Macrosomia and Related Adverse Pregnancy Outcomes: The Role of Maternal Obesity

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Abstract

Fetal overgrowth is associated with adverse outcomes for offspring and with maternal obesity. Results from a systematic review and meta-analysis showed that maternal obesity is associated with fetal overgrowth, defined as birthweight ≥4000g (OR 2.17, 95% CI 1.92, 2.45), birthweight ≥4500g (OR 2.77, 95% CI 2.22, 3.45) and birthweight ≥90%ile for gestational age (OR 2.42, 95% CI 2.16, 2.72). A retrospective cohort study revealed that mothers whose infants are macrosomic are more likely to require induction of labour (OR 1.42, 95% CI 1.10-1.98) and delivery by Cesarean section (OR 1.45, 95% CI 1.04-2.01), particularly for maternal indications (OR 3.7, 95% CI 1.47-9.34), if they are obese. Infants from these pregnancies are significantly more likely to require neonatal resuscitation in the form of free flow oxygen (OR 1.57, 95% CI 1.03, 2.42) than macrosomic infants of non-obese mothers. Thus, co-existing maternal obesity and macrosomia increases the risk of adverse pregnancy outcomes.

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3. SYSTEMATIC REVIEW

ABBREVIATIONS

Acronym	Full Form
BMI	Body Mass Index
OR	Odds Ratio
CI	Confidence Interval
CHMS	Canadian Health Measures Survey
LGA	Large for Gestational Age
IBR	Individualized Birthweight Ratio
UK	United Kingdom
GWG	Gestational Weight Gain
OGTT	Oral Glucose Tolerance Test
SGA	Small for Gestational Age
AGA	Average for Gestational Age
OR	Odds Ratio
CI	Confidence Interval
PPROM	Preterm Pre-labour Rupture of Membranes
TOLAC	Trial of Labour After Cesarean Section
NICU	Neonatal Intensive Care Unit
hsCRP	High Sensitivity C-Reactive Protein
MCP	Monocyte Chemotactic Protein
IGFBP	Insulin-like Growth Factor Binding Protein
QUORUM	Quality of Reporting of Meta-analyses
BORN	Better Outcomes Registry and Network
QA	Quality Assessment

1. INTRODUCTION

1.1 Background

The term macrosomia describes a newborn with an excessively high birth weight indicative of fetal overgrowth. Fetal overgrowth is typically identified in one of two ways. Most studies define macrosomia as a birth weight greater than or equal to 4000g, however others use 4500g as the cut-point.[3;4] There has been further interest in the group of infants whose birthweight exceeds 5000g.[5] We propose that macrosomia can be subdivided into Class I (birth weight 4000-4499g), Class II (4500-4999g) and Class III (≥5000g). Alternatively, fetal overgrowth can be defined as a birth weight greater than the 90th percentile, corrected for gestational age.[6]

Excessive growth in the fetus is a major contributor to adverse obstetrical outcomes. Smyth et al. examined the perinatal outcomes of 1842 macrosomic newborns in British Columbia, and identified significantly increased maternal risks of emergency Caesarean section, obstetrical trauma, postpartum hemorrhage and maternal diabetes (all outcomes had a p-value <0.001).[7] Further, the infants were at higher risk of having birth trauma, of needing resuscitation and of having an Apgar score less than seven at five minutes of life (p-values <0.001).[7] There is also evidence that macrosomia is associated with shoulder dystocia, brachial plexus injury, skeletal injuries, meconium aspiration, perinatal asphyxia, hypoglycemia and fetal death.[8] There is little doubt, based on existing literature, that fetal

macrosomia is associated with adverse pregnancy outcomes for both mother and infant. In addition, there is a recognized association between fetal macrosomia and long-term consequences for the newborn, including obesity, diabetes and heart disease.[9-22]

Determinants of macrosomia have also been studied extensively. Identified risk factors include maternal pre-pregnancy diabetes (adjusted OR 4.6, 95% CI 2.57, 8.24), previous macrosomic birth (OR 3.1, 95% CI 2.61, 3.74), post-term pregnancy greater than 42 weeks gestation (OR 3.1, 95% CI 2.47,3.86), maternal excess weight with BMI greater than 25 before pregnancy (OR 2.0, 95% CI 1.72, 2.32), male infant gender (OR 1.9, 95% CI 1.66, 2.21), gestational diabetes mellitus (OR 1.6, 95% CI 1.26, 2.16) and non-smoking (OR 1.4, 95% CI 1.14, 1.82).[23]

There is a plethora of information available in the literature regarding the contribution of maternal obesity, both pre-existing and due to excessive gestational weight gain, to fetal macrosomia.[6;24-42] Studies have universally found that maternal obesity contributes to excessive fetal growth, but the exact effect size of this relationship remains uncertain. There is variation in the effect size observed in the existing studies. Fetal growth is a complex biologic process that is regulated by both maternal and fetal factors including genes and environment. Identified risk factors for macrosomia include maternal obesity, maternal birth weight, grand multiparity (≥5 deliveries), prior macrosomic fetus, maternal diabetes, and excessive weight gain in pregnancy.[41] Maternal obesity likely contributes to macrosomia via mechanisms including increased insulin resistance (even in women who do

not have diabetes) resulting in higher fetal glucose and insulin levels.[43] Placental lipases metabolize triglycerides in maternal blood, allowing free fatty acids to be transferred to the growing fetus.[44] High triglycerides in obese women may thereby contribute to excessive fetal growth via increased availability of free fatty acids.[45]

The most accepted method of classifying an obstetrical patient's weight involves the calculation of her pre-gestational body mass index (BMI). BMI is determined by dividing the patient's weight (in kilograms) by her height squared (in meters).[46] The resulting value is then compared to a set of standard ranges that define the patient's weight classification. Several standard ranges exist with the most extensively used being the World Health Organization Classification of Obesity (see Table 1.1).[2]

Recommendations for appropriate gestational weight gain are made based on a woman's pre-gravid BMI. The most widely accepted guidelines were issued by the Institute of Medicine in 2009, and are shown in Table 1.2.[47]

The association between macrosomia and adverse perinatal outcomes has been thoroughly examined in previous studies, as has the relationship between maternal obesity and adverse pregnancy outcomes, including macrosomia. We believe that the combined effect of maternal obesity and fetal macrosomia will further increase the risk for related adverse outcomes. This "double-hit" phenomenon is clinically crucial. Currently, there is much debate in the obstetrical community regarding the preferred management of pregnancies

complicated by maternal obesity. The discussion regarding mode of delivery for macrosomic infants is longstanding and, as yet, unresolved. The goal of this study was to provide evidence that confirms the intuitive feeling that excessively large infants from obese mothers have poorer pregnancy outcomes than macrosomic infants from mothers of normal weight. This information can then be used to better inform clinical care for obese mothers.

It is becoming increasingly apparent that maternal obesity has profound implications for both mother and fetus. The modifiable risk factors for macrosomia of obesity and excessive maternal weight gain in pregnancy should therefore be targeted as potential preventative strategies.

1.2 Research Goal and Hypothesis

In this thesis, the overarching theme is improving the health of pregnant Canadian women who carry extra body weight and their offspring. We hypothesized that maternal obesity is a significant contributor to fetal overgrowth and that the combined effect of maternal obesity and excess fetal growth would have a greater impact on adverse pregnancy outcomes for both mother and baby than either factor alone. First, information regarding the contribution of maternal obesity to fetal macrosomia was synthesized. Then, the impact of maternal obesity on pregnancy outcomes related to fetal macrosomia was assessed

2. LITERATURE REVIEW

2.1 Prevalence of Maternal Obesity and Current Trends

Obesity has become a health concern of epidemic proportions, particularly among citizens of developed countries. Canadian adults in general have become increasingly heavy over the last 25 years.[48] The most recent Canadian Health Measures Survey (CHMS) executed from 2007 to 2009 found that 37% of Canadian adults were overweight and 24% were obese.[49] Women of reproductive age are certainly not immune to excess weight – 21% of Canadian women between the ages of 20 and 39 who participated in the 2007-2009 CHMS were obese compared with 4% in the 1981 Canada Fitness Survey.[48] This marked increase in obesity rates among young Canadian adults has corresponded to an increase in the body mass of pregnant women with time.

In the United States, approximately one in five women (75,403 women surveyed) reported a pre-pregnancy weight that placed their BMI in the obese range.[50] When obesity was examined by race/ethnicity and state, the prevalence was as high as one in three.[50] The authors state that this prevalence makes maternal obesity the most common preventable risk factor for pregnancy complications in the United States.[50]

A longitudinal database study of 36,821 women was undertaken in the United Kingdom, designed to identify trends in prevalence of maternal obesity incidence between 1990 and

2004. The authors found that the proportion of women who were obese at the start of pregnancy has increased significantly over time from 9.9 to 16.0% ($p<0.01$).[51] Even more alarming, the rate of increase was accelerating, such that the predicted rate of obesity in early pregnancy in 2010 was 22%.[51]

It is clear that obesity is common among women of reproductive potential and that the prevalence has increased significantly over the last generation. It is therefore important that primary and maternity care providers be cognizant of the impact of obesity on pregnancy outcomes.

2.2 Characteristics of Obese Mothers

Several risk factors for maternal obesity have now been clearly identified. Obesity is more common in women who are older, multiparous, single and black.[45;50-55] Overweight and obese women are also more likely to have longer inter-pregnancy intervals (≥4 years) than women of normal weight.[56] This finding is likely in part to decreased fertility rates among obese women.[57;58] Studies have shown that smoking is more common among pregnant women who are obese than among normal weight mothers.[27;59]

Obesity is less common in very young mothers (<20 years of age).[38;60] In general, women with higher education (>12 years) are less likely to be obese.[24;32;42;56;61] There is conflicting evidence regarding the association between obesity and social deprivation; some studies

show obesity to be associated with decreased socioeconomic status, while others show obesity affecting women of all social standing.[51;62-64]

2.3 Health Effects of Obesity Among Women of Reproductive Age

It is well known that obesity is associated with many medical conditions (such as hypertension and diabetes) in the non-pregnant population.[39] These conditions then complicate subsequent pregnancy. Schrauwers et al showed that the blood pressure at the initial prenatal visit differs significantly with increasing BMI, with average systolic blood pressures of 109 in women with BMI 19.1-25 kg/m^2, 113 in women with BMI 25.1-30 kg/m^2, and 119 in obese and morbidly obese women.[52] Similar changes were noted in the average initial diastolic blood pressures with values of 63 for normal weight women, 66 for overweight women, 70 for obese women and 72 for morbidly obese women.[52] Other authors have confirmed that chronic hypertension is significantly more common among obese women.[59;65] In one study, 9.1% of women who weighed >120kg had pre-existing hypertension compared to 0.6% in women who weighed 55-75kg ($p<0.001$).[66]

Diabetes predating pregnancy is also more prevalent among obese women.[35;67] The risk of pre-existing diabetes is approximately 1% in women of normal weight and 3-5% in obese women.[35;52;54;65] This increase is not strictly due to insulin resistance - one study found that there is also an increased risk of Type I diabetes in morbidly obese women (1.9% versus 0.2% in women with a normal BMI).[25] It is estimated that 3.7% of adults aged 20 to 44

years living in the United States have diagnosed or undiagnosed diabetes.[68] The estimated prevalence of undiagnosed diabetes among women between the ages of 30 and 59 in the United States is 2.1%.[69] This rate is likely considerably higher among young obese women, particularly in select ethnic groups. Since periconceptual glucose control is crucial for the prevention of congenital anomalies, undiagnosed pre-gestational diabetes places a significant burden of illness on infants of obese mothers.

Composite pre-existing morbidity (including depression, cardiovascular disorders, diabetes, epilepsy, and asthma) also increases with increasing BMI – only 38.3% of morbidly obese women are free of pre-existing medical conditions, compared to 69% of normal weight women.[52] Not surprisingly, obese women are on more medications that women of normal weight, and often enter pregnancy taking one or more prescription drugs.[52]

Mental health disorders (both pre-pregnancy and related to pregnancy/delivery) become increasingly more common as BMI rises.[52]

Obesity-related health concerns that are present prior to pregnancy may impact pregnancy outcomes. Discussion of increased risks ideally occurs pre-pregnancy and patients should be encouraged to attain as normal a body mass as possible prior to conception. A detailed medical history should be obtained early in gestation from pregnant women who are overweight or obese in order to identify those most at risk for pregnancy complications.

2.4 Effect of Maternal Obesity on Fetal Growth

Maternal obesity is associated with increased fetal growth among mothers of all ages.[41;70-73] The frequency of both small for gestational age (<10%ile) and appropriate for gestational age (10%ile to 89%ile) infants is decreased in obese women compared to normal weight women in a dose-dependent fashion ($p<0.01$).[74] Large for gestational age infants, in contrast, are more common in obese women than in women of normal weight.[25;54;74-76] Birthweight has been observed to increase with maternal fat-free body mass as well as maternal fat mass.[77] In the infant, however, maternal obesity appears to result in an increase only in neonatal fat mass, not lean body mass.[78]

The prevalence of neonatal macrosomia has recently increased. In a Canadian hospital-based cohort of 61,437 live singleton births, both mean birthweight and %LGA increased significantly (p-value <0.001) between 1978/79 (mean birthweight 3419g, % LGA 8.0%) and 1994-6 (mean birthweight 3476g, %LGA 11.5%).[79] In a large German cohort of 206,308 newborns, the prevalence of a birthweight ≥ 4000g increased significantly from 9.1% to 10.1% between 1993 and 1999.[80] The authors postulate that the major determinant of this increase was a corresponding increase in maternal BMI over the same time period.[80] They also speculate that the increase in macrosomia will contribute to the increasing burden of excess weight under the current affluent socioeconomic environment.[80] Other authors have also observed increasing rates of macrosomia.[40;81]

When birthweights are compared, infants of obese women are, on average, 105-162g heavier than women of normal weight.[28;52;82] This increase is accentuated in morbidly obese women, whose infants average 235g more.[52] When extremes of BMI are considered, women with a BMI of 40-44.9 kg/m^2 have infants that are, on average, 600g heavier than women with a BMI of 10-14.9 kg/m^2.[83]

Fetal macrosomia (defined as birthweight >4000g) is more common in women with class III obesity (OR 4.04, 95% CI not given), as demonstrated in a retrospective cohort study of 370 Australian women.[52] This finding was confirmed in a study of 508,926 pregnant women from Germany, in which 7.9% of infants whose mothers had a normal BMI (18.50-24.99 kg/m^2) were macrosomic (birthweight ≥ 90 th percentile) compared to 22.2% of infants of mothers whose BMI was between 40.00 and 44.99 kg/m^2, and 25.9% of infants born from mothers with a BMI ≥ 45.00 kg/m^2.[84] Abenhaim performed a retrospective cohort study of 18,643 women who delivered at the Royal Victoria Hospital in Montreal.[35] They were able to demonstrate a significant increase in the odds of delivering an infant with macrosomia (birthweight >4500g) with increasing BMI: BMI <20kg/m^2 OR 0.43 (95% CI 0.28,0.68), BMI 20-24.9kg/m^2 OR 1, BMI 25-29.9kg/m^2 OR 1.66 (95% CI 1.23, 2.24), BMI 30-39.9 kg/m^2 OR 2.32 (95% CI 1.58, 3.41), BMI 40+ OR 2.10 (95% CI 0.64, 6.86).[35] Other studies have confirmed similar findings.[28] Infants are more likely to be large for gestational age as their mother's BMI increases.[6;25;35;61] In a population of ethnically Chinese women, the odds of having a birth weight at or above the 90th percentile was 0.40 (95%CI 0.31, 0.52) for underweight women, 1.71(95%CI 1.53, 1.90) for maternal BMI 23-24.9 kg/m^2, 2.22 (95%CI

1.96, 2.51) for BMI 25-27.4 kg/m^2, 2.86 (95%CI 2.43, 3.36) for BMI 27.5-29.9 kg/m^2 and 3.39 (95%CI 2.78, 4.13) for BMI≥30 kg/m^2.[54]

Khashan et al completed a population based cohort study of 99,403 singleton births occurring to women in Northwestern UK.[63] Their objective was to examine whether a dose-dependent effect between BMI and adverse pregnancy outcome exists.[63] Birthweight-related outcomes included macrosomia (birthweight >4500g) and LGA (defined by individualized birthweight ratio (IBR) ≥ 97%ile).[63] There was a dose-dependent increase in risk for both outcome measures.[63] For macrosomia, the relative risk increased from 0.82 (95% CI 0.51, 1.31) in underweight women to 1.70 (95%CI 1.50, 1.92) in overweight women, 2.71 (95%CI 2.38, 3.07) in obese (BMI 30.0-40.0 kg/m^2) women and 4.8 (95%CI 3.86, 5.92) in morbidly obese (BMI >40 kg/m^2) women.[63] The findings for LGA were similar: relative risk increased from 0.56 (95% CI 0.43,0.74) in underweight women to 1.12 (95% CI 1.04, 1.21) in overweight women, 1.63 (95% CI 1.51, 1.77) in obese women and 3.15 (95% CI 2.73, 3.64) in morbidly obese women.[63] IBR is a valuable method of estimating excessive fetal growth, as it corrects birthweight for gestational age, taking into account maternal height, weight, ethnic origin, parity and infant sex.[63] It may, therefore, reflect true fetal overgrowth.

Gilboa et al. performed a novel analysis of the association between maternal pre-pregnancy BMI and birthweight, in which they set out to determine whether using spline regression would provide additional insight into the exposure-response relationship.[85] Their results showed that overweight and obesity were associated with an increase in the risk of both

macrosomia (birthweight >4500g) and large-for-gestational-age (birthweight≥90%ile). [85] Furthermore, they demonstrated that the a restricted quadratic spline model was a better fit for their data than the traditional categorical analysis.[85] Using the categorical model, there was a non-significant increase in the risk of macrosomia among obese patients (OR 2.07, 95% CI 0.89-4.80) as well as a significant increase in risk of large-for-gestational-age (OR 1.96, 95% CI 1.34-2.88).[85] Using the restricted spline model, there was a monotonic increase in odds of both macrosomia and large-for-gestational-age for every 2 unit increase in BMI when BMI was ≥30. [85] Spline modelling, therefore, appears to provide additional insight into dose-response relationships for maternal pre-pregnancy BMI and birthweight.[85]

In an attempt to better understand the effect of maternal weight on infant birthweight, Hutcheon et al examined differences in outcomes between siblings of the same mother, where both first and second pregnancies were complicated by gestational diabetes.[86] They found that controlling gestational weight gain may reduce offspring birth weight and that elevated maternal pre-pregnancy BMI may represent a predisposition to increased birth weight.[86]

Gestational weight gain (GWG) can ameliorate or accentuate the effects of maternal obesity on fetal growth.[87;88] Crane et al completed a population-based cohort study of 5377 women from the Eastern Health-Avalon region of Newfoundland and Labrador, in which they investigated the effects of GWG on maternal and perinatal outcomes in women according to their pre-pregnancy BMI.[53] In their population obesity is relatively prevalent

with 3.0% of patients being underweight, 46.3% normal weight, 26.4% overweight, 24.3% obese and 4.3% morbidly obese.[53] Overall, 30.6% of women had an appropriate gestational weight gain, while 17.1% gained less than the recommended amount, and 52.3% of patients exceeded the recommended target range.[53] Worse, a linear relationship was noted between likelihood of excessive GWG and BMI: 48.7% of normal weight women and 67% of obese women exceeded recommended targets.[53] The study further highlighted the contribution of GWG to fetal macrosomia (defined as birth weight ≥4000g). The odds of having a macrosomic infant increased with increasing BMI, with an odds ratio of 1.21(95% CI 1.10, 1.34) for women with a normal pre-pregnancy BMI who exceeded the recommended weight gain goals and an odds ratio of 1.30 (95% CI 1.15, 1.47) in overweight women.[53] The trend was less clear in the obese population, with an odds ratio of 1.20 (95% CI 1.07, 1.34).[53] Interestingly, when overweight and obese categories were combined, weight gain below the recommended range resulted in a decreased odds of having a macrosomic infant (OR 0.60, 95% CI 0.41,0.89).[53] This was in large part reflected in the increased odds of a small for gestational age infant (<2500g) with an odds ratio of 2.58 (95% CI 1.16, 5.75).[53] This important study provides further evidence of the benefits of restricting GWG to the target ranges, particularly in patients who begin their pregnancies carrying excess weight (providing fetal growth is monitored).

