n/a
44	n/a	n/a	n/a	n/a	n/a

Table F.8: Twin male 90th percentile

GEST AGE	Kramer(2001)	Robertson (2002)	Joseph (2009)	Ghi (2017)	Arbuckle (1993)
16	n/a	n/a	n/a	145	n/a
17	n/a	n/a	n/a	191	n/a
18	n/a	n/a	n/a	246	n/a
19	n/a	n/a	n/a	310	n/a
20	n/a	n/a	n/a	384	n/a
21	n/a	n/a	n/a	469	n/a
22	n/a	574	n/a	565	n/a
23	n/a	662	n/a	671	n/a
24	n/a	750	n/a	789	n/a
25	n/a	967	n/a	919	n/a
26	n/a	1090	n/a	1059	n/a
27	n/a	1153	n/a	1211	n/a
28	n/a	1420	n/a	1375	1420
29	n/a	1614	n/a	1550	1600
30	n/a	1732	n/a	1735	1720
31	n/a	1920	n/a	1932	1900
32	n/a	2158	n/a	2139	2100

33	n/a	2392	n/a	2356	2360
34	n/a	2532	n/a	2582	2550
35	n/a	2780	n/a	2818	2780
36	n/a	2960	3033	3063	2950
37	n/a	3170	3204	n/a	3160
38	n/a	3354	3350	n/a	3380
39	n/a	3475	3459	n/a	3520
40	n/a	3588	3487	n/a	3570
41	n/a	3730	n/a	n/a	3890
42	n/a	n/a	n/a	n/a	n/a
43	n/a	n/a	n/a	n/a	n/a
44	n/a	n/a	n/a	n/a	n/a

G: Predictors in the Multivariable Model

The 'full' adjusted models are presented here with an overview of each variables individual effect on the outcome of infant odds of being small or large for gestational age. As the primary aim of this thesis was not to build an explanatory model, not every possible 'predictor' variable was included in the adjusted model. This was explored further in the discussion chapter. The final multivariable model comprised of variables explored in the literature review for which there were sufficient sample sizes (i.e. no "zero cells") across each category of Maternal pre-pregnancy BMI for both singletons and twins. Twin models were also more likely to have "zero cells" for potential covariates, again due to decreased sample sizes, which prevented the statistical software from generating confidence intervals or p-values for the calculated odds ratios. This is also why Underweight mothers were not used in the twin analyses. Important to note here is that the overall pattern of Odds Ratios by Maternal BMI category does not change considerably before and after adjustment. Increased maternal BMI is associated with decreased odds of giving birth to a small for gestational age infant, with this association achieving statistical significance for singleton pregnancies only, and increased maternal BMI is associated with increased odds of giving birth to a large for gestational age infant, and this association achieved statistical significance for both singleton and twin pregnancies. Overall, the effects of predictor variables on infant odds of small for gestational age or large for gestational age varied between singleton and twin pregnancies. The variables smoking, hypertensive disorders and preterm birth overall contributed to infant SGA and the variables parity, diabetes and carbohydrate disorders overall contributed to infant LGA

Predictor variables

Parity

Multiparity decreases the likelihood of SGA, and increases likelihood of LGA in singleton pregnancies only in this study population.

SGA

Compared to nulliparous mothers, multiparous mothers had 0.66x decreased odds of giving birth to a small for gestational age singleton. There was no evidence to suggest that increased parity was associated with odds of SGA in twins in this study population.

LGA

Compared to nulliparous mothers, multiparous mothers had 1.57x increased odds of giving birth to a large for gestational age singleton, holding maternal BMI and all other predictor variables constant. There was no evidence to suggest that increased parity was associated with odds of LGA in twins in this study population.

Current (pre-existing) Diabetes

Diabetes decreased likelihood of SGA, and increased likelihood of LGA in singleton pregnancies only in this study population.

SGA

There was no evidence to suggest an association between maternal diabetes and infant SGA in either singletons or twins in this study population.

LGA

Compared to non-diabetic mothers, diabetic mothers had 6.36x increased odds of giving birth to a large for gestational age singleton. There was no evidence to suggest an association between maternal diabetes and infant LGA in twins in this study population.

Smoking

Smoking increases likelihood of SGA and decreases likelihood of LGA in singletons only in this study population.

SGA

Compared to non smokers, smoking mothers have 2.25x increased odds of giving birth to a small for gestational age infant, holding maternal BMI and all other predictor variables constant. There was no evidence to suggest that an association between smoking and infant SGA exists in twins in this study population.

LGA

Compared to non smokers, smoking mothers have 0.62x decreased odds of giving birth to a large for gestational age infant, hold maternal BMI and all other predictor variables constant. There was no

evidence to suggest that an association between smoking and infant LGA exists in twins in this study population.

Hypertensive disorders

Maternal hypertensive disorders increase the likelihood of SGA in both singletons and twins in this study population.

SGA

Compared to healthy mothers, mothers with any hypertensive disorders have 2.03x increased odds of giving birth to a small for gestational age singleton, holding maternal BMI and all other predictor variables constant. This is slightly decreased in twin pregnancies; Compared to healthy mothers, hypertensive mothers have 1.59x increased odds of giving birth to a small for gestational age twin

LGA

There was no evidence to suggest that the associations between maternal hypertensive disorders and infant odds of being born large for gestational age were not significant in either singletons or twins.