Nohr et al. published a cohort study in which they attempted to determine whether gestational weight gain should be individualized.[89] When GWG for primiparous women was between 10-15kg, the prevalence of LGA increased with BMI class: 2% in underweight

women, 5% in normal weight women, 9% in overweight women and 13% in obese women.[89] When multiparous women gained 10-15kg, the risk of LGA increased more dramatically: 4% in underweight women, 10% in normal weight women, 17% in overweight women and 23% in obese women.[89] If GWG was in excess of 25kg, primiparous patients experienced an increased risk of LGA of 6% in underweight women, 15% in normal weight women, 19% in overweight women and 29% in obese women.[89] Multiparous women gaining more than 25kg were at highest risk - 17% in underweight women, 28% in normal weight women, 35% in overweight women and 32% in obese women.[89] Therefore, it appears that limiting gestational weight gain among women carrying excess weight is important and should be particularly emphasized for multiparous women.[89]

Getahun et al. performed an analysis of a longitudinal population-based retrospective cohort of 146227 women from Missouri, in which they sought to determine if changes in BMI between the first two pregnancies are associated with an increase in the risk of large-for-gestational-age in the second pregnancy.[56] Rates of large-for-gestational-age in the second pregnancy were 3.8% for underweight women, 8.7% for normal weight women, 13.0% for overweight women and 16.4% for obese women.[56] An increase in BMI between pregnancies was associated with an increased risk of large-for-gestational-age in the second pregnancy, even after controlling for diabetes.[56] They were able to show that women whose pre-pregnancy BMI shifts from obese to normal remain at increased risk for a large-for-gestational-age birth.[56] It is possible that birthweight in a second pregnancy could be influenced by overweight or obese status in a previous pregnancy, demonstrating long-term

effects of excess weight on future pregnancies.[56;90] Furthermore, an increased BMI in the second pregnancy showed stronger association with large-for-gestational-age and macrosomia than in first pregnancies.[56]

One of the difficulties with determining the relative contribution of maternal obesity to excessive fetal growth is the intricate relationship of obesity with abnormal glucose metabolism. Altered glucose metabolism, in varying degrees from subtle impairments in glucose tolerance to overt diabetes, plays a clear role in excessive fetal growth.[91-93] Overgrowth is related to factors such as altered glucose and fatty acid transport and increased placental hormones, including human placental lactogen, cortisol and estrogen. It is very difficult to separate the independent effects of obesity and glucose control on fetal growth; there is conflicting data regarding the relative importance of these factors.[94] Furthermore, infant gender may be an effect modifier in the relationship between abnormal glycemic control and birthweight.[95] Male fetuses exposed to an abnormal glycemic environment were found to have an increased risk of macrosomia while female fetuses were not.[95]

Regardless of BMI, abnormal glycemic status plays an important role in the increased risk of macrosomia.[96-99] There is good evidence to show that glucose values correlate strongly with infant birthweight.[100] One recent retrospective cohort study of 233 women with a diagnosis of gestational diabetes attempted to determine the roles of maternal weight, severity of gestational diabetes and glycemic control on the prevalence of LGA infants.[101]

Severity of gestational diabetes was determined using the fasting plasma glucose at the time of a three hour oral glucose tolerance test (OGTT).[101] Glycemic control was considered "good" if more than 75% of readings fell in the optimal range (fasting plasma glucose <95mg/dL and two-hour values <120mg/dL).[101] A total of 51 LGA infants were born, with higher odds in women who were obese (BMI ≥30 kg/m^2) compared to women of lower BMI (OR 3.55, 95% CI 1.5, 7.9).[101] They noted that there was no difference in the proportion of women delivering an LGA infant based on glycemic control.[101] Maternal weight, however, appeared to be a significant and independent predictor of LGA infants in this population of women with gestational diabetes.[101] When birthweight was considered instead, maternal weight at delivery and fasting glucose levels on OGTT were significant predictors of increased birthweight.[101] Infants of women with gestational diabetes mellitus have increased body fat, for which maternal fasting glucose levels are the best predictor.[102] Macrosomic infants of diabetic mothers have larger shoulder and extremity circumferences, a decreased head-to-shoulder ratio, significantly higher body fat and thicker extremity skin-folds compared to infants of similar birth weight and birth length of non-diabetic mothers.[103]

Yogev et al studied the effect of mode of treatment of gestational diabetes, as well as level of glycemic control, on pregnancy outcome, including birthweight in a retrospective cohort study of 4830 patients with gestational diabetes treated at a single center.[104] They demonstrated an increase in the risk of fetal macrosomia (birthweight ≥4000g) among

obese women (BMI 30.0-34.9 kg/m^2) who were treated with diet alone (OR 1.70, 95%CI 1.10, 2.84), suggesting that a low threshold for starting insulin should be employed.[104]

Ultrasound is frequently used to estimate fetal weight when mode of delivery of an infant with suspected macrosomia is being contemplated. There is always a degree of inaccuracy in such estimates, which is known to worsen with increasing BMI.[105] In general, the trend is to overestimate fetal weight when using ultrasound, particularly if the mother is obese.[52] One study showed a mean difference between the estimated fetal weight and the delivery weight of 367g in normal weight women, 391g in obese women and 435g in morbidly obese women.[52]

2.5 Optimal Fetal Phenotype Among Offspring of Obese Women

Excess fetal growth may actually be protective to the newborn. Salihu et al. performed a retrospective cohort study designed to assess the success of fetal programming among obese mothers in general, and across obesity subtypes.[74] They included 728,144 normal weight or obese women with singleton pregnancies between 20 and 44 weeks' gestation. The crude overall neonatal mortality rate increased from 4.9/1000 in women of normal weight to 6.2/1000 in obese women.[74] Further, the risk of neonatal mortality exhibited a dose-dependent increase across obesity classes: class I (5.8/1000), class II (6.7/1000) and class III (7.1/1000).[74] Interestingly, neonatal morality rates were 72% higher for small for gestational age (SGA) fetuses and 45% higher for appropriate for gestational age (AGA)

fetuses born to obese mothers compared to women of normal weight.[74] Large for gestational age (LGA) infants, however, had similar neonatal survival rates when born from obese women.[74] The authors imply that fetal macrosomia represents an adaptive mechanism of obese women, whereby survival of offspring is improved.[74] The physiologic mechanism behind this finding is yet to be elucidated, but may represent either more effective adaptation of the substrate-enriched environment of the obese mother or a state of relative placental insufficiency resulting in SGA and AGA fetuses.[74]

2.6 Pregnancy Complications Related to Maternal Obesity

In general, obese women have more complicated pregnancies than women of normal weight – a concept that was first described in the literature in 1945.[24;29;39;67;106-108] There appears to be a dose-dependent response, as those with the most severe obesity (ex: BMI ≥ 40.0kg/m^2 or BMI ≥ 50.0kg/m^2) have the worst pregnancy outcomes.[27;109-113]

Obese patients commonly enter pregnancy with chronic hypertension (eight-fold increase – 2.7 % compared to 0.33% of women of normal weight), but are also more likely to develop hypertension associated with pregnancy.[74] Although even women with modest obesity are at increased risk, gestational hypertension is significantly more likely in morbidly obese patients (OR 2.98, 95% CI 1.09, 8.18).[52;114] Another study showed an adjusted odds ratio of 1.5 (95% CI 1.4, 1.7) among overweight women, 2.2 (95% CI 2.1, 2.6) among obese women, and 3.1 (95% CI 2.0, 4.3) among morbidly obese women.[25] In the morbidly obese group, the

incidence of gestational hypertension was 42.2%.[25] Further, preeclampsia is more common as BMI increases, reaching a range of 3-5% for obese and morbidly obese women.[52] The odds of developing pre-eclampsia increase with BMI; one study demonstrated odds ratios of 1.6 (95% CI 1.2-1.8) among overweight women, 3.1 (95% CI 2.8-3.5) among obese women and 7.2 (4.7-11.5) among morbidly obese women.[25] Interestingly, obesity (with its co-existent insulin resistance, hyperlipidemia, inflammation and impaired endothelial function) appears to eliminate the protective effect of smoking on the development of pre-eclampsia.[115] Eclampsia is also more prevalent in obese women (two-fold increase).[74] There is emerging evidence that the risk for gestational hypertension and pre-eclampsia can be ameliorated by minimizing gestational weight gain.[116;117]

Impaired glucose metabolism is another well-recognized association of obesity, and increases in a linear trend with BMI.[118] The association is stronger in select racial groups, including women of First Nations or Asian descent.[119;120] The risk of gestational diabetes is increased (OR 5.61, 95% CI 4.61-6.83) in women with a BMI≥35 kg/m^2, particularly among those with increased central compared to peripheral fat.[121;122] Central adiposity is difficult to assess in pregnancy, but results in increased risk of gestational carbohydrate intolerance, hypertension and birthweight and more accurately predicts adverse perinatal outcomes than traditional weight assessment.[122;123] The metabolic changes behind obesity persist into pregnancy, with a significant proportion of obese women developing gestational diabetes.[54] In a retrospective cohort study of 370 pregnant women, the odds of developing gestational diabetes were 8.82 (95% CI 1.10, 70.97) for obese women and 27.38 (95%CI

3.48, 215.68) for morbidly obese women.[74] Of all women with gestational diabetes, approximately 30% are obese.[104] It has been shown that the need for insulin therapy increases with BMI, such that morbidly obese women are more likely than obese women to need insulin.[104]

Obesity limits the ability of ultrasound to detect major fetal anomalies. The detection rate for anomalies decreases linearly with increasing BMI, from 66% in women of normal weight to 25% in morbidly obese mothers.[124] As a corollary, the residual risk of delivering a live or stillborn infant with a major fetal anomaly after a normal standard ultrasound increases from 0.4% in women of normal weight to 1.0% for obese women.[124] The detection rate is worsened further in women with pre-gestational diabetes.[124] Obese women should be counselled regarding the limitations of excess weight on the sensitivity of prenatal ultrasound.

Data on preterm delivery is somewhat conflicting. Several studies showed that there does not appear to be a difference in the mean gestational age at delivery when obese women are compared to women of normal weight.[45;65;74;125] Some studies have indicated an increased rate of preterm birth, although not spontaneous preterm labour.[25;54;125;126] This is attributed to an increase in indicated preterm delivery; obesity appears to be protective against spontaneous preterm labour.[127] There is, however, evidence to suggest that preterm pre-labour rupture of membranes (PPROM), a condition that commonly leads to preterm birth, is more common among obese women.[128]

It is difficult to determine the impact of obesity on maternal mortality; given that maternal death is a rare event, studies are generally underpowered to evaluate this outcome. Of note, however, in the most recent Confidential Enquiry into Maternal and Child Health (2011), over one-third of mothers who died were obese and more than 15% were morbidly obese or super morbidly obese.[129]

Weight gain during the inter-pregnancy interval (defined as difference between the first trimester weights in the first and second consecutive singleton births) is strongly associated with the risk of major maternal and perinatal complications.[90] A weight gain of 1-2 BMI units over a two year period increases the risk of gestational hypertension, gestational diabetes and large-for-gestational-age birth by 20-40% with further linear increase in risk following weight gain.[90] Furthermore, pre-pregnant weight gain increases the risk of adverse pregnancy outcomes even in women who are not overweight.[90] The authors suggest that counselling of women to minimize or reduce inter-pregnancy weight gain is of critical importance.[90]

2.7 Intrapartum Complications Related to Maternal Obesity

Labour and delivery are more complicated for patients carrying excess weight. The probability of spontaneous onset of labour decreases with increasing BMI.[52;54;121] A trend

between increased BMI in the first trimester and decreased chance of spontaneous labour at term was clearly demonstrated by Denison et al in a Swedish population-based retrospective study of 186 087 primiparous women.[121] In this study, the odds of spontaneous labour were as follows: BMI <20 kg/m^2, OR 1.21 (95% CI 1.15-1.27); BMI 25-29.9 kg/m^2, OR 0.71 (0.69-0.74); BMI 30-34.9 kg/m^2, OR 0.57 (0.54-0.60); BMI ≥35 kg/m^2 OR 0.43 (0.40-0.47).[121] Higher BMI in the first trimester was associated with longer gestation.[121] Furthermore, a greater change in BMI between the first and third trimesters was associated with a lengthening of gestation from 280.7 to 283.2 days.[121] In another retrospective cohort study of 310 pregnant women, spontaneous onset of labour occurred in 67% of women of normal weight, in 55% of overweight women, in 48% of obese women and in 37% of morbidly obese women.[52]

There is a corresponding increase in the rate of induction of labour as BMI increases.[25;30;52;54;130-132] Obesity is thought to be an independent predictor of need for induction.[45;130] The reasons behind this continue to be unclear, but may relate to decreased production of, or responsiveness to, endogenous oxytocin, or increased prevalence of medical or obstetrical factors necessitating induction (insulin-dependent diabetes, for example).[130] Obese women undergoing induction of labour require higher doses of oxytocin than their normal weight counterparts.[75] Unfortunately, there is a corresponding higher rate of failed induction in this population.[54;133]

Monitoring of the general health and progress of labour of both mother and fetus becomes more difficult as maternal weight increases.[131] There are significant differences in the incidence of difficult vaginal examination due to excess perineal tissue and failure to adequately monitor uterine contractions.[131]

Providing anesthesia during labour also becomes increasingly difficult as maternal BMI increases.[134] Further, obese women require more medication in order to achieve the same level of comfort as women with a normal BMI.[131] Obese patients are more likely to use regional anesthesia, but are more likely to have multiple attempts and failure of epidural and spinal than their normal weight counterparts.[131] Unfortunately, if general anesthesia is required, dangerous complications, such as inability to intubate, are more frequent.[129;131]

The rate of normal vaginal delivery decreases with increasing BMI, from 76% in women of normal weight, to 59% in overweight women, 49% in obese women, and 37% in morbidly obese women.[52] Unfortunately, obese women are more likely to require delivery by alternative methods, including both instrumental vaginal delivery and elective or emergency Caesarean section.[52;135]

Obesity has been identified as a risk factor for third and fourth degree perineal lacerations (p-value <0.01).[130] This is likely related to increased birth weight as well as greater need for operative vaginal delivery in this population, although some studies have shown a decreased need for operative delivery (with a corresponding increase in the Caesarean

section rate).[54] This may be due to reluctance on the part of intrapartum care providers to proceed with vacuum- or forceps-assisted delivery in obese women in whom fetal overgrowth is suspected. The authors also identified pre-gestational inactivity as an independent risk factor for severe perineal injury.[130]

The need for Caesarean section increases with increasing maternal weight.[34;36;131;136-150] The relative risk of Caesarean section was increased 5.82 times (95% CI 1.70, 19.86) in obese women in one group of 126 parturients in the United Kingdom who participated in a prospective cohort study.[138] Using the Swedish Medical Birth Registry, a retrospective analysis was carried out to investigate the cause of this increase.[38] In general, the risk of non-elective Caesarean section increased linearly with increasing BMI across all categories.[38;83] The odds of requiring Cesarean section for delivery increased linearly from 1.00 in the reference category (BMI 10-14.9 kg/m^2) to 3.6 (95% CI 2.49, 5.10) for women with BMI 40-44.9 kg/m^2.[83] Three indications for non-elective Caesarean section were analyzed. Both ineffective uterine contractility and fetal distress were significantly associated with maternal BMI in a dose-dependent manner.[83] Obstructed labour (due to fetal malposition and malpresentation or maternal pelvic abnormality) was not associated with increasing maternal BMI.[83] These findings support other clinical and experimental data that imply that myometrial response to oxytocin is altered in the obese patient.[151] They also suggest that the increased central adiposity of obesity is not a contributor to the increased risk of Caesarean section, a finding that differs from that of other groups.[83]

The risk of both elective and emergency Caesarean section increases with increasing BMI and gestational weight gain.[34;130;131;152;153] In the Voldner prospective cohort study of 553 pregnant women and their offspring, the risk of Caesarean section increased to approximately 36%, compared to a baseline of 21%, in women whose BMI exceeded 30 kg/m^2.[130] They hypothesized that this was, at least in large part, due to increased fetal birthweight when ≥4200g. Overall, 35% of infants weighing more than 4200g required Caesarean section for delivery.[130]

The increase in the odds of emergency Caesarean section appears to be consistent across studies.[25;64] In a retrospective cohort study of 24,241 women, Bhattacharya et al noted that the odds ratio for emergency Caesarean section was 1.5 (95% CI 1.3-1.6) for overweight women, but increased to 2.0 (95% CI 1.8-2.3) for obese women and 2.8 (95% CI 2.0-3.9) for morbidly obese women.[25] In an emergency situation, time is of the essence. Unfortunately, operative times (including skin to delivery times) are longer in obese patients and wound infections and thromboses are more common.[154-157]

Obese women who have previously delivered by Cesarean section may be interested in a trial of labour after Cesarean (TOLAC). Discussion of the risks and benefits should include information on the cumulative risks of obesity and the presence of a previous uterine scar.[158]

Obese patients are at risk for increased blood loss at the time of delivery, with normal weight women losing an average of 306mL, compared to 360mL for overweight women, 441mL for obese women and 514mL for morbidly obese women.[52] Both obesity (OR 4.2, 95% CI 1.2-17.7) and macrosomia (OR 4.2, 95% CI 1.2-4.7) predict blood loss more than 1000cc.[130]

2.8 Adverse Fetal and Neonatal Outcomes and Maternal Obesity

Offspring of heavier mothers also face increased risks. Perhaps most importantly, there appears to be a notable increase in the risk of perinatal mortality.[159-164] One Swedish retrospective cohort study of 186,087 primiparous women demonstrated an association between BMI≥35 kg/m^2 and stillbirth, with an odds ratio of 3.90 (95% CI 2.44-6.22).[121] Another retrospective cohort study, this time of 24,241 Scottish women showed an odds ratio for intrauterine fetal demise of 1.8 (95% CI 1.1-2.9) among obese women.[25] The increase in risk appears to extend into the neonatal period, such that case fatality rates (fetal + neonatal deaths/1000 births) increase significantly among obese women (135/1000 versus 39/1000 among infants of normal weight mothers).[165] In another study, the odds of both neonatal death (OR 1.57, 95% CI 1.30-1.90) and postnatal death (OR 1.28, 95% CI 1.02-1.61) were increased among infants of obese mothers, with risk escalating with increasing gestational weight gain.[166] The reasons behind this increased risk of intrauterine demise have not fully been elucidated, but there is some evidence to suggest placental dysfunction as an underlying cause.[162] Rapid fetal growth associated with increased maternal insulin

levels, combined with relative or absolute placental insufficiency, may result in the increased rate of intrauterine fetal demise.[25]

As detailed in section 2.4, fetal overgrowth is common among infants of obese mothers. There may also be an important increase in the prevalence of small-for-gestational-age (SGA) fetuses among these mothers; in one prospective Danish cohort of 8 092 women the odds ratio was 2.8 (95% CI 1.4-5.6) and in a case-control study of 434 Brazilian pregnancies the odds of delivering a SGA fetus decreased with a BMI of <30 kg/m^2 (1.2%), but increased in women with a BMI≥ 30 kg/m^2 (5.8%).[31;167] Since both delivery of a small-for-gestational age infant and pre-pregnancy obesity predict maternal mortality, these mother-infant dyads are of particular concern.[168]

Maternal obesity has also been shown to be associated a 2.7-fold increase in shoulder dystocia (95% CI 1.5-5.1) in a retrospective cohort study of 9667 vaginal deliveries with 138 cases of shoulder dystocia.[169] Such an increase would not be unexpected, since maternal obesity results in larger infants. The causal role of maternal obesity in shoulder dystocia remains in question. Obesity has been found to be an independent risk factor for shoulder dystocia (OR 3.14, 95% CI 1.86-5.31) in a prospective population-based cohort study of 3480 women.[27;170] In contrast, an Albertan case-control study of 45 877 live singleton cephalic deliveries with 413 shoulder dystocias demonstrated no increased risk after adjustment for potential confounding variables.[171]

It appears that cord artery pH is significantly lower in infants of obese mothers.[34] Several studies have found a significant increase in the number of infants born with a cord artery pH <7.10.[34;172] In that study, there was also a higher rate of 1-minute and 5-minute Apgar <8.[172] Chen et al. also noted an increase in the risk of low Apgar score (4-6) in the obese population (OR 1.4, 95% CI 1.1-1.7 in women with a BMI ≥ 30 kg/m^2 and OR 2.0, 95% CI 1.5-2.7 in women with a BMI ≥ 40 kg/m^2).[173]

Several studies support an increase in the incidence of admission to a Neonatal Intensive Care Unit (NICU) for infants born from obese mothers.[34;59;174-177] In one study, 2.2% of infants born to mothers with normal first trimester BMI (20.01-25 kg/m^2) required admission to an NICU, compared to 8.6% of infants born from obese mothers (BMI ≥30).[34]

Other neonatal complications that appear to be more common among infants of obese mothers include congenital anomalies, mechanical ventilation, meconium aspiration syndrome, hypoglycemia and jaundice.[59;178] Further, birth trauma (such as brachial plexus injury after shoulder dystocia) is more common among infants of obese mothers.[174] Many of these outcomes are, not surprisingly, also more common in macrosomic infants.[8]

Obese mothers are less likely to breastfeed their infants.[179] There is an increase in risk of failure to initiate breastfeeding (OR 2.2, 95%CI 1.8, 2.6) as well as a failure to sustain breastfeeding (OR 2.2, 95%CI 1.8, 2.6) – both scenarios appear to increase linearly with degree of obesity.[179]

2.9 Mechanisms Behind Altered Pregnancy Outcomes for Obese Women

There is now ample evidence showing an increase in pro-inflammatory and immunomodulatory cytokines in obese non-pregnant patients.[115] Data is beginning to accumulate on the role that these signals play in pregnancies complicated by obesity. Madan et al. completed a cross-sectional study in which they studied 80 serum samples from the early second trimester of women from varying BMI classes.[137] They then looked at seven different pro-inflammatory analytes to determine the association between biomarker levels and maternal BMI.[137] Both leptin and high sensitivity C-reactive protein (hsCRP) were found to increase significantly and linearly with increasing BMI.[137] Monocyte chemotactic protein (MCP)-1 was found to be increased in morbidly obese women.[137] The observed increase in inflammation may correlate with increased rates of pregnancy complications, including diabetes, pre-eclampsia and adverse neonatal outcomes (ex: preterm delivery, intraventricular hemorrhage).[137] Further work is needed to explore the role that gestational diabetes plays in altering the levels of pro-inflammatory cytokines.[137]

Investigators have long sought to determine the underlying cause of pre-eclampsia and to identify measurable predictors for its development. One common hypothesis involves increased oxidative stress. Since obese patients constitute a particularly high risk group, they are a logical choice for investigating potential biomarkers of oxidative stress. In a prospective cohort study of 385 obese nulliparous women, authors found that low plasma

ascorbic acid was predictive of small-for-gestational-age delivery but that this and other biomarkers were not associated with preeclampsia.[180]

2.10 Pregnancy Complications Related to Macrosomia

From the mother's perspective, there are relatively few antepartum complications related to fetal overgrowth. It is certainly conceivable that maternal discomfort is increased when carrying a macrosomic infant, although there is no evidence of this in the literature. Pelvic and back pain, for example, are common in pregnancy and exaggerated in women who are carrying excess intrauterine weight for other reasons (such as multiple gestation).