Carbohydrate disorders

Carbohydrate disorders increased the likelihood of LGA in singletons in the study population.

SGA

There was no evidence to suggest that the association between maternal carbohydrate disorders and infant SGA was significant in either singleton or twin populations.

LGA

Compared to healthy mothers, mothers with carbohydrate disorders have 1.54x increased odds of giving birth to a large for gestational age singleton, holding maternal BMI and all other predictor variables constant. There was no evidence to suggest a significant association between carbohydrate disorders and LGA in twin pregnancies.

Preterm birth

Preterm birth increases odds of SGA, and decreases odds of LGA in singletons only, likely due to gestational age being a main component of the size for gestational age measure

SGA

Compared to term infants, preterm singletons have 1.33x increased odds of being small for gestational age holding maternal BMI and all other predictor variables constant. For twin pregnancies, there was no evidence to suggest that an association exists between preterm birth and odds of SGA.

LGA

Compared to term infants, preterm singletons have 0.61x decreased odds of being born large for gestational age. There was no evidence to suggest that the association between preterm births and LGA was significant in the twin populations.

POTENTIAL STATISTICAL CONFOUNDING

We also further explored why some odds changed significantly (i.e. greater than 10% change in odds, in either increasing or decreasing direction) after adjustment to determine if confounding was present in the models. Smoking (singletons), parity and hypertensive disorders (twins) may be potential confounders in the association between maternal obesity and infant small for gestational age. Maternal diabetes and carbohydrate disorders may be potential confounders in the association between maternal obesity and infant large for gestational age – in singletons only. There was no evidence of statistical confounding in the model testing the association of maternal obesity on twin odds of being large for gestational age. Note that the overall relationships between maternal pre-pregnancy BMI and infant small or large for gestational age do not change before and after adjustment, regardless of inclusions of potential confounding variables in the model.

Small for Gestational Age:

Singleton:

The odds of underweight mothers having an SGA singleton decreased from 1.91 to 1.70 (a decrease of 11%) after adjustment, and this was likely due to maternal smoking. (i.e. this was seen when maternal

smoking was entered into the model). The odds of obese class III mothers giving birth to an SGA singleton decreased by 19% from 0.83 to 0.67, likely due to the effect of adding maternal hypertensive disorders into the model.

Twins:

The odds of obese class III mothers of twins giving birth to an SGA twin increased from 0.32 to 0.38 (an increase of 19%), potentially due to the effect of adding maternal parity and hypertensive disorders into the model.

Large for Gestational age:

Singletons:

The odds of obese class III mothers having an LGA singleton were reduced significantly from 3.40 to 2.85 (a 16% decrease), and this was likely due to a combination of maternal diabetes and carbohydrate disorders. (i.e. this decrease was seen when maternal diabetes and carbohydrate disorders were entered into the model).

Twins:

No confounding is readily apparent in the twin LGA model for this study population.

Table G.a: Adjusted Odds of being Small for gestational age in singletons and twins using Robertson (2002) values – all covariates (male and female combined)

	Singleton		Twin	
	OR *(95%CI)*	**P value**	**OR** *(95%CI)*	**P value**
Maternal BMI				
Underweight	1.70 (1.47-1.96)	<0.0001	n/a*	n/a*
Normal	*Ref*	-	*Ref*	-
Overweight	0.76 (0.69-0.85)	<0.0001	0.78 (0.50-1.21)	0.26
Obese Class I	0.65 (0.56-0.74)	<0.0001	0.91 (0.52-1.60)	0.75
Obese Class II	0.62 (0.50-0.76)	<0.0001	1.12 (0.53-2.34)	0.77
Obese Class III	0.67 (0.53-0.85)	0.001	0.38 (0.10-1.47)	0.16
Covariates				
Maternal Pre-Pregnancy Variables				
Parity	0.66 (0.61-0.72)	<0.0001	0.81(0.54-1.21)	0.31
Current (Pre-existing) Diabetes	0.96 (0.60-1.55)	0.87	0.86 (0.19-3.81)	0.84
Pregnancy-related Variables				
Smoking	2.25 (2.05-2.46)	<0.0001	1.36 (0.81-2.30)	0.25
Hypertensive Disorders	2.03 (1.78-2.31)	<0.0001	1.59 (1.01-2.50)	0.04
Carbohydrate Disorders	1.01 (0.84-1.22)	0.91	0.77 (0.39-1.51)	0.45
Infant Variables				
Preterm Birth	1.33 (1.14-1.54)	0.0002	1.18 (0.80-1.73)	0.40

Two tailed Wald test derived p-values and confidence intervals are reported

**Note that Underweight mothers were omitted from analyses due to zero cells impeding model fit*

Wald chi-square p value: singletons (df=5) <0.0001 (SGA), twins (df=4) 0.50 (SGA),

Table G.b: Adjusted Odds of being Large for gestational age in singletons and twins using Robertson (2002) values – all covariates (female and male combined)

	Singleton		Twin	
	OR *(95%CI)*	**P value**	**OR** *(95%CI)*	**P value**
Maternal BMI				
Underweight	0.37 (0.26-0.52)	<0.0001	n/a*	n/a*
Normal	*Ref*	-	*Ref*	-
Overweight	1.60 (1.46-1.76)	<0.0001	1.27 (0.73-2.21)	0.40
Obese Class I	1.97 (1.76-2.21)	<0.0001	1.19 (0.64-2.20)	0.59
Obese Class II	2.72 (2.35-3.14)	<0.0001	1.80 (0.84-3.87)	0.13
Obese Class III	2.85 (2.42-3.36)	<0.0001	4.51 (2.29-8.86)	<0.0001
Covariates				
Maternal Pre-Pregnancy Variables				
Parity	1.57 (1.44-1.70)	<0.0001	1.33(0.84-2.12)	0.23
Current (Pre-existing) diabetes	6.36 (4.98-8.12)	<0.0001	1.36 (0.26-7.03)	0.71
Pregnancy-related Variables				
Smoking	0.62 (0.54-0.71)	<0.0001	0.49(0.23-1.02)	0.06
Hypertensive Disorders	1.11 (0.96-1.28)	0.15	1.05(0.61-1.83)	0.85
Carbohydrate Disorders	1.54 (1.34-1.76)	<0.0001	0.86(0.45-1.63)	0.64
Infant Variables				
Preterm Birth	0.61 (0.50-0.75)	<0.0001	1.20(0.79-1.84)	0.39

Two tailed Wald test derived p-values and confidence intervals are reported

**Note that Underweight mothers were omitted from analyses due to zero cells impeding model fit*

Wald chi-square p value: singletons (df=5) <0.0001 (LGA); twins (df=4) 0.0004(LGA)

H: Interaction Between Hypertensive Disorders and Maternal Pre-Pregnancy BMI

We also tested for a potential interaction occurring in the model. The interaction of maternal pre-pregnancy BMI and maternal hypertensive disorders on the odds of infant small for gestational age or large for gestational age were also explored, and there was no evidence of statistical interaction, for all comparisons, in either singletons or twins before and after adjustment for relevant confounders.

There is no evidence to suggest that in this study population, maternal hypertensive disorders influence the relationship between maternal obesity and infant size for gestational age.

Table H.a Odds of Singleton Small or Large for Gestational Age due to the Interaction of Maternal Pre-pregnancy BMI and Maternal Hypertensive Disorders - Crude

SGA Wald Statistics For Joint Tests For GEE			
Effect	**DF**	**Chi-Square**	**Pr > ChiSq**
Small for Gestational Age			
BMI	5	185.0558	<.0001
Hypertensive Disorders	1	87.3185	<.0001
BMI* Hypertensive Disorders	5	4.6956	0.4542
Large for Gestational Age			
BMI	5	478.0064	<.0001
Hypertensive Disorders	1	0.7515	0.3860
BMI* Hypertensive Disorders	5	7.5140	0.1851

Table H.b Odds of Singleton Small or Large for Gestational Age due to the Interaction of Maternal Pre-pregnancy BMI and Maternal Hypertensive Disorders - Adjusted

SGA Wald Statistics For Joint Tests For GEE			
Effect	**DF**	**Chi-Square**	**Pr > ChiSq**
Small for Gestational Age			
BMI	5	130.2384	<.0001
Hypertensive Disorders	1	72.9120	<.0001
BMI* Hypertensive Disorders	5	4.6859	0.4554
Large for Gestational Age			
BMI	5	367.4383	<.0001
Hypertensive Disorders	1	0.3414	0.5590
BMI* Hypertensive Disorders	5	7.6252	0.1781

Table H.c Odds of Twin Small or Large for Gestational Age due to the Interaction of Maternal Pre-pregnancy BMI and Maternal Hypertensive Disorders - Crude

SGA Wald Statistics For Joint Tests For GEE			
Effect	**DF**	**Chi-Square**	**Pr > ChiSq**
Small for Gestational Age			
BMI	4	2.42	0.6599
Hypertensive Disorders	1	2.32	0.1273
BMI* Hypertensive Disorders	4	2.60	0.6266
Large for Gestational Age			
BMI	4	11.90	0.0181
Hypertensive Disorders	1	0.32	0.5727
BMI* Hypertensive Disorders	4	4.94	0.2936

Table H.d Odds of Twin Small or Large for Gestational Age due to the Interaction of Maternal Pre-pregnancy BMI and Maternal Hypertensive Disorders - Adjusted

SGA Wald Statistics For Joint Tests For GEE			
Effect	**DF**	**Chi-Square**	**Pr > ChiSq**
Small for Gestational Age			
BMI	4	2.21	0.6980
Hypertensive Disorders	1	1.71	0.1906
BMI* Hypertensive Disorders	4	3.36	0.4991
Large for Gestational Age			
BMI	4	12.02	0.0172
Hypertensive Disorders	1	0.46	0.4957
BMI* Hypertensive Disorders	4	4.70	0.3200

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