2.11 Intrapartum Complications Related to Macrosomia

The risk of Cesarean section rises significantly with infant birthweight – for infants weighing 4000-4499g the rate is 13.9% (OR 1.69, 95% CI 1.62-1.76), for those weighing 4500-4999g the rate is 21.1% (OR 2.99, 95% CI 2.76-3.24), and the rate is 32.6% (OR 5.46, 95% CI 4.40-6.78) for infants with birthweight ≥ 5000g.[181;182] Rates of Cesarean delivery among macrosomic infants appear to be rising over time, despite a lack of evidence regarding the role of operative delivery in this population.[183]

Propensity for excessive maternal blood loss is also clearly related to infant birthweight. Women who deliver macrosomic infants are at significantly higher risk of post-partum

hemorrhage (OR 2.01, 95% CI 1.93, 2.10) with a trend toward needing more blood transfusions (OR 1.26, 95% CI 0.99, 1.60).[75;181;182] Risk for chorioamnionitis is also markedly increased (OR 1.94, 95% CI 1.8, 2.10), as is the risk for forth degree perineal laceration (OR 2.45, 95% CI 2.16, 2.79).[181]

Regardless of mode of delivery, mothers who deliver a macrosomic infant require longer hospital stays than those who deliver infants of normal birthweight.[181]

2.12 Adverse Fetal and Neonatal Outcomes and Macrosomia

Macrosomia increases the risk of several intrapartum complications. Shoulder dystocia is considerably more common among macrosomic infants – the rate in one study was 3/1000 births when the birthweight was 2500-3499g, 73/1000 births with a birthweight of 4500-4999g and 146/1000 for infants weighing ≥ 5000g.[184] Further to this, the rate of birth injury is also increased (27/1000, 65/1000 and 110/1000 respectively).[184]

Fetal macrosomia remains the strongest predictor for shoulder dystocia; infants with birthweight ≥ 4000g have odds that are 9.0 times higher (95% CI 6.5-12.6) while those with birthweight ≥ 4500g have odds that are 39.5 times higher (95% CI 19.1-81.4).[171] Rates of shoulder dystocia increase linearly with infant birthweight, and are highest among infants of mothers with diabetes.[185] For example, the rate of shoulder dystocia is an astonishing 34.8% for infants of diabetic mothers who weigh 4750 to 5000g at birth.[185] Although birth

trauma (such as Erb's palsy) related to delivery is not uncommon among macrosomic infants, increased use of caesarean section has not been shown to reduce the risk.[3;186]

Macrosomic infants are more likely to have low 5-minute Apgars, ≤3 and ≤6.[182] An infant with grade III macrosomia (birthweight ≥ 5000g) has more than 5 times the odds of having a 5-minute Apgar ≤3 (OR 5.20, 95% CI 4.09, 6.62).[182] The need for assisted ventilation was also markedly increased among all classes of macrosomia, but most impressive in the infants with grade III macrosomia (OR 3.96, 95% CI 3.45, 4.55).[182] Similarly, risks for hyaline membrane disease (OR 3.70, 95% CI 3.11, 4.40) and meconium aspiration (OR 2.61, 95% CI 2.15, 3.16) were significantly higher among infants with grade III macrosomia than among non-macrosomic infants.[182]

Those infants with very severe macrosomia (birthweight ≥ 5000g) are also at increased risk of neonatal (OR 2.69, 95% CI 1.91, 3.80), post-neonatal (OR 1.62, 95% CI 1.16, 2.26) and infant death (OR 2.01, 95% CI 1.58, 2.55).[182]

2.13 Mechanisms Behind Altered Pregnancy Outcomes for Macrosomic Fetuses

Altered outcomes in offspring may result from several mechanisms. One hypothesis suggests that greater adiposity in offspring results from increased delivery of glucose, amino acids and free fatty acids to the developing fetus in utero, as well as to the infant after delivery via breastfeeding.[187;188] This effect, known as the developmental

overnutrition hypothesis, appears to be, at least in part, hormonally-mediated. There is a strong positive correlation between BMI and insulin and leptin concentrations and a negative correlation with adiponectin and insulin-like growth factor binding protein-1 (IGFBP-1).[189] Low levels of IGFBP-1 correspond with increased bioavailability of insulin-like growth factor-I, which in turn results in increased placental nutrient transport and fetal overgrowth.[189]

Alternatively, offspring may inherit their mother's genetic predisposition to gain weight.[187] This could, in part, explain the association between greater maternal GWG and greater offspring BMI.

2.14 Economic Impact of Obesity in Pregnancy

From a strictly economic perspective, obesity in pregnancy is costly to the health care system.[190;191] On average, obese women have longer hospital stays than women of normal weight.[52;192] Chu et al performed a retrospective cohort study of 19,538 pregnancies in western Oregon and Washington, in which they estimated the increase in use of maternal health care services associated with obesity during pregnancy.[192] They found a linear trend between increasing BMI and length of hospital stay for delivery: BMI 25.0-29.9 kg/m^2, 3.7±0.1 days; BMI 30-34.9 kg/m^2, 4.0±0.1 days; BMI 35-39.9 kg/m^2, 4.1±0.1 days; BMI≥40 kg/m^2, 4.4±0.1 days).[192] The increase in length of stay was primarily related to increased rates of Caesarean section and obesity-related complications.[192] Moreover, increasing BMI

was associated with the need for more interaction with the health care system, including increased prenatal tests, obstetrical ultrasounds, dispensed medications, phone calls to the department of obstetrics and gynaecology and prenatal visits.[192]

A retrospective case review demonstrated an increase risk of developing minor pregnancy complications among obese women, including symphysis pubis dysfunction, heartburn and chest infection.[193] The cost increase for the National Health Service in the United Kingdom for these minor complications was significant.[193]

In a qualitative study, maternity care professionals in North East England were interviewed about their perceptions of the impact of maternal obesity on maternity services.[194] Participants felt that obesity has a major impact on services and resources, on the health of both mother and child and on the psychological wellbeing of the mother.[194]

2.15 Maternal Long Term Sequelae of Excess Weight in Pregnancy

The most significant long-term health consequence of obesity in pregnancy is related to the tendency for obese women to have excessive gestational weight gain (GWG). The Institute of Medicine (IOM) has suggested target weight gain ranges for pregnancies that are based on pre-pregnancy BMI.[47] Using these ranges, excessive GWG can be defined. Chu et al performed a retrospective cohort study of 52,988 singleton full-term births among women from the United States that aimed to provide recent estimates of GWG among various BMI

categories.[60] The strongest predictor of excessive GWG was obesity, followed by parity, race/ethnicity, age and education.[60] In that study 25% of obese women gained ≥35 pounds (the upper limit for women of normal weight), suggesting that many obese women are likely exceeding necessary weight gains.[60]

Women who are overweight pre-pregnancy are at increased risk of obesity in subsequent pregnancies and beyond the reproductive years. In a retrospective cohort study of 1035 overweight nulliparous women, 12% of parturients had a low or normal BMI immediately before their subsequent pregnancy, while 55% remained overweight and 33% fell in the obese range.[195] Factors associated with shifting from overweight to obese included being unmarried (OR 2.69, 95% CI 1.74-4.15) and having ≥18 months between deliveries (OR 1.98, 95% CI 1.21-3.28).[195] Avoiding excess weight gain in the index pregnancy increased the odds of attaining a low or normal BMI before the subsequent pregnancy (OR 1.93, 95% CI 1.10-3.39).[195] Of overweight women, 76% gained more than the recommended maximum gestational weight gain. Of these, 33% were obese at the start of their second pregnancy.[195] It is imperative that care providers emphasize appropriate gestational weight gain to this group at high risk for long-term weight gain.

2.16 Offspring Long Term Sequelae of Macrosomia and Excess Maternal Weight in Pregnancy

Parental BMI plays a significant role in predicting overweight in children, particularly among those from low-income families.[19;196;197] It has been shown that maternal pre-pregnancy BMI is positively associated with offspring fat mass assessed at age 9 or 11 years, a finding likely attributable to overnutrition during key developmental periods; these finding support the developmental overnutrition hypothesis.[198;199] Further, the effect of maternal size during pregnancy outweighs the effect of shared familial mechanisms that would results in an association with paternal BMI.[200]

Maternal glycemic control also appears to play a role in obesity risk for children.[201] Offspring whose mothers had gestational diabetes are at higher risk of being overweight as children if both parents were obese, compared to children whose parents were non-obese (67% versus 19%).[196] This study concluded that both the pre- and the postnatal environment contributes to childhood overweight.[196]

Evidence suggests that birthweight is directly associated with later body mass index, with magnitude ranging from 0.5 to 0.7 kg/m^2 for each 1kg increment in birth weight.[202] Larger babies are, therefore, at risk for obesity and related co-morbidities, including type II diabetes later in life. Attention should also be paid to small babies of obese mothers, since low birthweight is associated with central adiposity, insulin resistance and the accompanying metabolic risk – all of which places them at higher risk of future cardiovascular disease.[203]

Mamun et al. analyzed data from a prospectively collected birth cohort.[187] They included 2532 mother-offspring pairs from South Brisbane, Australia, and assessed offspring mean BMI as well as systolic and diastolic blood pressures at 21 years of age.[187] Results showed that the mean BMI was 0.3kg/m^2 higher for each 0.1kg/week greater GWG.[187] Furthermore, systolic blood pressure was 0.2mmHg higher with each 0.1kg/week GWG.[187] The authors suggest that as this association persists into young adulthood, it provides evidence that maternal weight influences long-term cardiovascular risks for offspring.[187]

2.17 Potential Interventions to Reduce Macrosomia in Obese Pregnancies

Minimizing gestational weight gain has consistently been shown to improve pregnancy outcomes for both mother and baby.[37;38;204;205] In fact, among the most severely obese women (BMI≥ 40kg/m^2), the lowest risks for large for gestational age, low birth weight, pregnancy induced hypertension and Cesarean delivery occurred with maternal weight loss during pregnancy.[26]

It has been shown that advised and target weight gains are strongly associated with actual gestational weight gain.[206] Setting appropriate weight goals for pregnancy may be an important intervention for limiting gestational weight gain. Intuitively, one would expect higher GWG in patients who do not accurately perceive their body weight. Compared to normal weight women who accurately assess their weight, the odds of excessive GWG increased to 2.9 (95% CI 2.2,3.9) for overweight/obese women who accurately assess their

weight, and to 7.6 (95% CI 3.4,17.0) for overweight/obese women who underestimate their weight.[207] This final group tended to be younger, non-white, and single, and had lower income and education.[207] This provides a potential point for intervention, by emphasizing the importance of informing women of the status of their pre-pregnancy weight and reinforcing appropriate GWG.

The majority of interventions to date have focused on strategies to prevent excess gestational weight gain. Dietary manipulation is the strategy that is most commonly manipulated; this often involves use of a low glycemic-load diet.[208]

A randomized control trial of 257 obese patients was completed in which half received a complex intervention consisting of a balanced nutritional regime and daily diary monitoring of all foods eaten during the day.[209] The other half of the women made up the control group, which received conventional dietary management. Three outcomes showed significant differences in favour of the intervention: gestational hypertension, mother's last weight before delivery and mother's six-week post-partum weight.[209] The authors concluded that obese women can be placed on a well-balanced monitored nutritional program during pregnancy without adverse perinatal outcomes.[209]

3. SYSTEMATIC REVIEW

3.1 Research Objectives

It was hypothesized that maternal obesity is associated with a statistically significant increase in the prevalence of fetal macrosomia, as primarily defined by a birthweight that is greater than or equal 4000g and secondarily by a birthweight that is greater than or equal to 4500g and birthweight that is large-for-gestational age.

The objective of this project is to systematically review the literature regarding maternal obesity and fetal macrosomia and to complete a meta-analysis of the observational studies that will provide the best possible estimate for the increase in macrosomia that can be attributed to maternal obesity. Although the effect of maternal obesity on fetal overgrowth is widely reported in individual studies, this review will provide the most contemporaneous meta-analysis available in which the effect is examined as the primary outcome.

The systematic review and meta-analysis of the effect of maternal obesity on fetal growth was undertaken to obtain a precise estimate of the effect. Although this relationship is examined in nearly every study of the effect of maternal obesity on pregnancy outcome, the effect size varies between studies. It was felt that meta-analysis would provide the best possible information regarding risk. This would then allow for better interpretation of the results of the second component of this thesis – the retrospective review. In reviewing the

literature, only one previous meta-analysis could be identified, in which the relationship between obesity and fetal overgrowth was examined as a secondary outcome.[210] This meta-analysis, published in 2008, included data from articles published prior to June 2007. Since that time, there have been multiple studies published that add to the available literature. We undertook this meta-analysis, therefore, to provide the most contemporary evidence available regarding the contribution of excess maternal weight to fetal overgrowth, analyzed as a primary outcome (thereby minimizing the chance of Type I and II error).

3.2 Methodology

The QUOROM Statement was used to guide the methodology and reporting of this systematic review and meta-analysis.[211]

3.2.1 Search Strategy

The following databases were searched: PubMed, Medline (In-Process & Other Non-Indexed Citations and Ovid Medline, 1950-present) and EMBASE Classic+ EMBASE.

Databases were searched using a comprehensive and sensitive search strategy aimed at identifying as many studies as possible. The search strategy was formulated with the assistance of the librarians at the University of Ottawa library. Results were filtered to include studies involving human subjects.

The terms used in PubMed were as follows:

1. body mass index[mh] AND obesity[mh] AND (pregnancy complications[majr]OR pregnancy outcome[majr])
2. ((inprocess[sb]) OR (publisher [sb])) AND (pregnan*[Title] AND obes*[Title])

The terms used in Medline were as follows:

1. Exp Obesity/or obesity.mp
2. Exp Body Mass Index/ or BMI.mp
3. 1 and 2
4. Exp Pregnancy Complications or pregnancy complica*.mp
5. Exp Pregnancy Outcome/ or pregnancy outcome*.mp
6. 3 or 4
7. 3 and 6

The terms used in EMBASE Classic + EMBASE were as follows:

1. exp MORBID OBESITY/or exp ABDOMINAL OBESITY/ or exp OBESITY/ or obesity.mp
2. exp body mass/ or body mass index.mp
3. 1 and 2
4. exp pregnancy complication/ or pregnancy complic*.mp

5. exp pregnancy outcome/ or pregnancy outcome*.mp
6. 3 or 4
7. 3 and 6

The references for the resulting studies were then reviewed to identify any additional studies that were not identified in the preliminary search. The full texts of articles that were felt to be potentially relevant were obtained. Finally, review articles on obesity and maternal outcomes published between 2000 and 2009 were reviewed and their reference lists searched for additional potential studies. We did not attempt to locate unpublished studies. Electronic messages were sent to some authors to obtain clarification where necessary.

3.2.2 Inclusion Criteria

Types of Studies

Observational studies, including prospective and retrospective cohort studies as well as case-control studies were sought for inclusion. An initial literature screen was completed for randomized control trials, but none were identified. This was not surprising, since the review question does not inherently lend itself to investigation using randomized control trials – it is impossible to randomize pre-pregnancy weight or infant birth weight. Rather, all studies investigating the impact of maternal pre-pregnancy (or the proxy of early

pregnancy weight) on fetal growth are observational in nature. Thus, randomized controlled trials were not specifically excluded, but none could be identified for inclusion.

Types of Participants

All participants were pregnant women. To be eligible for inclusion, studies had to identify cases using the Institute of Medicine Guidelines on Weight Gain in Pregnancy to define obesity (BMI ≥ 30.0 kg/m^2).[47] Maternal obesity defined as BMI ≥ 30 kg/m^2 comprised the exposure variable for this review; the obesity measure had to be obtained pre-pregnancy, in the first trimester or at the first antenatal visit. There had to be sufficient data present to allow for quantification of the number of obese patients included in the study.

Studies also had to identify a control group of women with a BMI in the underweight range (BMI < 18.5 kg/m^2), normal weight range (BMI 18.5 – 24.9 kg/m^2) or combined underweight + normal weight range (BMI <25.0 kg/m^2), obtained pre-pregnancy, in the first trimester or at the first antenatal visit. We elected to include both underweight and normal weight women in the control group. A total of twelve of the thirty eligible studies utilized a combined control group; exclusion of these studies would have reduced the power of the meta-analysis. Although it is recognized that maternal underweight increases the incidence of many adverse pregnancy outcomes (including fetal undergrowth), it is known to be protective against fetal overgrowth.[25;212] The prevalence of underweight among women entering pregnancy ranges from 3.0-11.7%, depending on the population studied.[25;53;212]

The rate of macrosomia among this group is small (3.5%), with the odds reduced by 50% (OR 0.5, 95% CI 0.4-0.6) compared to women of normal weight.[212] While inclusion of underweight women, therefore, magnifies the effect of maternal obesity, we felt that this would serve to highlight the association between excess maternal weight and fetal overgrowth. The impact of inclusion of underweight women is small, given the small proportion of normal weight to underweight women (7:1).[212] A final inclusion criterion for the control group was the presence of sufficient data to allow for quantification of the number of control patients included in the study.

Data on overweight women (BMI 25-29 kg/m^2) were excluded from this meta-analysis because the majority of studies did not include data on this subgroup. This precluded exploration of data stratified by BMI to explore gradient of risk.

Determination of Maternal Weight and Infant Birth Weight

Studies were included if maternal weight was obtained by self-report or direct measurement and infant birth weight was reported. Information was sought from the studies regarding method of determination of both maternal weight and infant birth weight.

Types of Outcome Measures

The outcome measures of interest represented measures of fetal overgrowth. Studies had to include data that allowed for quantitative measurement of risk of overgrowth, defined as large for gestational age (≥ 90%ile) or fetal macrosomia (≥ 4000g and/or ≥ 4500g).

The outcome measure of fetal overgrowth was captured in two different ways (large for gestational age and macrosomia) for several reasons. Clinically, both are well-recognized and commonly-used means of determining excess fetal growth. Since identification of large-for-gestational-age infants involves correction for the gestational age at birth, it allows inclusion of "overgrown" newborns at all gestational ages (even though the absolute birth weight may be relatively light). These infants may also face adverse outcomes related to fetal overgrowth, although intuitively these adverse outcomes are more likely to be fetal or neonatal in nature, rather than maternal. Macrosomia using any cut-point, on the other hand, is based entirely on absolute birth weight. Fetal overgrowth using this definition almost exclusively occurs in term infants. The sheer size of these fetuses contributes to adverse maternal outcomes, with the infants themselves also facing significant neonatal sequelae. Since both measures of fetal overgrowth add to the clinical picture, data were collected for both.

3.2.3 Exclusion Criteria

All studies that met inclusion criteria and language restrictions were included in the review.

3.2.4 Language restrictions

All studies with an English abstract were considered for inclusion. Studies that did not have full text in English were translated for review.

3.2.5 Study selection

All potential studies were assessed for eligibility by the first reviewer (LG) according to the pre-specified criteria outlined in the previous sections. Studies and abstracts were screened and duplicates were removed. Data were extracted from each publication by the first reviewer. All identified studies were then reviewed by a second reviewer (ZF) and data extraction completed. Discrepancies regarding inclusion and extraction were then resolved by consensus.

3.2.6 Quality assessment

The quality of included studies was assessed using criteria from the Newcastle-Ottawa Quality Assessment Scale.[213] The representativeness of the exposed and control groups, the means by which the exposure was ascertained and follow-up rates were assessed. Data regarding age, parity, presence of diabetes, presence of hypertension, socioeconomic status, race and multiple gestations were extracted to allow for comparison of included study populations.

The overall quality of the included studies was then graded as low, moderate or high according to pre-specified criteria, including representativeness of the exposed cohort, representativeness of the non-exposed cohort, ascertainment of exposure, comparability of cohorts and adequacy of follow-up. Outcomes were considered to have a high risk of bias if there was a major methodologic flaw in the study and as low risk of bias if BMI was calculated using a measured first trimester weight and there were no major methodologic flaws. Studies were therefore graded as high if height and weight were measured and ≥4 of the quality assessment criteria were rated as high. Moderate quality studies were those in which height and/or weight were self-reported and there were ≥3 quality assessment criteria graded as high or if height and/or weight were measured but there were <4 criteria graded as high. Studies were designated as low quality if height and/or weight were self-reported and >3 quality assessment criteria were graded as less than high. All data were extracted independently by both reviewers and quality grades assigned; discrepancies were resolved by consensus.

3.2.7 Data abstraction

A structured data form was developed prior to beginning data abstraction (Appendix 3.1). The form consisted of four sections. The first was designed to determine whether a study met inclusion criteria for the review. If inclusion criteria were met, the second section containing data necessary to answer the question of whether maternal obesity contributes

to macrosomia was completed. In addition to information pertaining to the exposures and outcome measures, data regarding study design, study setting, geographic location, time period of the study, ethnicity and inclusion and exclusion criteria were extracted. The final two sections allowed quality assessment of the study designs used in the review (cohort studies and case control studies); they were developed using the Newcastle-Ottawa Scale.[213] The abstraction form was reviewed by the thesis supervisors.

All information regarding cases, controls and outcomes were extracted as raw numbers and resulting unadjusted odds ratios compared to those calculated from the raw numbers. Adjusted odds ratios were also abstracted.

3.2.8 Data analysis

Data from the different studies were then combined by meta-analysis. The control group included women who did not carry excess weight (BMI <25 kg/m^2, underweight and normal weight women). The exposure group consisted of obese women (BMI ≥ 30 kg/m^2).

Studies were grouped according to outcome measure (≥ 90th percentile, birthweight ≥4000g or ≥4500g). Frequencies were then used to generate unadjusted odds ratios and confidence intervals and Forest plots were generated.

Meta-analysis was completed using the Comprehensive Meta-analysis Version 2.0. A random effect model was used to estimate the overall effect.[214] This was chosen over a fixed-effects model because it was felt that the effect size would vary between studies, depending on the exact population included (for example, depending on method of ascertainment of maternal BMI, parity, ethnicity, glycemic control, etc.).[215] To assess statistical heterogeneity and its magnitude, we used Cochran's Q (α=0.10) and the I^2 statistic respectively.

A sensitivity analysis was then undertaken, in which several key aspects that could result in heterogeneity were examined, including study quality (high versus moderate/low), ascertainment of height and weight (self-report versus measured), restriction of the control group (normal weight women only versus normal weight + underweight women), diagnosis of diabetes (all patients with diabetes versus some patients with diabetes versus no patients with diabetes), region/country of origin (high wealth country versus not lower wealth country as defined by the World Bank Classification), and date of study publication (≥ 2009 versus < 2009 – the year of publication of the most recent IOM guidelines on gestational weight gain).[47;216] Other aspects of interest included diagnosis of hypertension, gestational weight gain and maternal age – these could not be assessed as there was insufficient information available from the available studies for quantitative analysis. Again, a random effect model was used to estimate the overall effect.[214] To assess and compare statistical heterogeneity and its magnitude, we used Cochran's Q (α=0.10) and the I^2 statistic respectively.

3.3 Results

The search strategy yielded 285 articles (see Figure 3.1. Study flow diagram). Four duplicate articles were excluded. An additional 14 articles were identified by cross-referencing, reviewing reference lists and email-based discussion with authors. Six articles were not retrieved for review because they could not be obtained via interlibrary loan or because they were non-English articles without an English abstract. Thus, 289 full articles were retrieved and reviewed for inclusion. It was necessary to retrieve the full article in order to determine inclusion; the necessary detail was not available from abstracts alone. Characteristics of the included studies are detailed in Table 3.1.

After reviewing titles and abstracts, 259 articles were rejected because they did not meet inclusion criteria. Reasons for rejection are included in Table 3.2 (Characteristics of Excluded Studies):

The majority of excluded studies were published prior to 1997, at which time the World Health Organization standardized the classification system for body mass. Due to the lack of standardization prior to that point, studies used differing definitions for categories including normal weight, overweight and obese. The data resulting from these studies could not be included.

3.3.1 Description of Studies

Thirty studies met the inclusion criteria of the study. A list of the included studies and their characteristics is provided in Table 3.1 (Characteristics of Included Studies).

Of the included studies, nine were conducted in the United States, four in the United Kingdom, four in Denmark, two in Canada, two in Germany and one in each of Hong Kong, Australia, Norway, Italy, India, France, Finland, Saudi Arabia and the West Indies. Thus, the information in this review applies primarily to upper/middle income countries according to the World Bank classification.[216]

The year of publication ranged from 1992 to 2010. Of included studies, eight had prospective cohort design, twenty-one had retrospective cohort design and 1 was a retrospective case-control study. Eleven of the studies were conducted using population-based databases; these studies contributed 1,443,449 women to the meta-analysis.

When studies were reviewed, the outcome measures of interest were identified. Six studies reported on more than one outcome measure; information for all relevant outcome measures was abstracted. Thus, thirteen studies reported on LGA, sixteen reported on macrosomia ≥ 4000g and eight reported on macrosomia ≥ 4500g.

Table 3.3 contains details of the patients from the included studies, as well as the reported effect size.

3.3.2 Large for Gestational Age

In the thirteen studies that examined the relationship between maternal obesity and infant birthweight ≥ 90%ile, there were a total of 162,183 obese parturients. The control group consisted of 1,072,397 underweight or normal weight women. A total of 214,385 infants were large for gestational age (17.4%). Of these, 36,293 were born to obese mothers; thus, 22.4% of obese mothers gave birth to an LGA baby. By comparison, 16.6% of underweight or normal weight mothers gave birth to an LGA baby (n=178,092).

The calculated unadjusted odds ratios for the included studies ranged from 0.86 to 4.33. All studies, except one, demonstrated a positive relationship between maternal obesity and a large for gestational age infant. The singular study that failed to show this positive relationship demonstrated a non-significant decrease (OR 0.86, 95% CI 0.37, 2.02).[195]

Meta-analysis revealed an overall unadjusted odds ratio of 2.42 [2.16, 2.72], Table 3.4. Thus, an obese woman has a 113% increase in the odds of having an LGA infant. The large number of maternal-infant dyads in the literature allows for a highly statistically-significant measure. Figure 3.2 (Forest Plot for Large for Gestational Age >90%ile) visually displays the results of the meta-analysis.

3.3.3 Macrosomia (Birthweight ≥ 4000g)

In the sixteen studies that examined the relationship between maternal obesity and macrosomia ≥ 4000g, there were a total of 20,693 obese parturients. The control group consisted of 110,696 underweight or normal weight women. A total of 13,612 infants had a birthweight ≥ 4000g (10.4%). Of these, 3,275 were born to obese mothers; thus, 15.8% of obese mothers gave birth to a macrosomic baby weighing ≥ 4000g. By comparison, 9.3 % of underweight or normal weight mothers gave birth to a macrosomic baby weighing ≥ 4000g (n=10,337).

The calculated unadjusted odds ratios for the included studies ranged from 1.43 to 25.58. All studies demonstrated a positive relationship between maternal obesity and infant birthweight ≥ 4000g.

Of note, two studies appeared to have notably different results than the remainder. The first of these, by Sahu et al, investigated the effect of obesity on birthweight ≥ 4000g and found an increased odds of 25.58 [95%CI 1.02, 642.21].[217] They studied 281 women from Northern India - the effect of this small sample size is evidence in the wide confidence intervals. This ethnic population is recognized to have lower birthweights than babies of Caucasian descent. As such, a birthweight exceeding 4000g is more extreme in this population and likely contributes to a more prominent association. The second study, by Le

Thai et al, revealed increased odds of 23.89 [3.09, 184.72].[218] The small sample size is again evident, and in this particular study there was a marked difference between the control and exposed populations; obese women were considerably more likely to be hypertensive, diabetic, post-term and advanced maternal age and less likely to deliver preterm than their control counterparts. As a result, it again seems that two extremes are being compared.

Meta-analysis revealed an overall unadjusted odds ratio of 2.17 [1.92, 2.45], Table 3.4. Thus, an obese woman has a 101% increase in the odds of delivering an infant whose birthweight is ≥4000g. Figure 3.3 (Forest Plot for Macrosomia (>/= 4000g) visually displays the results of the meta-analysis.

3.3.4 Macrosomia (Birthweight ≥ 4500g)

In the eight studies that examined the relationship between maternal obesity and macrosomia ≥ 4500g, there were a total of 18,909 obese parturients. The control group consisted of 62,712 underweight or normal weight women. A total of 1,739 infants had a birthweight ≥ 4500g (2.1%). Of these, 746 were born to obese mothers; thus, 3.9% of obese mothers gave birth to an LGA baby. By comparison, 1.6% of underweight or normal weight mothers gave birth to an LGA baby (n=993).

The calculated unadjusted odds ratios for the included studies ranged from 1.87 to 4.68. All studies demonstrated a positive relationship between maternal obesity and infant birthweight ≥ 4500g.

Meta-analysis revealed an overall unadjusted odds ratio of 2.77 [2.22, 3.45], Table 3.4. Thus, an obese woman has a 201% increase in the odds of delivering an infant whose birthweight is ≥4500g. Figure 3.4 (Forest Plot for Macrosomia (>/= 4500g) visually displays the results of the meta-analysis.

3.3.5 Quality Assessment

The quality of studies was also assessed (details in Table 3.5). Criteria for quality assessment were determined *a priori* (Table 3.6 Quality Assessment Criteria). Four studies were judged to be of high quality, fifteen were of moderate quality and eleven were of low quality. All high-quality studies had exposed and non-exposed cohorts that were felt to be representative of the general population and had measured heights and weights. In general, moderate-quality studies had representative cohorts but used self-reported heights and weights. Low quality studies used self-reported height and weight and had other major methodological flaws.

3.3.6 Clinical and Statistical Heterogeneity

There appeared to be important clinical heterogeneity between the included studies. For example, some studies included only normal weight patients in the control (17/30) while others included normal weight and underweight women (13/30). Also, most studies determined BMI using self-reported pre-pregnancy weight or did not provide information on how BMI was derived (20/30), while those studies that used measured weights had differing criteria for when that weight was measured (varied from <8 weeks to <16 weeks). Furthermore, some studies excluded women with hypertension or diabetes, while others included them. Thus, clinical heterogeneity was apparent.

There was also a marked amount of statistical heterogeneity, as assessed by the I^2 statistic. For obese women, the I^2 value for LGA was 97%, for macrosomia of ≥4000g the I^2 value was 69% and for macrosomia of ≥4500g the I^2 value was 48%. These indicate diverse results and a large amount of heterogeneity that cannot be explained by chance alone.

3.3.7 Sensitivity Analyses

Given the degree of observed heterogeneity, a number of sensitivity analyses were performed in an attempt to improve the utility of the results.

Including only high quality studies decreased heterogeneity for LGA (Figure 3.5); the I^2 value improved to 0% from 97%. As there was only one high quality study for macrosomia

≥4000g, a similar analysis could not be undertaken (Figure 3.6). For macrosomia ≥ 4500g, the I^2 value worsened slightly, from 48% to 62% (Figure 3.7). Including only high quality studies for LGA gives an odds ratio of 2.54 (95% CI 2.22, 2.92).

Using measured height and weight also seems to decrease the heterogeneity across all three outcomes. For LGA, the I^2 value improved slightly to 80% from 97% (Figure 3.8), for macrosomia ≥4000g the I^2 value improved marginally to 61% from 69% (Figure 3.9), and for ≥4500g the I^2 value improved to 14% from 48% (Figure 3.10). Using only measured height and weight gives odds ratios for the effect of maternal obesity of 2.46 (95% CI 2.39, 2.52) for LGA, 3.08 (95% CI 1.88, 5.05) for macrosomia ≥4000g and 3.09 (95% CI 2.57, 3.72) for macrosomia ≥ 4500g.

Interestingly, whether the control group consists of only normal weight women or if underweight women are included groups all are essentially equally heterogeneous. Sensitivity analysis of national wealth and date of study publication also failed to reveal significant improvement in heterogeneity. Finally, discrepancies in reporting of diabetes and hypertension precluded interesting and important examination of their potential mediating role.

3.4 Discussion

3.4.1 Summary of Key Findings

There is a large amount of data in the literature that investigates the relationship between maternal obesity and fetal overgrowth, including millions of maternal-infant dyads. Quality of included studies was variable. The majority of included studies were of retrospective cohort design and relied on self-reported pre-pregnancy weight and height. Most mother-infant dyads were obtained from large population-based databases.

This systematic review and meta-analysis confirms that maternal obesity is clearly associated with fetal overgrowth. The odds of delivering a large for gestational age infant ($\geq 90^{th}$ percentile) are increased 142%. The odds of having a baby with a birthweight ≥ 4000g are increased 117%. Maternal obesity appears to be associated with the heaviest newborns (birthweight ≥ 4500g), with odds that are 277% increased.

3.4.2 Interpretation of Findings and Implications

The findings from this meta-analysis provide clinicians with very precise information on the increase in risk of fetal overgrowth among obese women. This information can be used for several purposes. It is important that women contemplating pregnancy be aware of potential risks related to their weight – the possibility of fetal overgrowth should be discussed. As obese women approach the end of their pregnancy, consideration should be given to obtaining a growth ultrasound in the third trimester. Although the limitations of ultrasound estimation of fetal weight should be considered, it is useful to be aware if fetal

macrosomia or small-for-gestational age status is suspected. This is especially important in the obese diabetic population, in whom operative delivery is considered when the estimated fetal weight exceeds 4500g. Although there is no consensus, some clinicians advocate offering operative delivery to non-diabetic women with a fetal weight exceeding 5000g. If these criteria are not met, a trial of vaginal delivery should be undertaken. The accoucheur and the expectant parents should be aware of the potential for macrosomia, particularly if operative vaginal delivery is entertained, due to the increased risk of birth complications including shoulder dystocia, perineal trauma and post-partum hemorrhage.

3.4.3 Strengths

This review is based on a thorough review of the literature. It incorporates, to our knowledge, all of the data available world-wide concerning the risk of fetal overgrowth among infants of obese mothers. Study selection and data abstraction were both performed by two reviewers, resulting in increased confidence in the comprehensiveness of the review.

Strict inclusion and exclusion criteria were applied. Despite clear descriptions of the BMI classification system by the World Health Organization, there continues to be a large degree of variation in the definitions of underweight, normal weight and obesity among studies.[2] This resulted in the exclusion of a large number of studies that also examined the effects of excess maternal weight on fetal overgrowth. Nonetheless, by adhering to the

World Health Organization definitions in this review, meta-analysis could be performed with confidence.

The inclusion of a quality assessment is a valuable asset of this review that allows readers to judge the strength of the results. There was a wide variation in the quality of studies, with several being of low quality (non-representative cohorts, self-reported weight and height). For the most part, it does not appear as though there was a substantial difference in the results obtained from low, moderate and high quality studies as demonstrated in the sensitivity analysis, a finding that adds to the strength of the relationship. The exception to this statement is found with studies of the association between obesity and large for gestational age, in which high quality studies were far less heterogeneous. It should be noted that there are only two studies that were graded as high-quality, a fact that largely accounts for the increased homogeneity.

The sensitivity analyses that were completed add to the available literature substantially. To the best of our knowledge, a similar analysis has not been completed previously. This process suggested the importance of conducting well-designed high-quality studies. Of particular importance is ensuring that weight and height are determined by direct measurement, as early in pregnancy as possible.

3.4.4 Limitations

The original data used in this meta-analysis are obtained from observational studies because of the nature of the research question. As such, all of the potential biases that pertain to observational studies should be considered.

One limitation of this study is the inclusion of studies that use self-reported data on height and weight. There are no studies in the literature that use measured pre-pregnancy weight to define pre-pregnancy obesity. The timing of conception cannot be accurately predicted and few patients have a measured, recorded weight documented immediately prior to conception. Rather, authors rely on self-reported first trimester weight or use measured weight (generally in the first trimester) as a proxy for measured pre-pregnancy weight. The exact pattern of weight gain in the first trimester is difficult to determine, but it is generally accepted that there is minimal (< 1kg) weight change in the first trimester for most women. It has been clearly shown that women in general under-report their weight. Data from a recent prospective cohort study found that pregnant women of all body masses under-report their pre-pregnancy weight when first trimester weight is used as a proxy.[219] The limitations of using either self-reported pre-pregnancy weight or first trimester weight as a surrogate for pre-pregnancy weight must be considered. Few women, however, will enter a different class of body mass on the basis of this potential misclassification bias.

A relatively large proportion of obese pregnancy women develop abnormalities with glycemic control. Diabetes (pre-existing or gestational) likely acts as an effect modifier on the relationship between maternal obesity and fetal overgrowth. A few of the studies in

this meta-analysis excluded women with diabetes from the analysis, while a few others included only women with diabetes. Determining the contribution of abnormal glycemic control was beyond the scope of this project, but almost certainly plays a crucial role in the development of fetal overgrowth. The odds ratios from this meta-analysis should be used only to discuss the overall impact of maternal obesity on excess fetal weight, and do not represent the independent contribution of maternal obesity.

The generalizability of the results should be interpreted with caution. The majority of the studies included in this review (including several national population-based cohorts) were completed in North America and Western Europe. Few studies examined the role of maternal obesity on fetal overgrowth in women from Africa, Asia or South America. As there are fundamental differences in nutrition, socioeconomic and educational status and prenatal/intrapartum care in these regions, results may or may not be applicable.

3.4.5 Conclusions

The results from this meta-analysis provide convincing evidence of the positive relationship between maternal obesity and fetal overgrowth. Maternity care providers should be aware of the increased risk among obese women, encourage lifestyle modifications that decrease gestational weight gain and manage abnormal glucose metabolism to optimize fetal growth. This is important to decrease both intrapartum complications and neonatal sequelae (such as birth trauma and hypoglycemia). Furthermore, optimal fetal growth

contributes to *in utero* epigenetic programming that favours a healthy long-term weight trajectory and metabolic profile. The association between maternal obesity and fetal overgrowth may well represent the first opportunity through which obese mothers can modify the inter-generational obesity cycle and result in healthier, happier families.

4. RETROSPECTIVE COHORT

4.1 Research Objectives

The primary objective was to determine the combined effect of macrosomia (infant birthweight ≥ 4000g) and maternal obesity (pre-pregnancy BMI > 30kg/m^2) on adverse outcomes.

The secondary objective was to describe the occurrence of adverse pregnancy outcomes in macrosomic infants (birthweight ≥4000g) of non-obese (pre-pregnancy BMI ≤ 30kg/m^2) and obese (pre-pregnancy BMI > 30kg/m^2) mothers.

4.2 Methodology

4.2.1 Study Design

This is a retrospective cohort study derived from the Better Outcomes Registry and Network (BORN) Ontario dataset. BORN is a population-based database that strives to capture information on all births in Ontario. The BORN dataset includes 100% of hospital births in the province of Ontario. These data are regularly validated for quality assurance purposes using multiple mechanisms, including duplicate entry of important data elements (including birth weight), built-in safety checks/cues, individual center verification of key

outcomes (such as number of births per center) and chart audit.[220] For the purpose of this study, all data were used anonymously.

4.2.2 Ethics Approval

The study was approved by the Research Ethics Board at the Ottawa Hospital and at the Children's Hospital of Eastern Ontario.

4.2.3 Study Population

The study population consisted of all deliveries at The Ottawa Hospital, Civic Campus, between December 1, 2007 and March 31, 2010. The Civic Campus was chosen from the Ontario dataset because, at the time that the study was completed, they were the only site to reliably input data regarding maternal height and pre-pregnancy weight. Mother-infant pairs with a macrosomic infant (birthweight ≥ 4000g) were included in the final study population (835 pairs).

Figure 4.1 details the selection of the study population. Initially, all women with a singleton pregnancy that delivered a live-born infant at 24 weeks gestation and beyond (n=7458) were screened for inclusion. From this group, mother-infant pairs were excluded if there was missing data required to calculate pre-pregnancy BMI (498/7458, 6.7%) or infant birthweight (0/7458, 0%). Baseline characteristics of women with data required to

calculate BMI were compared to those of women who were missing data for BMI calculation.

4.2.4 Exposure Variables

The exposure of interest was pre-pregnancy obesity (BMI ≥ 30 kg/m^2). In the BORN dataset, pre-pregnancy BMI is calculated from either self-reported pre-pregnancy weight or measured weight from the first antenatal visit and self-reported or measured height.

The mother-infant pairs were divided into two cohorts (as shown in Table 4.1) on the basis of the exposure of maternal pre-pregnancy BMI: non-obese (BMI <30.0 kg/ m^2) or obese (BMI ≥ 30.0 kg/ m^2). These categories were chosen for the same reasons outlined in the systematic review – essentially to focus on the effect of marked excess maternal weight (obesity) and to be consistent with the established literature and clinical practice patterns and guidelines. The limitations of grouping underweight, normal weight and overweight women were considered.

From the database, the following information was abstracted: maternal age at conception, parity, smoking habits, infant sex, presence of gestational hypertension, and presence of gestational diabetes. Gestational hypertension was defined as new onset hypertension during pregnancy in the absence of proteinuria. At least one of the following criteria were met: blood pressure was ≥ 140/90 on at least two occasions at least 6 hours apart, there

had been a rise in systolic pressure of at least 30 mmHg or a rise in diastolic pressure of at least 15 mmHg, a diastolic pressure of at least 90 mmHg or a mean arterial pressure ≥ 105 was obtained. Gestational diabetes was defined as carbohydrate intolerance of varying severity with onset of first recognition during the present pregnancy, as assessed using the oral glucose tolerance test.

4.2.5 Outcome Variables

4.2.5.1 Primary Outcome Variable

The primary outcome for this study was the rate of Cesarean section (for any indication: failure to progress/descend, non-reassuring fetal heart rate, breech presentation or maternal indication), a variable that was chosen for several reasons. First, there has been extensive work done previously by our group and others regarding the contribution of excess maternal weight to rate of operative delivery and to the rate of macrosomia.[4;36;66;138;192;195;221;222] To the best of our knowledge, however, there is no data on the combined effect of these two exposures to operative delivery. The six perinatologists at the Ottawa General Campus were, therefore, asked to estimate the increase in rate of Cesarean section among obese women in whom the fetus is macrosomic. An average value of these answers was then used in the power calculation. The second reason Cesarean section was chosen as the primary outcome variable was that we suspected that operative delivery would be the most common adverse pregnancy outcome in this population. Finally, Cesarean section represents the culmination of excess maternal

and fetal weight and contributes to further adverse outcomes (such as prolonged hospital stay, wound infection and transient tachypnea of the newborn). For these reasons, we felt this was the most valuable primary outcome variable.

4.2.5.2 Secondary Maternal Outcome Variables

Secondary maternal pregnancy outcomes felt to be related to fetal macrosomia were identified from the dataset. Relevant labour management issues included induction of labour (for any indication or for suspected large-for-gestational-age fetus), labour augmentation with oxytocin and prolonged second stage (≥ 3 hours). Delivery outcomes consisted of operative vaginal delivery (vacuum, forceps and vacuum or forceps) and Caesarean section (for any indication, failure to progress/descend, non-reassuring fetal heart rate, breech presentation or maternal indication). In addition, the type of regional analgesia (epidural, spinal or combined spinal-epidural) was examined.

Due to small outcome rates (n<6 – a value pre-set by BORN), several variables had to be excluded from the study due to risk of re-identification (Caesarean section for failed operative vaginal delivery, elective Caesarean section, vacuum and forceps assisted vaginal delivery, grade III/IV perineal laceration, general anaesthesia and postpartum hemorrhage).

4.2.5.3 Secondary Fetal/Neonatal Outcome Variables

Adverse pregnancy outcomes for offspring were also interrogated as secondary outcomes. These included rates of fetal monitoring during labour (auscultation (not an adverse outcome), continuous external fetal monitoring and continuous internal fetal monitoring), meconium (presence of meconium in the amniotic fluid) and cord artery base excess >12.0. The level of neonatal resuscitation required was examined, including no resuscitation, free flow oxygen, positive pressure ventilation, and intubation.

Variables excluded due to small outcome rates included NICU admission, shoulder dystocia, five minute Apgar <4, cord artery pH <7.0, need for chest compressions during resuscitation and need for administration of drugs for resuscitation.

4.2.6 Statistical Analyses

A sample size calculation was performed *a priori*. The primary outcome of interest was the change in Cesarean section rate due to fetal overgrowth. Cesarean section was chosen as the primary outcome because it is common, has been shown to be increased in the presence of both maternal obesity and fetal overgrowth, and has been clearly shown previously in the literature.[25;39] Bhattacharya and colleagues found that maternal morbid obesity resulted in a doubling of the risk of fetal macrosomia as defined by a birth weight ≥4000g (7.6% for BMI 20-24.9 kg/m^2 and approximately 14% for BMI >30 kg/m^2).[19] In addition, Sebire and colleagues found that the rate of Cesarean section increased from roughly 9% to 13.4% as maternal BMI increased from 20-29.9 kg/m^2 to greater than 30

kg/m^2 (odds ratio 1.83, 95% CI 1.74, 1.93).[42] Approximately 20% of normal weight infants born to non-obese mothers are born by Cesarean section at the Ottawa Hospital. Using the data from Bhattacharya, it is estimated that 35% of macrosomic infants born to non-obese mothers are delivered by Cesarean section. In the absence of available evidence in the literature, it was anticipated that there would be a 25% increase in the rate of Cesarean section for obese women with a macrosomic fetus. For the primary analysis, we compared the occurrence of Cesarean section in the cohort of non-obese women with macrosomic infants to the cohort of macrosomic fetuses of obese women. The effect size, therefore, is 0.25. Alpha is set at 0.05, and beta at 0.8. In order to detect a 25% increase in the occurrence of Cesarean section in these groups, 62 infants were required in each group, for a total of 124 subjects.

Maternal and neonatal characteristics of the two cohorts were compared using Fisher's exact test for categorical variables and a t-test for continuous variables.

Univariate logistic regression modeling was then performed for maternal and neonatal outcomes to determine the unadjusted odds of association. Variables used in the model were identified from the existing literature. Here, the predictor or independent variable was presence of co-existing maternal obesity and fetal macrosomia (maternal BMI ≥ 30 kg/m^2 and infant birthweight ≥ 4000g). The primary outcome variable of Cesarean section was entered as the primary dependent variable (Cesarean section for any reason = 1, delivery other than by Cesarean section = 0). Secondary maternal outcomes included

induction of labour (yes=1), induction of labour for the indication of large for gestational age (yes=1), augmentation with oxytocin (yes=1), prolonged second stage >3 hours (yes=1) Cesarean section for failure to progress/descend (yes=1), Cesarean section for non-reassuring fetal heart rate (yes=1), Cesarean section for breech presentation (yes=1), Cesarean section for maternal indication (yes=1), vacuum-assisted vaginal delivery (yes=1, vacuum- or forceps-assisted vaginal delivery (yes=1) and placement of regional anesthesisa (yes=1). Secondary fetal/neonatal outcomes included use of auscultation of the fetal heart rate in labour (yes=1), use of internal fetal monitoring in labour (yes=1), use of external fetal monitoring in labour (yes=1), presence of meconium (yes=1), cord artery base excess >12.0 (yes=1), no resuscitation required (yes=1), use of free flow oxygen during resuscitation (yes=1), use of positive pressure ventilation during resuscitation (yes=1), intubation during resuscitation (yes=1), stillbirth (yes=1), early neonatal death prior to 7 days of life (yes=1), late neonatal death between 7 and 28 days of life (yes=1) and perinatal mortality from 0 to 28 days of life (yes=1).

Using multivariate logistic regression, variables were entered as described under univariate analysis. All variables identified from the existing literature appeared notable following univariate analysis. The odds of independent association were assessed by adjusting for characteristics and lifestyle factors that are known to correlate with the endpoints under study, including maternal age, smoking, infant sex, presence of gestational diabetes and presence of gestational hypertension. Given that length of gestation can also influence

both infant birthweight and risk of adverse pregnancy outcome, gestational age at birth was also adjusted for as a continuous variable.

In order to examine the robustness of the association between maternal obesity combined with fetal macrosomia and adverse pregnancy outcomes, the control group (non-obese women, BMI 25.0-29.9 kg/m^2) was broken down into three classes: underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2) and overweight (25.0-29.9 kg/m^2). The univariate and multivariate logistic regressions were then performed for each class individually, for both maternal and fetal/neonatal outcomes.

The impact of confounding variables was further examined. First, the strength of the association between obesity and fetal overgrowth was compared to the strength of association of the confounding variables that were used to calculate adjusted ORs. Then, since gestational diabetes and gestational hypertension appeared to play an important role in contributing to Caesarean delivery of obese mothers with macrosomic babies, the crude and adjusted relations between macrosomic infants exposed to maternal obesity and gestational diabetes (and, separately, gestational hypertension) and the odds of operative delivery were assessed.

4.2.7 Missing Values

For the majority of outcome variables, there were very few missing values (Table 4.2). If fewer than 5% of observations had a missing value, correction was not completed. Missing values greater than 5% were adjusted for in the multivariate models (including prolonged second stage and augmentation with oxytocin). The missing data were considered to be missing at random. For data analysis involving both dependent and independent variables, an "unknown" category was created with missing data and included in the regression model for subjects with missing data.

4.3 Results

4.3.1 BMI of Women Delivering at the Ottawa Hospital Civic Campus, December 1, 2007 to March 31, 2010

A total of 7458 women delivered at the Ottawa Hospital Civic Campus between December 1, 2007 and March 31, 2010. Figure 4.1 provides details of the derivation of the cohort. In total, 6,960 women had information present that allowed calculation of pre-pregnancy BMI. The pre-pregnancy BMI of the patients was determined and classified using the World Health Organization system.[2] Of women with calculable BMI, 19% were obese (Table 4.3). The majority of women in the control cohort were of normal weight or were overweight (76.81%).

The only significant difference between women with data necessary to calculate BMI and those without involved the presence of gestational hypertension (Table 4.4). Women included in this study were more likely to have gestational hypertension than those who were excluded due to missing date needed to calculate BMI (3.57% versus 1.26%, $p<0.0073$).

4.3.2 Macrosomia

There were 835 women who delivered macrosomic infants (birthweight ≥ 4000g), representing 12% of births. There were significantly more ($p<0.0001$) macrosomic infants born to women who were obese (240/1328, 18.1%) than to women who were non-obese (595/5632, 10.6%). Of macrosomic infants, approximately half were born to women of normal weight, one in four were born to overweight women and one in four were born to obese women (Table 4.5).

As a group, macrosomic infants were heavier if their mothers were obese. Mean birthweight was significantly higher (4328 +/- 276.44g versus 4268 +/- 233.15g, p-value <0.001). The proportion of infants who were large for gestational age (>90%ile) was also significantly increased (84.17% versus 68.40%, p-value <0.001). Grade II macrosomia, defined as birthweight ≥ 4500g was more common in macrosomic infants of obese mothers (25.00% versus 15.80% of infants in the dataset) as was grade III macrosomia, defined as birthweight ≥ 5000g (data not presented due to risk of re-identification).

Table 4.6 reviews the maternal and fetal characteristics within the two cohorts. There is a significant difference in gestational age between the cohorts, with non-obese mothers of macrosomic infants delivering approximately 4 days later than obese mothers of macrosomic infants. Gestational diabetes was more common in pregnancies that produced macrosomic infants if the mother was obese (11.72% versus 2.70%, $p<0.001$). There was a trend towards increased incidence of gestational hypertension in obese mothers of macrosomic infants (5.44% versus 2.53%, $p=0.05$). Smoking during pregnancy was significantly more common among obese women who delivered a macrosomic infant than among non-obese women (6.25% versus 2.69%, $p=0.02$).

4.3.3 The Effect of Macrosomia and Maternal Obesity on Maternal Pregnancy Outcomes

The combination of fetal macrosomia and maternal obesity was found to increase the chance of complications for the mother (Table 4.7). Specifically, labour was more likely to be induced in obese women who delivered macrosomic fetuses after adjustment for maternal age, parity, gestational age at delivery, smoking and infant sex (OR 1.42, 95% CI 1.10, 1.98). Induction of labour for the indication of suspected large for gestational age infant was examined separately and not found to be more common (OR 0.83, 95% CI 0.45-1.56). Thus, the difference in induction rates is related to other indications (for example, maternal indications or post-dates pregnancy).

Delivery by Caesarean section was increased in obese women who delivered macrosomic fetuses. There is an increase in the odds of operative delivery for all indications (OR 1.45, 95% CI 1.04, 2.01), when adjusted for maternal age, parity, gestational age at delivery, smoking, infant sex, presence of gestational diabetes and presence of gestational hypertension. When common indications for Caesarean section were considered, there was a clear association between maternal obesity with fetal macrosomia and operative delivery for a maternal indication (OR 3.71, 95% CI 1.47, 9.36). Data regarding elective Caesarean section and Caesarean section for failed operative vaginal delivery could not be presented due to risk of re-identification.

4.3.4 The Effect of Macrosomia and Maternal Obesity on Fetal/Neonatal Outcome Variables

Several important fetal and neonatal outcomes were examined (Table 4.8). There did not appear to be a decrease in the use of auscultation for monitoring or an increase in the rate of internal or external fetal monitoring of macrosomic fetuses of obese women, and meconium was not more common. As data regarding fetal monitoring may lack accuracy, this information should be interpreted with caution.

Neonatal resuscitation was significantly different in macrosomic babies of obese women compared to macrosomic babies of non-obese women. Macrosomic newborns were significantly less likely avoid resuscitation of any type (OR 0.64, 95 % CI 0.43, 0.95) if their

mother was obese. They were significantly more likely to require free flow oxygen after delivery (OR 1.57, 95% CI 1.03, 2.42). There was a statistically significant increase in need for positive pressure ventilation (OR 1.57, 95% CI 1.03, 2.42) and a statistically non-significant trend towards increased need for intubation (OR 1.57, 95% CI 0.91, 2.71) during resuscitation of macrosomic infants of obese mothers. All resuscitation outcomes were adjusted for maternal age, parity, gestational age at delivery, smoking and infant sex.

4.3.5 Sensitivity Analysis of the Effect of Increasing Maternal BMI Class on Adverse Pregnancy Outcomes

We further explored the effect of maternal weight on adverse pregnancy outcomes by separating the control group of non-obese women (BMI ≤30 kg/m^2) into the standard subcategories: underweight (BMI ≤18.5 kg/m^2), normal weight (BMI 18.5-24.9 kg/m^2) and overweight (BMI 25.0-29.9 kg/m^2). Unfortunately, due to risk of re-identification, data for several variables could not be reported (particularly for the underweight category) (Tables 4.9 and 4.10). Although analysis of trends could not be completed for this reason, it was observed that, in general, the effect of maternal obesity became more pronounced the lighter the comparison group.

4.3.6 Comparison of the Strength of Association Between the Main Exposure of Interest (Maternal Obesity) and Confounding Variables

The strength of the association between maternal obesity combined with fetal macrosomia and adverse pregnancy outcomes was compared to the strength of association between the confounding variables combined with fetal macrosomia in Table 4.11 and 4.12. Generally, the association of maternal obesity was less pronounced than many of the confounding variables, a finding that was observed across multiple outcomes.

4.3.7 Combined Effect of Maternal Obesity, Macrosomia and Gestational Diabetes or Hypertension on Risk of Cesarean Section

Although data cannot be presented due to risk of re-identification, it was found that there was not a significant association between maternal obesity, macrosomia and gestational diabetes in predicting Caesarean delivery for any indication or for maternal indications as compared to non-obesity, macrosomia and no diagnosis of gestational diabetes (Table 4.13). For Caesarean section for any indication, the adjusted odds ratio was 1.20 (95% CI 0.51-2.81) and for Caesarean delivery maternal indication, the adjusted odds ratio was 2.41 (95% 0.58-9.92).

Moreover, it was found that there was not a significant association between maternal obesity, macrosomia and gestational hypertension in predicting Caesarean delivery for any indication as compared to non-obesity, macrosomia and no diagnosis of gestational hypertension (adjusted odds ratio 0.43, 95% CI 0.13-1.43) – see Table 4.14. For Caesarean section for maternal indication, there was, however, a statistically significant increase in the

odds of operative delivery in the presence of maternal obesity, fetal macrosomia and gestational hypertension (adjusted odds ratio 8.63, 95% CI 1.10-67.84).

As there were few cases of gestational diabetes and gestational hypertension in the study population, these results must be interpreted with caution.

4.4 Discussion

4.4.1 Summary of Key Findings

The results of this study confirm our hypothesis that pregnancies complicated by macrosomia have poorer maternal and fetal/neonatal outcomes if the mother is obese. Birthweight ≥ 4000g occurs in 12% of all births and in 18% of pregnancies in obese women. Pregnancies in obese women that result in macrosomic fetuses are more likely to be complicated by gestational diabetes, gestational hypertension, and smoking than pregnancies in non-obese women. Obese mothers are more likely to be induced and to require Cesarean section for delivery. Although the odds of undergoing Cesarean section for any indication were increased, the most striking reason for operative delivery was maternal indications. Macrosomic infants required more resuscitation if their mother was obese – they were significantly more likely to require free flow oxygen and positive pressure ventilation after delivery, with a trend toward needing more intubation. There

was a concurrent decrease in the odds of not requiring resuscitation among macrosomic infant of obese mothers.

4.4.2 Interpretation of the Findings and Implications

These findings confirm previous reports that fetal overgrowth is a common complication of pregnancy in obese women. The finding that pregnancies complicated by macrosomia are also more likely to be complicated by maternal disorders such as gestational diabetes and hypertension is not surprising, as these conditions are related to the severity of metabolic abnormality. Women with significantly aberrant metabolic status are more likely to have a macrosomic fetus; maternal metabolic abnormalities are likely a contributing factor to fetal overgrowth. Alternatively, the abnormal maternal environment may result in altered *in utero* epigenetic programming, leading to expression of genes that promote fetal overgrowth. In either case, maternity care providers should be aware that obese women with gestational diabetes or gestational hypertension are at higher risk of delivering a macrosomic fetus.

The major focus of this study was to determine whether intrapartum outcomes were substantially different in pregnancies complicated by both maternal obesity and fetal macrosomia. Clinically, it often seems as though there is a higher rate of obstetrical intervention for macrosomic fetus when there is co-existing maternal obesity. Our results confirmed that labour was more likely to be induced if there is both maternal obesity and

fetal overgrowth. The reasons behind this phenomenon could not be elicited from the BORN dataset, but are likely related to induction for risk related to maternal conditions (such as diabetes or hypertension) as well as suspected macrosomia. Although it was also anticipated that there would be an increased need for oxytocin augmentation, prolonged labour, prolonged second stage and post-partum hemorrhage, these associations could not be confirmed. Unfortunately, there was a large amount of missing data for the outcomes of oxytocin augmentation and prolonged second stage.

The data from this study suggests that rates of Cesarean section for all indications (including failure to progress/descend, non-reassuring fetal heart rate, breech presentation, maternal indication, failed operative vaginal delivery, and elective) are increased for macrosomic fetuses of obese women. For many indications, a definite association could not be shown due to small numbers. It is clear, however, that obese women with macrosomic fetuses have much higher odds of undergoing Cesarean section if there is a maternal indication for delivery, particularly gestational hypertension. The reasons behind this increase remain unclear and are likely complex. Cesarean section is neither a benign nor a simple operation in an obese patient. The risks are dramatically increased in the emergency setting. Logistically, it is preferable to perform a Cesarean section on an obese patient when optimal resources are available. This usually means a planned operation with more than one skilled surgeon and preparation for a complicated anesthetic and neonatal course, as well as resources such as bariatric beds, assisted patient transfer and invasive maternal monitoring. It is difficult to orchestrate the ideal setting when a patient is in

labour, particularly in community hospital settings. Furthermore, maternity care providers who are aware of the potential for fetal overgrowth and the resulting birth complications of shoulder dystocia and fetal injury may be reluctant to have an obese patient deliver vaginally. It is probable that the combination of maternal pregnancy complications and and logistical considerations in the presence of obesity leads intrapartum care providers to have a lower threshold for proceeding with Cesarean section in this population.

Macrosomic fetuses were more likely to require resuscitation if their mother was obese. This finding may reflect need for resuscitation after a more difficult vaginal delivery or after Cesarean section. It is well-recognized that infants born by Cesarean section are more likely to suffer from transient tachypnea of the newborn, a condition that often requires respiratory support.

It makes intuitive sense that pregnancy, and particularly delivery, are more complicated when fetal macrosomia and maternal obesity co-exist. This study confirms several associations with adverse outcomes for both mother and baby. This information supports the utility of prenatal diagnosis of macrosomia, although the limitations of ultrasound for diagnosis of macrosomia must be realized. A third trimester growth scan should be considered for all obese women and recommended for those with pregnancies complicated by gestational diabetes or hypertension. If macrosomia is identified, the patient should be informed of the increased risks of induction or labour and Cesarean section, particularly

those undergoing delivery for maternal reasons. Until the reasons behind the increased need for resuscitation are elicited, neonatal support should be available for macrosomic fetuses of obese mothers, since more aggressive support may be required.

4.4.3 Strengths

The nature of the study question precluded experimental study design since it is not possible to "randomize" macrosomic fetuses to the exposure of maternal obesity. Given that an observational design was required, a cohort study offered several advantages. The dataset provided an efficient means to identify maternal-infant dyads of interest. Only 12% of births were included in the study because they produced macrosomic infants. These births were then divided into cohorts on the basis of the exposure of maternal obesity. The primary outcome of Cesarean section is not rare in this population. The cohort design then offered the opportunity to evaluate multiple effects of exposure of macrosomic fetuses to maternal obesity. The study was performed retrospectively given the relatively long induction and latent period (pregnancy) and the time limitations imposed on the study. In addition, the low cost of the study design was an advantage.

The use of the BORN dataset was an important advantage. BORN is a carefully structured and maintained dataset that has attained its goal of population-based maternal child data collection (>99% of all births). The target population (all births in the province of Ontario) is large, yielding adequate numbers and therefore power to answer questions regarding

perinatal health. The robust BORN dataset collects information on recognized relevant variables and includes data on maternal, fetal and neonatal outcomes. The involvement of clinicians and perinatal researchers has resulted in the generation of a highly useful data resource. For this study, this allowed the examination of well-defined outcomes with little debate over their definition. Finally, the dataset has been previously validated by the Association of Public Health Epidemiologists in Ontario (AOHEO) through "an ongoing program of data verifications, quality checks, and formal training sessions for individuals collecting and entering data [that] assures a high level of data quality is maintained"; the dataset is, therefore, considered to be a reliable data source.[223]

Since 2007, The Ottawa Hospital Civic Campus has included maternal height and weight as variables in the dataset. Restricting the study to women delivering at that site generated a sufficient sample to answer the question of interest. By limiting to a single site, the consistency of data collection regarding height and weight is improved. In all, only 6.7% of births had to be excluded due to missing information on either maternal height or weight.

The question addressed in this study circumvents one of the traditional negative features of a cohort study – loss to follow-up. Essentially, this is a closed cohort. Potential inclusion was based an irrevocable event, birth, during a defined period. As such, the cohort cannot gain new members. Further, the ascertainment of macrosomia occurs at a single time point. Since data concerning the birth and neonatal course is obtained over a short period of time, there is no loss to follow-up.

In the descriptive component of the study, sufficient information regarding mothers and infants are included so that readers can easily compare to their own population to determine generalizability.

The analytic component of the study focused on determining the relationship between the exposure and the outcomes of interest. There are many potential confounding variables in the relationship between maternal obesity and pregnancy outcomes for macrosomic fetuses, including the presence of gestational diabetes, hypertension or smoking and the length of gestation. Multivariate regression was used to control for these important confounding factors. Therefore, the outcome is as clearly related to exposure as possible.

4.4.4 Limitations

As with any study, several limitations are identified. There are recognized concerns with a retrospective cohort design, particularly using an established dataset. Information regarding exposures and outcomes is limited to the data as it is collected. For example, the presence of gestational diabetes is included in the dataset using one specific definition and is either present or absent based on glucose tolerance testing. More subtle abnormalities in glycemic control may result in an abnormal result on the initial screening glucose challenge test or in impaired glucose tolerance identified on the oral glucose tolerance test.

This information may be important to control for in assessing the outcome of neonatal hypoglycemia, but cannot be obtained from the dataset.

The Ottawa Hospital, Civic Campus, is an urban hospital that performs deliveries for pregnancies that reach 32 weeks' gestation. As many complicated pregnancies require delivery at the nearby General Campus of The Ottawa Hospital, there may be selection bias against some of the sickest pregnancies. Patients may choose the Civic Campus for reasons of personal preference; it is conceivable that patients who choose the Civic Hospital differ from those that deliver at one of the three other hospitals in the city (including one community English hospital and one community French hospital). These differences could also limit generalizability.

We elected to restrict the analyses in this study to categorical variables (obese versus non-obese women and fetal overgrowth versus no fetal overgrowth since the primary objective was to determine the impact of the combined effect on adverse neonatal outcomes. At present, clinical guidelines for pregnancy management and weight are based on the categorical WHO definitions of weight classification.[47;58;224;225] Consideration was given to maintaining BMI and neonatal weight as continuous variables, a strategy that would provide additional information on the progression of adverse outcomes as both obesity and fetal overgrowth increase. However, since clinical practice is strongly rooted in categorical classification, we felt that our data would be most useful in the same format.

In performing this cohort study, we sought to examine multiple outcomes, including maternal, fetal and newborn outcomes. The total number of outcomes of interest exceeded twenty, resulting in increased potential for type I or II error. The use of composite maternal and offspring outcomes was considered, but it was felt that the individual outcomes were too varied to be useful when combined and that there was increased value from obtaining data on the separate outcomes. The potential for statistical error must be considered while interpreting the data, however it should be noted that our results are consistent with those from previous studies.

Misclassification bias is a clear risk for the exposure of maternal BMI. There are clearly established problems with determination of pre-pregnancy BMI in the form of recall bias. Traditionally, patients are asked to report their pre-pregnancy weight and height at the initial antenatal visit. Recall of pre-pregnancy weight is notoriously poor, although the exact degree of error is difficult to quantify because very few patients have an available recorded weight in the immediate pre-pregnancy period. When non-pregnant women are asked for their current weight, there is a tendency to underestimate weight with values ranging from -0.1kg to -6.5kg.[226] It is anticipated that pregnant women may follow the same trend when asked to report their weight several weeks previously, often in the presence of their partner. First measured weight in the first trimester is sometimes used as a proxy for pre-pregnancy weight. Unfortunately, there is a wide variation in pattern of weight change in the first trimester – some women gain a significant amount of weight

while others lose weight due to nausea and/or vomiting. Thus, there is no reliable way to classify women's pre-pregnancy BMI and the risk of misclassification must be accepted.

Gestational weight gain is an important modifier of pregnancy outcomes among obese women, particularly with respect to fetal overgrowth. In the majority of patients patients, decreased gestational weight gain (or, in fact, gestational weight *loss*) counters the effect of pre-pregnancy obesity. Unfortunately, information regarding gestational weight gain is not contained within the BORN dataset and these relationships could not be explored.

In conducting this study, we defined macrosomia as birthweight ≥ 4000g because this is by far the most common value used in this field of research. Macrosomia has also been defined as birthweight ≥ 4500g and occasionally ≥ 5000g. Therefore, we considered this to be the basis for a staging system for macrosomia (Grades I/II/III). Clinically significant outcomes are more likely to occur with grade II or III macrosomia. While it would be very interesting to examine the relationship between macrosomia and maternal obesity for these higher stages, a larger dataset would be needed to provide statistical power. The limitations of using a more liberal threshold for macrosomia are recognized.

While the BORN dataset is very comprehensive, there are some known concerns with the dataset. For some outcomes, there is a large proportion of missing data (labour augmentation with oxytocin and prolonged second stage, for example). This occurs primarily because trained data coders have difficulty extracting data for certain variables

from the patient charts. For example, on many charts the time that the second stage starts and ends is incomplete; since prolonged second stage is derived from these times, it is frequently coded as missing. Such variables must be used with caution. Further, some variables are not ideally coded. The coding is done by unit clerks on labour and delivery units. For some variables, such as birthweight, there is virtually no interpretation required and therefore little room for error. For other variables, the accuracy of the coding is less clear. Take, for example, post-partum hemorrhage. For a post-partum hemorrhage to be coded, the clinician must identify the diagnosis on the chart, the coder must locate that diagnosis and determine if it meets the criteria for entry. In the current dataset, the accuracy of certain variables is suspect (including reason for Cesarean section, auscultation and delivery room resuscitation).

4.4.5 Conclusions

The presence of maternal obesity appears to result in an increase in adverse pregnancy outcomes among macrosomic infants, including labour induction, delivery by Cesarean section (particularly for maternal indications) and need for neonatal resuscitation. Therefore, maternal obesity is likely an effect modifier of the relationship between macrosomia and adverse pregnancy outcomes. Obese women should be made aware early in the pregnancy that macrosomia is a possibility (in our study 18%) and that those mothers and babies are more likely to require intervention. Obese women should be encouraged to make healthy lifestyle choices, including consuming a nutritious diet of appropriate caloric

composition and participating in regular appropriate physical activity, and to limit their gestational weight gain to minimize the odds of delivering a macrosomic fetus.

Labour attendants should be aware of the increased need for labour induction and Cesarean section and carefully consider the reason behind these interventions. For obese parturients, decisions regarding labour and delivery should be individualized and take into account the anticipated size of the fetus, antepartum pregnancy complications and resources available for delivery and neonatal resuscitation.

5. CONCLUSIONS AND FUTURE WORK

Obesity commonly complicates pregnancy and is clearly associated with fetal overgrowth as demonstrated in our novel systematic review and meta-analysis. There appears to be an additive effect of obesity and excess fetal growth on adverse intrapartum outcomes, including induction of labour, Cesarean section (particularly for maternal medical indications) and need for neonatal resuscitation.

One important area of future research is the exploration of the effect of maternal diabetes (pre-existing glucose intolerance, type I and type II diabetes, as well as gestational glucose intolerance and diabetes) and hypertension (pre-existing/chronic and gestational hypertension, as well as pre-eclampsia) on the relationship between maternal obesity and fetal overgrowth. It is expected that abnormal glycemic control is an important contributor to *excess* fetal growth, while hypertension is more likely to contribute to *reduced* fetal growth. As both conditions are relatively common among obese individuals, their importance should not be underestimated. Such research should also include an evaluation of the effect of adequate treatment of the obese pregnant population on fetal growth. Ideal treatment may have the potential to optimize fetal growth, thereby decreasing related antenatal, intrapartum and postpartum complications.

Additional research is needed on the reasons behind the move to Cesarean section among obese women with macrosomic fetuses. Classification of the underlying indication using

the Robson criteria may be of benefit.[227] Furthermore, differences in maternal and neonatal outcomes in pregnancies complicated by factors such as hypertension and diabetes deserve further exploration. It continues to be unclear if interventions such as induction of labour and Cesarean section truly result in improved outcomes.

Future work should focus on decreasing the incidence of macrosomia, especially among obese mothers. Targeted education campaigns designed to inform women of reproductive age of the impact of excess weight on pregnancy outcomes is essential – ideally this will encourage women to attain as normal a body weight as possible prior to pregnancy. When an obese patient presents for prenatal care, maternity care providers must review weight-related concerns, set realistic target gestational weight gain and perform important diagnostic tests (such as glucose tolerance testing).

Although the reasons behind increased fetal growth among obese women continue to be elucidated, it is likely that overt or subclinical abnormalities in glucose metabolism contribute via increased fetal insulin-like growth factors. As such, one option for future research is the role of oral hypoglycemics in decreasing fetal growth. Glyburide is one example of such an agent, and functions by increasing insulin production from the islet cells of the pancreas. Increasing maternal insulin levels may correct the underlying glucose abnormality. Meformin, an insulin sensitizer, has been studied in the overtly diabetic population and was found to be no better than insulin at preventing macrosomia. There are no studies of the effect of metformin in the non-diabetic obese pregnant population.

Certainly, studies of both safety are critical and would predate trials of efficacy. Positive results, however, could be useful in decreasing the incidence of macrosomia, as well as the resulting metabolic sequelae for offspring.

Past and current interventions have focused on modifying nutritional intake, physical activity or both. An ideal intervention would be applicable at a population level and focus on optimizing gestational weight gain among women of all body weights. An effective intervention would result in improved short- and long-term health of mothers and offspring alike.

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Table 1.1: World Health Organization Classification System for Pre-gestational Weight

Classification	**BMI Range**
Underweight	Less than 18.5
Normal weight	18.5 to 24.9
Overweight	25-29.9
Obese	More than 30.0
Class I Obesity	30.0-34.9
Class II Obesity	35.0-39.9
Class III Obesity	More than 40.0

Table 1.2: Institute of Medicine Recommended Gestational Weight Gain

(Based on Pre-gestational BMI)

Classification	**Target Gestational Weight Gain**
Underweight	28 - 40 pounds (12.7 – 18.2 kg)
Normal weight	25 - 35 pounds (11.4 – 15.9 kg)
Overweight	15 - 25 (6.8 – 11.4 kg)
Obese	11 - 20 pounds (5 – 9.1 kg)

Figure 3.1. Quorum Statement Study Flow Diagram

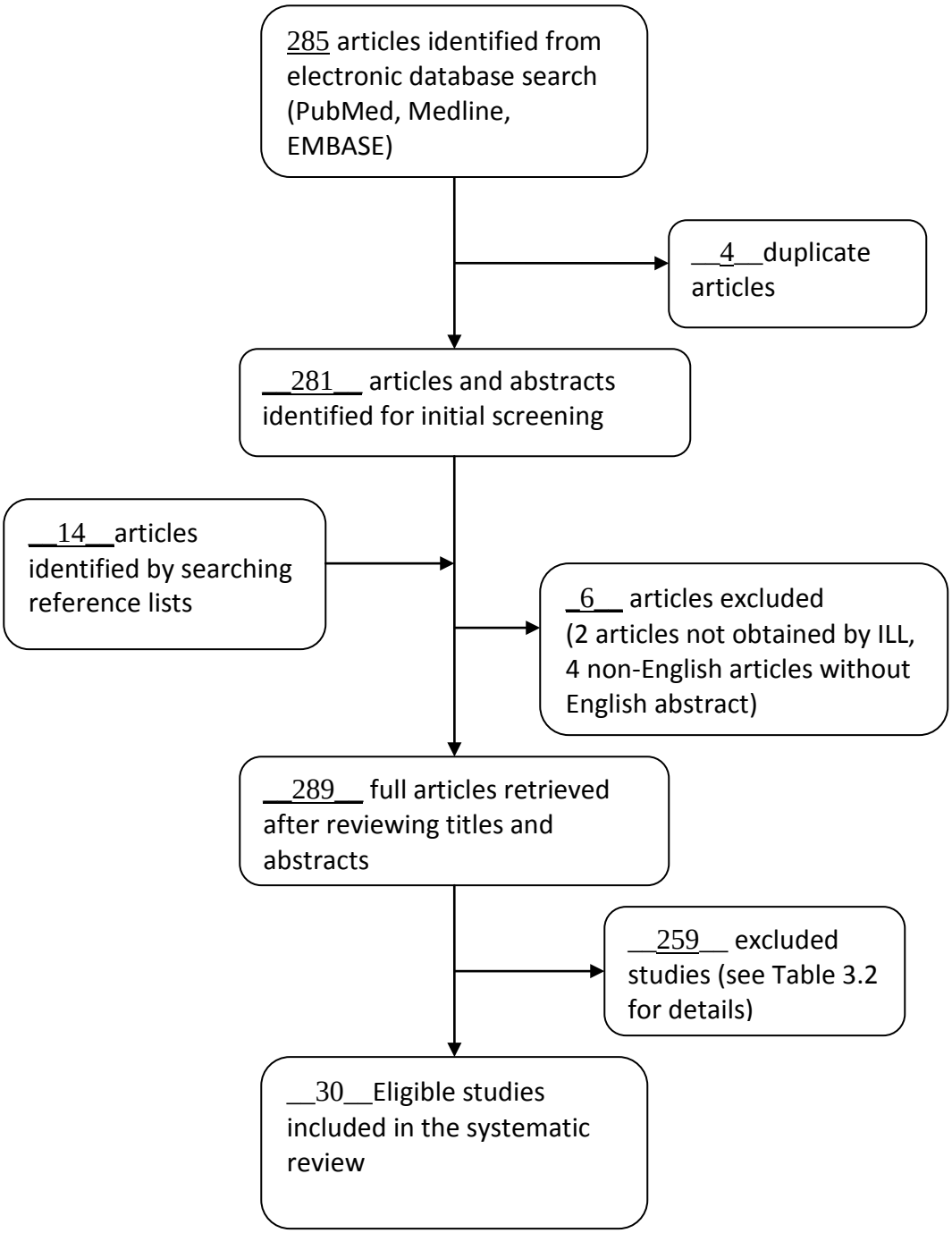


Table 3.1: Characteristics of Included Studies

Study Author and Year of Publication	Results Category	Results
Hoff 2009	Methods	Retrospective cohort (Population database extraction)
	Participants	467 overweight women from Kansas City, Missouri who were nulliparous initially, then had two successive singleton births
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI <25.0 kg/m^2
	Fetal overgrowth outcome	Large for gestational age infant (>90th percentile)
	Quality Assessment	Low
	Notes	All women were multiparous
Salihu 2009	Methods	Retrospective cohort (Population database extraction)
	Participants	728,136 normal weight or obese women from Missouri who delivered singleton pregnancies between 20 and 44 weeks gestation
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI 18.5-24.9 kg/m^2
	Fetal overgrowth outcome	Large for gestational age infant (≥ 90th percentile)
	Quality Assessment	Moderate
	Notes	
Crane 2009	Methods	Retrospective cohort (Population-based perinatal database extraction)
	Participants	3799 normal weight or obese women from the Eastern Avalon region of Newfoundland who delivered singleton pregnancies at or beyond 20 weeks gestation
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI 18.5-24.9 kg/m^2
	Fetal overgrowth outcome	1. Macrosomia (birthweight ≥ 4000g) 2. Macrosomia (birthweight ≥ 4500g)
	Quality Assessment	Moderate
	Notes	

Leung 2008	Methods	Prospective cohort
	Participants	22,718 ethnically Chinese women who were of normal weight or who were obese, delivering a singleton pregnancy of at least 24 completed weeks gestation and who presented for prenatal care at or before 20 completed weeks gestation
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI 18.5-24.9 kg/m^2
	Fetal overgrowth outcome	Large for gestational age infant (>90th percentile)
	Quality Assessment	Low
	Notes	
Nohr 2008	Methods	Prospective cohort (Population-based birth cohort)
	Participants	44,340 Danish women delivering a live-born singleton at or beyond 37 weeks gestation, who participated in both a first pregnancy interview and a first postpartum interview
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI 18.5-24.9 kg/m^2
	Fetal overgrowth outcome	Large for gestational age infant (>90th percentile)
	Quality Assessment	Moderate
	Notes	Excluded type 1 DM, age <18 years
Khashan 2009	Methods	Prospective cohort (Population database extraction)
	Participants	58,366 women from Manchester (UK) delivering a singleton infant
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI 18.5-24.9 kg/m^2
	Fetal overgrowth outcome	Fetal macrosomia (birthweight >4500g)
	Quality Assessment	High
	Notes	
Bhattacharya 2007	Methods	Retrospective cohort
	Participants	18,933 underweight, normal weight and obese women from Aberdeen, Scotland and district, who were primigravid and delivered singleton

		pregnancies beyond 24 weeks gestation and had an initial booking before 16 weeks gestation
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI <25.0 kg/m^2
	Fetal overgrowth outcome	Large for gestational age (birthweight >4000g)
	Quality Assessment	High
	Notes	
Getahun 2007	Methods	Retrospective cohort (Population database extraction)
	Participants	106,337 normal weight or obese women from Missouri who had two liveborn singleton deliveries beyond 20 weeks gestation in the time period
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI 18.5-24.9 kg/m^2
	Fetal overgrowth outcome	Large for gestational age infant (birthweight >90th percentile)
	Quality Assessment	Moderate
	Notes	
Sukalich 2006	Methods	Retrospective cohort study
	Participants	3841 normal weight or obese women from the Finger Lakes region of New York State who were less than 19 years of age and who delivered beyond 23 weeks gestation
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI 18.5-24.9 kg/m^2
	Fetal overgrowth outcome	Fetal macrosomia (birthweight ≥4000g)
	Quality Assessment	Low
	Notes	Adolescents only
Jensen 2003	Methods	Prospective cohort study
	Participants	1731 normal weight or obese women from four centers in Denmark who had a normal 75g 2 hour OGTT
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI 18.5-24.9 kg/m^2
	Fetal overgrowth outcome	1. Fetal macrosomia (birthweight ≥4000g) 2. Large for gestational age (≥ 90th percentile)

	Quality Assessment	Low
	Notes	Controls for diabetes
Stepan 2006	Methods	Retrospective cohort study
	Participants	3333 normal weight or obese women from Leipzig, Germany who had singleton pregnancies
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI 18.5-24.9 kg/m^2
	Fetal overgrowth outcome	Macrosomia (birthweight >4000g)
	Quality Assessment	Low
	Notes	
Athukorala 2010	Methods	Prospective cohort study
	Participants	1215 normal weight or obese women from Australia who were nulliparous and normotensive, had singleton pregnancies and were recruited between 14 and 22 weeks gestation
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI 18.5-24.9 kg/m^2
	Fetal overgrowth outcome	1. Large for gestational age (≥ 90th percentile) 2. Macrosomia (birthweight ≥ 4500g)
	Quality Assessment	High
	Notes	
Narchi 2010	Methods	Retrospective cohort study
	Participants	4588 underweight, normal weight or obese women from a single site in the UK who had singleton pregnancies and delivered after 24 completed weeks gestation
	Exposure	First visit BMI ≥30.0 kg/m^2
	Control	First visit BMI <25.0 kg/m^2
	Fetal overgrowth outcome	Large for gestational age (birthweight >90th percentile)
	Quality Assessment	High
	Notes	
Baeten 2001	Methods	Retrospective cohort study (population-based database extraction)
	Participants	79,141 underweight, normal weight or obese

		women from the state of Washington who were nulliparous and had singleton pregnancies
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI <25.0 kg/m^2
	Fetal overgrowth outcome	Fetal macrosomia (birthweight ≥ 4000g)
	Quality Assessment	Moderate
	Notes	Excluded diabetics and hypertensive women
Clausen 2005	Methods	Prospective cohort study
	Participants	1612 underweight, normal weight or obese women from Oslo, Norway who were of Norwegian ancestry and had a singleton pregnancy delivered beyond 37 weeks, who had an ultrasound at 17-19 weeks gestation and did not have pre-gestational diabetes
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI <25.0 kg/m^2
	Fetal overgrowth outcome	Macrosomia (birthweight > 4500g)
	Quality Assessment	Low
	Notes	
Driul 2008	Methods	Retrospective cohort study
	Participants	584 normal weight or obese women from Udine, Italy, who had singleton pregnancies
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI 18.5-24.9 kg/m^2
	Fetal overgrowth outcome	Macrosomia (birthweight ≥ 4000g)
	Quality Assessment	Low
	Notes	
Roman 2007	Methods	Retrospective case control study
	Participants	4116 normal weight or obese women from Reunion Island in the West Indies who delivered a live-born singleton infant after 22 weeks gestation
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI 18.5-24.9 kg/m^2
	Fetal overgrowth outcome	Macrosomia (birthweight ≥ 4000g)
	Quality	Moderate

	Assessment	
	Notes	
Sahu 2007	Methods	Retrospective cohort study
	Participants	281 underweight, normal weight or obese women from Northern India with singleton gestations who did not have diabetes or hypertension
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI <25.0 kg/m^2
	Fetal overgrowth outcome	Macrosomia (birthweight ≥ 4000g)
	Quality Assessment	Low
	Notes	
Van Wooten 2002	Methods	Retrospective cohort study
	Participants	50 underweight, normal weight or obese women from Southeastern university community in Florida who delivered a singleton pregnancy at term with a pregnancy complicated by gestational diabetes mellitus
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI <25.0 kg/m^2
	Fetal overgrowth outcome	Macrosomia (birthweight >4000g)
	Quality Assessment	Moderate
	Notes	All women had gestational diabetes
Rode 2005	Methods	Retrospective cohort
	Participants	6794 underweight, normal weight or obese women from Copenhagen, Denmark with singleton cephalic deliveries ≥ 37 weeks gestation
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI <25.0 kg/m^2
	Fetal overgrowth outcome	Macrosomia (birthweight ≥ 4000g)
	Quality Assessment	Moderate
	Notes	
Magann 2010	Methods	Retrospective cohort
	Participants	3149 normal weight or obese women from Jackson MS or Portsmouth VA with singleton pregnancies

	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI 18.5-24.9 kg/m^2
	Fetal overgrowth outcome	Large for gestational age (birthweight >90th percentile)
	Quality Assessment	Moderate
	Notes	
Langer 2005	Methods	Prospective cohort
	Participants	2794 normal weight or obese women from San Antonio, Texas
	Exposure	Pre-pregnancy BMI ≥ 30
	Control	Pre-pregnancy BMI 18.5-24.9
	Fetal overgrowth outcome	1. Large for gestational age (birthweight ≥ 90th percentile) 2. Macrosomia (birthweight ≥ 4000g)
	Quality Assessment	Low
	Notes	All women had GDM diagnosed before 33 weeks
Lumme 1995	Methods	Prospective population-based cohort (99% of deliveries)
	Participants	7776 underweight, normal weight or obese women from Northern Finland with singleton gestations
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI <25.0 kg/m^2
	Fetal overgrowth outcome	1. Large for gestational age (birthweight >90th percentile 2. Fetal macrosomia (birthweight ≥ 4500g)
	Quality Assessment	High
	Notes	
Jensen 1999	Methods	Retrospective cohort
	Participants	3531 underweight, normal weight or obese women from Herning, Denmark, with singleton, uncomplicated pregnancies
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI <25.0 kg/m^2
	Fetal overgrowth outcome	Fetal macrosomia (birthweight ≥ 4500g)
	Quality Assessment	Low

	Notes	
Mantakas 2010	Methods	Retrospective cohort
	Participants	4887 underweight, normal weight or obese women from Sheffield, UK who were nulliparous and had singleton pregnancies
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI <25.0 kg/m^2
	Fetal overgrowth outcome	1. Macrosomia (birthweight >4000g) 2. Macrosomia (birthweight >4500g)
	Quality Assessment	Low
	Notes	
El-Gilany 2010	Methods	Retrospective cohort
	Participants	533 normal weight or obese women from Al-Hassa, Saudi Arabia, who were healthy and had singleton pregnancies
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI 18.5-24.9 kg/m^2
	Fetal overgrowth outcome	Large for gestational age fetus (birthweight >4000g)
	Quality Assessment	Moderate
	Notes	
Bodnar 2010	Methods	Retrospective cohort
	Participants	24,500 normal weight or obese women from Pittsburgh Pennsylvania with live-born singleton infants with no congenital anomalies
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI 18.5-24.9 kg/m^2
	Fetal overgrowth outcome	Large for gestational age infant (birthweight >90th %ile)
	Quality Assessment	Moderate
	Notes	
Le Thai, 1992	Methods	Retrospective case control study
	Participants	140 underweight, normal weight or obese women from Paris delivering at the Maternite de las Pitie-Salpetriere
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI <25.0 kg/m^2
	Fetal overgrowth outcome	Fetal macrosomia (birthweight >4000g)

	Quality Assessment	Moderate
	Notes	
Voigt 2008	Methods	Retrospective population-based cohort
	Participants	371,654 normal weight or obese women from 8 German states delivering singleton infants
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI 18.5-24.9 kg/m^2
	Fetal overgrowth outcome	Large for gestational age infant (birthweight >90^{th} percentile)
	Quality Assessment	High
	Notes	
Brennand 2005	Methods	Retrospective cohort
	Participants	435 normal weight or obese Cree women from James Bay
	Exposure	Pre-pregnancy BMI ≥30.0 kg/m^2
	Control	Pre-pregnancy BMI 18.5-24.9 kg/m^2
	Fetal overgrowth outcome	1. Fetal macrosomia (birthweight >4000g) 2. Fetal macrosomia (birthweight >4500g)
	Quality Assessment	High
	Notes	All aboriginal women

Table 3.2: Characteristics of Excluded Studies

Reason for Exclusion	Number of Studies Excluded
Unrelated topic	62
Obesity not defined as BMI ≥ 30 kg/m^2	83
Obesity measure not pre-pregnancy, first trimester or first antenatal visit	5
Comparison group not one of BMI 18.5-24.9 kg/m^2 or BMI <25.0 kg/m^2	32
Data not present to allow quantitative analysis of obesity	15
Data not present to allow quantitative analysis of macrosomia	29
Meta-analysis	1
Review article	24
Comment	3
Case report	1
Duplicate articles	4
Total number excluded	**259**

Table 3.3: Results of Included Studies

Outcome or Subgroup Title	Study	Number of Participants: Exposed	Number of Participants: Control	Number of Exposed Participants with Outcome	Number of Control Participants with Outcome	Statistical Method	Covariates Adjusted For	Effect Size
Large for gestational age (≥90th percentile)	Hoff 2009	342	125	19	8	Multivariate Logistic Regression	Unclear	N/A
	Leung 2008	677	22041	142	1694	Multivariate Logistic Regression	Unclear	3.39 [2.78, 4.13]
	Nohr 2008	4084	40256	800	3284	Multivariate Logistic Regression	Maternal age, parity, height, smoking, alcohol, social status, exercise, gestational age	N/A
	Getahun 2007	21513	84823	3519	7352	Multivariate Logistic Regression	Maternal age, maternal race, education, initiation of prenatal care, marital status, inter-pregnancy interval, smoking, alcohol	N/A
	Narchi 2010	1266	3322	353	450	Multivariate Logistic Regression	Maternal age, parity, diabetes, hypertensive disorders	1.4 [1.3, 1.5]
	Magann 2010	1183	1966	138	91	Recursive Partitioning	African-American ethnicity, pre-existing diabetes, gestational diabetes, pre-eclampsia	3.10 [2.32, 4.15]
	Lumme 1995	353	7423	72	627	Multivariate Logistic Regression	Age, parity, education, smoking, antepartum diabetes, hypertension	2.3 [1.7, 3.0]
	Bodnar 2010	5550	18950	772	682	Multivariate Logistic Regression	Race-ethnicity, smoking, parity, height, education	N/A
	Voigt 2008	51506	320148	8320	23320	X^2	N/A	N/A
	Salihu 2009	91581	636555	17889	70021	Multivariate Logistic Regression	Maternal age, maternal education, marital status, maternal race, prenatal smoking, adequacy of	N/A

							prenatal care, sex of the neonate, year of birth, anemia and complications of pregnancy	
	Jensen 2003	637	1094	160	189	Multivariate Logistic Regression	2 hour glucose, maternal age, gestational weight gain, parity, smoking, screening for gestational diabetes, ethnicity, clinical center	N/A
	Athukorala 2010	272	943	45	76	Log Binomial Regression	No information	2.08 [1.47, 2.93]
	Langer 2005	1213	1581	230	179	Chi^2, Logistic Regression, ANOVA	Maternal age, parity, previous macrosomia, race/ethnicity, obesity, disease severity, weight gain in pregnancy, level of glycemic control, treatment modality, length of treatment	N/A
	Total	162183	960320	36293	178092	N/A	N/A	N/A
Macrosomia (≥ 4000g)	Bhattacharya 2007	2015	16918	280	1172	Multivariate Logistic Regression	"Relevant sociodemographic characteristics", year of delivery	N/A
	El-Gilany 2010	226	307	10	2	Unpaired t-test, X^2	N/A	N/A
	Stepan 2006	952	2381	169	167	X^2, Mann-Whitney	N/A	N/A
	Van Wooten 2002	28	19	10	2	Fisher's exact test	N/A	N/A
	Mantakas 2010	1048	3839	118	209	X^2, t-test, Relative Risk	N/A	1.9 [1.5, 2.5]
	Le Thai 1992	70	70	18	1	Student t test and X^2	N/A	N/A
	Brennand 2005	296	139	144	28	Univariate Logistic Regression	N/A	3.73 [2.41, 5.05]
	Crane 2009	1310	2489	145	156	Multivariate Logistic Regression	Maternal age, parity, smoking, partnered	N/A

							status, gestational age	
	Sukalich 2006	517	3324	52	196	Multivariate Logistic Regression	Gestational diabetes, parity, gestational weight gain	1.6 [1.2, 2.0]
	Jensen 2003	637	1094	189	249	Multivariate Logistic Regression	2 hour glucose, maternal age, gestational weight gain, parity, smoking, screening for gestational diabetes, ethnicity, clinical center	2.2 [1.6-3.1]
	Baeten 2001	9806	69335	1699	6726	Multivariate Logistic Regression	Maternal age, marital status, educational level, smoking, trimester care began, payer of prenatal care and gestational weight gain	2.1 [1.9, 2.3]
	Driul 2008	51	533	7	31	Univariate Logistic Regression	None	2.58 [1.08, 6.21]
	Roman 2007	2050	2066	166	57	Conditional Logistic Regression	None	3.1 [2.2, 4.3]
	Sahu 2007	30	251	1	0	Univariate Logistic Regression	None	N/A
	Rode 2005	444	6350	140	1249	Multivariate Logistic Regression	Gestational age >42 weeks, pre-eclampsia	1.8 [1.4,2.2]
	Langer 2005	1213	1581	127	92	Chi^2, Logistic Regression, ANOVA	Maternal age, parity, previous macrosomia, race/ethnicity, obesity, disease severity, weight gain in pregnancy, level of glycemic control, treatment modality, length of treatment	N/A
	Total	20693	110696	3275	10337	N/A	N/A	N/A
Macrosomia (> 4500g) Macrosomia	Khashan 2009	15271	43095	552	494	Log-linear Binomial Regression	Infant sex, maternal age, parity, social	2.71 [2.38, 3.07]

(≥ 4500g)							deprivation score, ethnicity	
	Clausen 2005	105	1507	11	46	Multivariate Logistic Regression	Maternal age, parity, smoking, gestational weight gain, placental weight, Gestational diabetes, gestational age at birth, gender of offspring	4.3 [1.5-12.1]
	Mantakas 2010	1048	3839	23	23	X^2, t-test, Relative Risk	N/A	8.7 [3.6-21.0]
	Brennand 2005	296	139	50	9	Univariate Logistic Regression	N/A	2.95 [1.87, 4.03]
	Crane 2009	1310	2489	55	57	Multivariate Logistic Regression	Maternal age, parity, smoking, partnered status, gestational age	N/A
	Athukorala 2010	272	943	13	10	Log Binomial Regression	No information	4.54 [2.01, 10.24]
	Lumme 1995	353	7423	24	235	Multivariate Logistic Regression	Age, parity, education, smoking, antepartum diabetes, hypertension	1.8 [1.1, 2.8]
	Jensen 1999	254	3277	18	119	X^2 or Fisher's exact test	None	N/A
	Total	18909	62712	746	993	N/A	N/A	N/A

Table 3.4: Meta-analysis Results

Outcome of Subgroup Title	Study	Calculated Unadjusted Odds Ratio	Reported Adjusted Odds Ratio
Large for gestational age (≥90th percentile)	Hoff 2009	0.86 [0.37, 2.02]	N/A
	Leung 2008	3.19 [2.63, 3.87]	3.39 [2.78, 4.13]
	Nohr 2008	2.74 [2.52, 2.99]	N/A
	Getahun 2007	2.06 [1.97, 2.15]	N/A
	Narchi 2010	2.47 [2.11, 2.89]	1.4 [1.3, 1.5]
	Magann 2010	2.72 [2.07, 3.58]	3.10 [2.32, 4.15]
	Lumme 1995	2.78 [2.12, 3.64]	2.3 [1.7, 3.0]
	Bodnar 2010	4.33 [3.89, 4.82]	N/A
	Voigt 2008	2.45 [2.39, 2.52]	N/A
	Salihu 2009	1.96 [1.93, 2.00]	N/A
	Jensen 2003	1.61 [1.27, 2.04]	N/A
	Athukorala 2010	2.26 [1.52, 3.36]	2.08 [1.47, 2.93]
	Langer 2005	1.83 [1.48, 2.26]	N/A
	Total	**2.42 [2.16, 2.72]**	N/A
Macrosomia (birthweight ≥4000g)	Bhattacharya 2007	2.17 [1.89, 2.49]	N/A
	El-Gilany 2010	7.01 [1.52, 32.33]	N/A
	Stepan 2006	2.86 [2.28, 3.60]	N/A
	Van Wooten 2002	4.72 [0.90, 24.75]	N/A
	Mantakas 2010	2.20 [1.74, 2.79]	1.9 [1.5, 2.5]
	Le Thai 1992	23.89 [3.09, 184.72]	N/A
	Brennand 2005	3.76 [2.34, 6.03]	3.73 [2.41, 5.05]
	Crane 2009	1.86 [1.47, 2.36]	N/A
	Sukalich 2006	1.78 [1.29, 2.46]	1.6 [1.2, 2.0]
	Jensen 2003	1.43 [1.15, 1.79]	2.2 [1.6-3.1]
	Baeten 2001	1.95 [1.84, 2.07]	2.1 [1.9, 2.3]
	Driul 2008	2.58 [1.07, 6.19]	2.58 [1.08, 6.21]
	Roman 2007	3.11 [2.28, 4.22]	3.1 [2.2, 4.3]
	Sahu 2007	25.58 [1.02, 642.20]	N/A
	Rode 2005	1.9 [1.53, 2.32]	1.8 [1.4-2.2]
	Langer 2005	1.89 [1.43,2.50]	N/A
	Total	**2.17 [1.92, 2.45]**	N/A
Macrosomia (birthweight ≥4500g)	Khashan 2009	3.23 [2.86, 3.66]	2.71 [2.38, 3.07]
	Clausen 2005	3.72 [1.86,7.41]	4.3 [1.5, 12.1]
	Mantakas 2010	3.72 [2.08, 6.66]	8.7 [3.6-21.0]
	Brennand 2005	2.94 [1.40, 6.16]	2.95 [1.87, 4.03]
	Crane 2009	1.87 [1.28, 2.73]	N/A

	Athukorala 2010	4.68 [2.03, 10.80]	4.54 [2.01, 10.24]
	Lumme 1995	2.23 [1.45, 3.45]	1.8 [1.1, 2.8]
	Jensen 1999	2.02 [1.21, 3.38]	N/A
	Total	**2.77 [2.22, 3.45]**	N/A

Table 3.5: Quality Assessment of Included Studies

Study	Representativeness of the Exposed Cohort	Source of Non-exposed Cohort	Ascertainment of Exposure (Obesity)	Comparability of Cohorts	Adequacy of Follow-up	Overall Rating
Hoff 2009	**Moderate** Outcome of second pregnancy in women who were overweight in their first pregnancy	**High** Same population as exposed cohort	**Low** No information	**Low** Comparable for parity and race Not comparable for age and socioeconomic status No information on diabetes or hypertension	**High** Retrospective Cohort, 100% "follow-up"	**Low**
Salihu 2009	**High** State-wide registry used to validate US national datasets	**High** Same population as exposed cohort	**Moderate** Self-reported pre-pregnancy weight, measured height	**Low** No comparable variables Not comparable for age, parity, diabetes, hypertension or race No information on socioeconomic status	**High** Retrospective Cohort, 100% "follow-up"	**Moderate**
Crane 2009	**High** Provincial perinatal database	**High** Same population as exposed cohort	**Low** Self-reported pre-pregnancy weight and height	**Low** Comparable for age Not comparable for parity, diabetes, hypertension No information on socioeconomic status or race	**High** Prospective Cohort, 100% "follow-up"	**Moderate**
Leung 2008	**Low** Not enough information to determine	**High** Same population as exposed cohort	**Low** BMI obtained from weight and height at antenatal booking – unclear whether self-report or measured	**Low** Comparable for age and race Not comparable for parity, presence of diabetes, presence of hypertension No information on socioeconomic status	**High** Prospective Cohort, 100% "follow-up"	**Low**
Nohr 2008	**High** Truly representative of the average obese pregnant woman in Denmark	**High** Same population as exposed cohort	**Low** Self-reported pre-pregnancy weight and height	**Low** Not comparable for age, parity, presence of diabetes, presence of hypertension, socioeconomic status No information on race	**Low** ~30% of women were excluded because they didn't participate in the second interview, no description given	**Low**
Khashan 2009	**High** Truly representative of the average obese	**High** Same population as	**High** Measured height and first	**Moderate** Comparable for age and socioeconomic	**High** Prospective Cohort, 100% "follow-up"	**High**

	pregnant woman in Manchester	exposed cohort	antenatal visit (around 16 weeks)	status Not comparable for parity or race No information on presence of diabetes or hypertension		
Bhattacharya 2007	**High** Truly representative of the average obese pregnant woman in Aberdeen and district	**High** Same population as exposed cohort	**High** Measured height and first antenatal visit (around 10 weeks)	**Low** Comparable for parity Not comparable for maternal age, presence of diabetes, presence of hypertension, socioeconomic status No information for race	**High** Prospective Cohort, 100% "follow-up"	**High**
Getahun 2007	**High** Truly representative of the average obese pregnant woman in Missouri	**High** Same population as exposed cohort	**Low** Self-reported pre-pregnancy weight and height	**Low** Not comparable for age, presence of diabetes, presence of hypertension or race No information for parity or socioeconomic status	**High** Retrospective Cohort, 100% "follow-up"	**Moderate**
Sukalich 2006	**Low** Selected group of users - <19 years old only	**High** Same population as exposed cohort	**Low** Self-reported pre-pregnancy weight and height	**Low** Comparable for presence of preexisting diabetes Not comparable for maternal age, parity, presence of hypertension, socioeconomic status or race No information on multiple gestation	**High** Retrospective Cohort, 100% "follow-up"	**Low**
Jensen 2003	**Low** Selected group of users – women with a normal 75g OGTT	**High** Same population as exposed cohort	**Low** No description of how pre-pregnancy BMI was obtained	**Low** Comparable for presence of diabetes Not comparable for age, parity, presence of hypertension or race No information for socioeconomic status or multiple gestation	**High** Prospective Cohort, 100% "follow-up"	**Low**
Stepan 2006	**High** Truly representative of the average obese pregnant woman in Leipzig	**High** Same population as exposed cohort	**Low** No description of how pre-pregnancy BMI was obtained	**Low** Comparable for maternal age No information for	**High** Retrospective Cohort, 100% "follow-up"	**Moderate**

				parity, presence of diabetes, presence of hypertension, socioeconomic status or race		
Athukorala 2010	**Low** Selected group of users – women enrolled in the Australian Collaborative Trial of Supplements with Antioxidants Vitamin C and Vitamin E	**High** Same population as exposed cohort	**High** Measured height and first antenatal visit	**Moderate** Comparable for age, parity and race Not comparable for presence of diabetes, presence of hypertension or socioeconomic status	Information not available	**Moderate**
Narchi 2010	**High** Truly representative of the average obese pregnant woman in the UK site	**High** Same population as exposed cohort	**High** Measured height and first antenatal visit (8-12 weeks)	**Low** Comparable for age Not comparable for parity, presence of diabetes, presence of hypertension, or race No information on socioeconomic status	**High** Retrospective Cohort, 100% "follow-up"	**High**
Baeten 2001	**High** Truly representative of the average obese pregnant woman in the state of Washington	**High** Same population as exposed cohort	**Low** Self-reported pre-pregnancy weight and height	**Low** Comparable for parity Not comparable for age, presence of diabetes, presence of hypertension, socioeconomic status or race	**High** Retrospective Cohort, 100% "follow-up"	**Moderate**
Clausen 2005	**Low** Selected group of users (participants in a larger cohort study)	**High** Same population as exposed cohort	**Low** No description of how obesity was ascertained	**Low** No information given on age, parity, presence of diabetes, presence of hypertension, socioeconomic status or race	**Low** Loss to follow-up 244/2294, 10.6%	**Low**
Driul 2008	**High** Truly representative of the average obese pregnant woman in the state of Washington	**High** Same population as exposed cohort	**Low** Self-reported pre-pregnancy weight and height	**Low** No information given on age, parity, presence of diabetes, presence of hypertension, socioeconomic status or race	**High** Retrospective Cohort, 100% "follow-up"	**Moderate**
Roman 2007	**High** Truly representative of the average obese pregnant woman on Reunion Island (consecutive cases)	**High** Controls derived from the same population as cases	**Low** No description of how obesity was ascertained	**Moderate** Comparable for age and parity Not comparable for presence of diabetes, presence of hypertension or race No information on	**High** Retrospectively-derived cases and controls	**Moderate**

				socioeconomic status		
Sahu 2007	**Moderate** Somewhat representative of the average obese woman in Northern India (had to deliver on site)	**High** Controls derived from the same population as cases	**Low** No description of how obesity was ascertained	**Moderate** Comparable for age and parity Not comparable for presence of diabetes or presence of hypertension No information on socioeconomic status or race	**High** Retrospectively-derived cohort	**Low**
Van Wooten 2002	**Low** Selected group – patients with gestational diabetes	**High** Controls derived from the same population as cases	**High** Measured height and first antenatal visit (8-9 weeks)	**Low** Comparable for presence of diabetes No information for age, parity, presence of hypertension, socioeconomic status or race	**Low** 14 women were missing height and weight information	**Moderate**
Rode 2005	**High** Truly representative of the average obese pregnant woman in Copenhagen	**High** Controls derived from the same population as cases	**Low** Self-reported pre-pregnancy weight and height	**Low** Not comparable for presence of diabetes or presence of hypertension No information on age, parity, socioeconomic status or race	**High** Retrospective Cohort, 100% "follow-up"	**Moderate**
Magann 2010	**Moderate** Somewhat representative of the average obese woman in Jackson or Portsmouth (two hospitals only, one naval)	**High** Controls derived from the same population as cases	**High** Measured height and first antenatal visit (all first trimester)	**Low** Not comparable for age, parity, presence of diabetes, presence of hypertension or race No information for socioeconomic status	**High** Retrospective Cohort, 100% "follow-up"	**Moderate**
Lumme 1995	**High** Truly representative of the average obese pregnant woman in Northern Finland	**High** Controls derived from the same population as cases	**High** Measured height and first antenatal visit (all first visit)	**Low** Not comparable for age, parity, presence of diabetes, or presence of hypertension No information for socioeconomic status or race	**High** Prospective Cohort, 100% "follow-up"	**High**
Langer 2005	**Low** Selected group of users (women with GDM)	**High** Controls derived from the same population as cases	**Low** No description of how pre-pregnancy BMI was derived	**Low** Not comparable for age or parity No information for hypertension, socioeconomic status, race or multiple gestation	**High** Prospective Cohort, 100% "follow-up"	**Low**

Jensen 1999	**Moderate** Somewhat representative of the average pregnant woman in Herning (several exclusion criteria)	**High** Controls derived from the same population as cases	**Low** No description of how obesity was ascertained	**Low** Comparable for presence of diabetes and presence of hypertension No information on age, parity, socioeconomic status or race	**High** Retrospective cohort (100% "follow-up"	**Low**
Mantakas 2010	**Low** Selected group of users (nulliparous women, one hospital site)	**High** Controls derived from the same population as cases	**Low** No description of how obesity was ascertained	**Low** Not comparable for age or race Comparable for parity No information for presence of diabetes, presence of hypertension or socioeconomic status	**High** Retrospective Cohort, 100% "follow-up"	**Low**
El-Gilany 2010	**Low** Selected group of users - volunteers	**High** Same population as exposed cohort	**High** Measured height and first antenatal visit	**Low** Comparable for socioeconomic status Not comparable for age, parity, presence of diabetes, or presence of hypertension No information on race	**Moderate** Subjects lost to follow-up unlikely to introduce bias (<5% and description given)	**Moderate**
Bodnar 2010	**High** Truly representative of the average obese pregnant woman in Pittsburgh, PA	**High** Same population as exposed cohort	**Low** Self-reported pre-pregnancy weight and height	**Low** Not comparable for age, parity or race No information on presence of diabetes, presence of hypertension or socioeconomic status	**High** Retrospective Cohort, 100% "follow-up"	**Moderate**
Le Thai 1992	**Moderate** Case definition adequate but not independently validated, consecutive cases	**High** Controls from same population as cases	**Low** Self-reported pre-pregnancy weight and height	**Low** Comparable for age Not comparable for parity, presence of diabetes, presence of hypertension No information for socioeconomic status or race	**High** Retrospective case control study, no loss to follow-up	**Low**
Voigt 2008	**High** Truly representative of the average obese pregnant woman in Germany	**High** Same population as exposed cohort	**High** Measured height and first antenatal visit	**Low** Comparable for age Not comparable for parity, presence of	**High** Retrospective Cohort, 100% "follow-up"	**Moderate**

				diabetes or presence of hypertension No information on socioeconomic status or race		
Brennand 2005	**High** Truly representative of the average obese pregnant Cree woman in James Bay	**High** Same population as exposed cohort	**High** Measured height and first antenatal visit (<14 weeks)	**Low** Comparable for race Not comparable for age, presence of diabetes or presence of hypertension No information on socioeconomic status or parity	**Low** 314 women were excluded because they did not have a recorded first weight <14 weeks (no description given)	**Moderate**

Table 3.6: Quality Assessment Criteria

Quality Assessment Variable	Quality Assessment Criteria		
	Low	**Moderate**	**High**
Representativeness of Exposed Cohort	Selected group of users (ex: nurses, volunteers)	Somewhat representative of the average obese pregnant woman in the community	Truly representative of the average obese pregnant woman in the community
Source of Non-exposed Cohort	Drawn from a different source than exposed cohort	N/A	Drawn from the same source as the exposed cohort
Ascertainment of Exposure (Obesity)	Self-report height and weight	Self-report height or weight	Measured height and weight
Comparability of Cohorts	Comparable for less than 3 of the variables assessed	Comparable for 3 or 4 of the variables assessed	Comparable for at least 5 of the variables assessed
Adequacy of Follow-up	Loss to follow-up rate >5% or no description of those lost	Subjects lost to follow-up unlikely to introduce bias (<5% loss to follow-up and description of those lost)	All subjects accounted for
Overall Rating	Few QA variables (≤3) rated as high, obesity self-reported	Some QA variables (≥3) rated as high with obesity self-reported OR height and weight measured but ≤4 QA variables rated as high	Majority of QA variables (≥4) rated as high, including ascertainment of exposure

Table 3.7 Heterogeneity Statistics for Methodologically and Clinically Important Sub-groups

Fetal Overgrowth Measure	Outcome/ Analysis	Category	Number of Studies	Heterogeneity Test			I^2
				Q	df	p-value	
Large for Gestational Age (>90th Percentile)	**Overall**	**All Studies**	**13**	**421.5**	**12**	**0.00**	**97**
	Study Quality	High	2	0.5	1	0.46	0
		Moderate	6	353.0	5	0.00	99
		Low	5	38.1	4	0.00	90
	Control Group Weight Class	Normal	10	410.6	9	0.00	97
		Normal/UW	3	6.6	2	0.04	70
	Ascertainment of Wt /Ht	Measured	5	19.7	4	0.001	80
		Self-report	8	280.1	7	0.00	98
	Presence of Diabetes	No Diabetics	1	N/A	N/A	N/A	N/A
		All Diabetics	0	N/A	N/A	N/A	N/A
	National Wealth	High	13	N/A	N/A	N/A	N/A
		Other	0	N/A	N/A	N/A	N/A
	Date of Study Publication	≥ 2009	6	217.4	5	0.00	97
		<2009	7	83.7	6	0.00	93
Macrosomia (Birthweight ≥4000g)	**Overall**	**All Studies**	**16**	**48.8**	**15**	**0.00**	**69**
	Study Quality	High	1	N/A	N/A	N/A	N/A
		Moderate	9	29.2	8	0.00	73
		Low	6	15.8	5	0.007	68
	Control Group Weight Class	Normal	9	35.9	8	0.00	78
		Normal/UW	7	12.0	6	0.062	50
	Ascertainment of Wt /Ht	Measured	4	7.61	3	0.06	61
		Self-Report	12	36.9	11	0.00	70
	Presence of Diabetes	No Diabetics	3	7.1	2	0029	72
		All Diabetics	1	N/A	N/A	N/A	N/A
	National Wealth	High	14	38.6	11	0.00	66
		Other	2	1.6	1	0.20	39
	Date of Study Publication	≥ 2009	3	3.5	2	0.17	43
		<2009	13	45.2	12	0.00	74
Macrosomia (Birthweight ≥4500g)	**Overall**	**All Studies**	**8**	**13.5**	**7**	**0.06**	**48**
	Study Quality	High	2	2.6	1	0.11	62
		Moderate	3	13.9	2	0.001	85
		Low	3	10.8	2	0.004	81
	Control Group Weight Class	Normal	4	8.3	3	0.04	64
		Normal/UW	4	10.9	3	0.012	72
	Ascertainment of Wt /Ht	Measured	4	3.5	3	0.32	14
		Self-Report	4	5.8	3	0.12	49
	Presence of Diabetes	No Diabetics	0	N/A	N/A	N/A	N/A
		All Diabetics	0	N/A	N/A	N/A	N/A
	National Wealth	High	8	13.5	7	0.06	48
		Other	0	N/A	N/A	N/A	N/A
	Date of Study Publication	≥ 2009	4	8.7	3	0.03	65
		<2009	4	2.3	3	0.5	0

Figure 3.2 Forest Plot for Large for Gestational Age (>90%ile)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Hoff	0.860	0.367	2.018	-0.346	0.729
Leung	3.188	2.632	3.861	11.863	0.000
Nohr	2.743	2.519	2.986	23.231	0.000
Getahun	2.061	1.973	2.152	32.709	0.000
Narchi	2.468	2.107	2.890	11.205	0.000
Magann	2.721	2.066	3.583	7.127	0.000
Lumme	2.777	2.117	3.644	7.374	0.000
Bodnar	4.328	3.886	4.821	26.635	0.000
Voigt	2.452	2.387	2.519	65.143	0.000
Salihu	1.964	1.929	2.000	72.996	0.000
Jensen	1.606	1.266	2.038	3.903	0.000
Athukorala	2.261	1.521	3.362	4.033	0.000
Langer	1.833	1.483	2.265	5.608	0.000
	2.423	2.159	2.719	15.060	0.000

Heterogeneity: Q=421.5, p=0.00, I^2=97

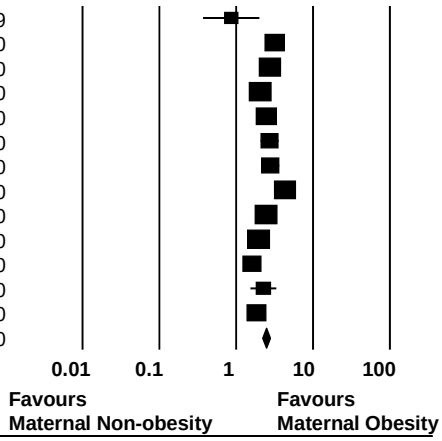


Figure 3.3 Forest Plot for Macrosomia (>/= 4000g)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Bhattacharya	2.168	1.886	2.493	10.875	0.000
El-Gilany	7.060	1.532	32.545	2.507	0.012
Stepan	2.861	2.276	3.597	9.004	0.000
Van Wooten	4.722	0.901	24.751	1.837	0.066
Mantakas	2.204	1.739	2.793	6.537	0.000
Le Thai	23.885	3.088	184.716	3.040	0.002
Brennand	3.756	2.340	6.027	5.483	0.000
Crane	1.861	1.469	2.359	5.143	0.000
Sukalich	1.785	1.295	2.460	3.538	0.000
Jensen	1.432	1.148	1.786	3.181	0.001
Baeten	1.951	1.841	2.067	22.570	0.000
Driul	2.576	1.073	6.187	2.117	0.034
Roman	3.106	2.284	4.223	7.225	0.000
Sahu	25.576	1.019	642.214	1.971	0.049
Rode	1.881	1.525	2.319	5.909	0.000
Langer	1.893	1.431	2.503	4.474	0.000
	2.169	1.917	2.453	12.311	0.000

Heterogeneity: Q=48.8, p=0.00, I^2=69

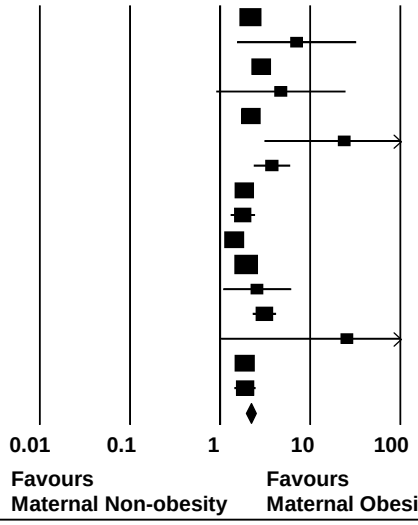


Figure 3.4 Forest Plot for Macrosomia (>/= 4500g)

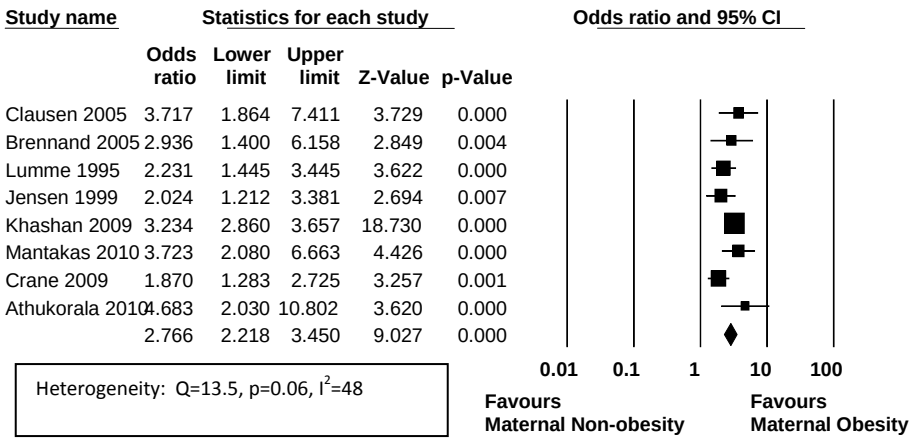
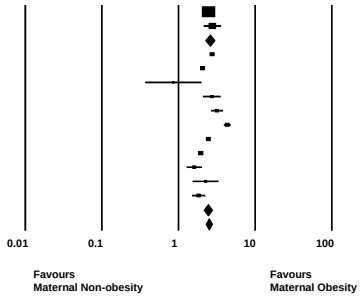


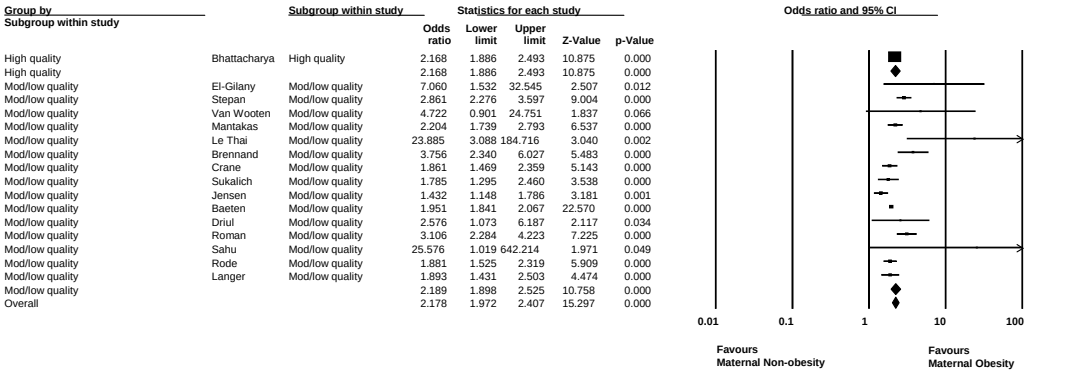
Figure 3.5 Forest Plot for Large for Gestational Age (>90%ile), Analysis by Study Quality

Group by Subgroup within study	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
High Quality	Narchi	High Quality	2.468	2.107	2.890	11.205	0.000
High Quality	Lumme	High Quality	2.777	2.117	3.644	7.374	0.000
High Quality			2.543	2.218	2.915	13.393	0.000
Mod/Low Quality	Nohr	Mod/Low Quality	2.743	2.519	2.986	23.231	0.000
Mod/Low Quality	Getahun	Mod/Low Quality	2.061	1.973	2.152	32.709	0.000
Mod/Low Quality	Hoff	Mod/Low Quality	0.860	0.367	2.018	-0.346	0.729
Mod/Low Quality	Magann	Mod/Low Quality	2.721	2.066	3.583	7.127	0.000
Mod/Low Quality	Leung	Mod/Low Quality	3.188	2.632	3.861	11.863	0.000
Mod/Low Quality	Bodnar	Mod/Low Quality	4.328	3.886	4.821	26.635	0.000
Mod/Low Quality	Voigt	Mod/Low Quality	2.452	2.387	2.519	65.143	0.000
Mod/Low Quality	Salihu	Mod/Low Quality	1.964	1.929	2.000	72.996	0.000
Mod/Low Quality	Jensen	Mod/Low Quality	1.606	1.266	2.038	3.903	0.000
Mod/Low Quality	Athukorala	Mod/Low Quality	2.261	1.521	3.362	4.033	0.000
Mod/Low Quality	Langer	Mod/Low Quality	1.833	1.483	2.265	5.608	0.000
Mod/Low Quality			2.393	2.110	2.713	13.604	0.000
Overall			2.420	2.166	2.720	19.080	0.000



Heterogeneity High Quality: Q=0.5, p=0.46, I^2=0
Heterogeneity Moderate/Low Quality: Q=415.0, p=0.00, I^2=97
Hererogeneity Overall: Q=421.5, p=0.00, I^2=97

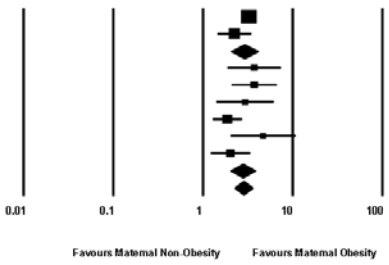
Figure 3.6 Macrosomia (>/= 4000g), Analysis by Study Quality



Heterogeneity High Quality: Q=N/A, p=N/A, I^2=N/A
Heterogeneity Moderate/Low Quality: Q=47.6, p=0.00, I^2=71
Heterogeneity Overall: Q=48.8, p=0.00, I^2=69

Figure 3.7 Forest Plot for Macrosomia (>/=4500g), Analysis by Study Quality

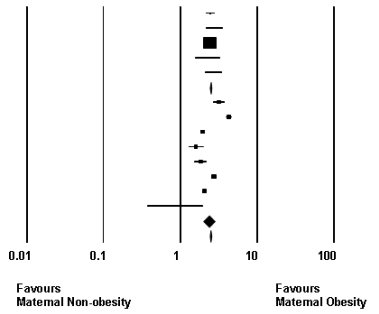
Group by Subgroup within study	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
High Quality	Khashan 2009	High Quality	3.234	2.860	3.657	18.730	0.000
High Quality	Lumme 1995	High Quality	2.231	1.445	3.445	3.622	0.000
High Quality			2.855	2.025	4.026	5.983	0.000
Mod/Low Quality	Clausen 2005	Mod/Low Quality	3.717	1.864	7.411	3.729	0.000
Mod/Low Quality	Mantakas 2010	Mod/Low Quality	3.723	2.080	6.663	4.426	0.000
Mod/Low Quality	Brennand 2005	Mod/Low Quality	2.936	1.400	6.158	2.849	0.004
Mod/Low Quality	Crane 2009	Mod/Low Quality	1.870	1.283	2.725	3.257	0.001
Mod/Low Quality	Athukorala 2010	Mod/Low Quality	4.683	2.030	10.802	3.620	0.000
Mod/Low Quality	Jensen 1999	Mod/Low Quality	2.024	1.212	3.381	2.694	0.007
Mod/Low Quality			2.736	2.006	3.732	6.352	0.000
Overall			2.789	2.215	3.511	8.724	0.000



Heterogeneity High Quality: Q=2.6, p=0.11, I^2=62
Heterogeneity Moderate/Low Quality: Q=8.3, p=0.14, I^2=40
Heterogeneity Overall: Q=13.5, p=0.06, I^2=48

Figure 3.8 Forest Plot for Large for Gestational Age (>90%ile), Analysis by Assessment of Weight and Height

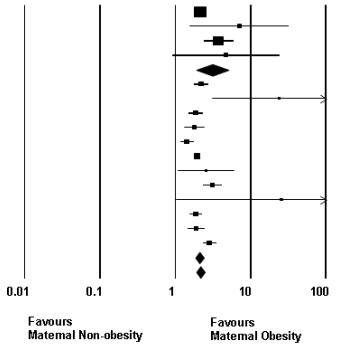
Group by Subgroup within study	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Measured	Narchi	Measured	2.468	2.107	2.890	11.205	0.000
Measured	Lumme	Measured	2.777	2.117	3.644	7.374	0.000
Measured	Voigt	Measured	2.452	2.387	2.519	65.143	0.000
Measured	Athukorala	Measured	2.261	1.521	3.362	4.033	0.000
Measured	Magann	Measured	2.721	2.066	3.583	7.127	0.000
Measured			2.457	2.393	2.522	67.001	0.000
Not measured	Leung	Not measured	3.188	2.632	3.861	11.863	0.000
Not measured	Bodnar	Not measured	4.328	3.886	4.821	26.635	0.000
Not measured	Salihu	Not measured	1.964	1.929	2.000	72.996	0.000
Not measured	Jensen	Not measured	1.606	1.266	2.038	3.903	0.000
Not measured	Langer	Not measured	1.833	1.483	2.265	5.608	0.000
Not measured	Nohr	Not measured	2.743	2.519	2.986	23.231	0.000
Not measured	Getahun	Not measured	2.061	1.973	2.152	32.709	0.000
Not measured	Hoff	Not measured	0.860	0.367	2.018	-0.346	0.729
Not measured			2.336	1.965	2.778	9.612	0.000
Overall			2.420	2.160	2.719	67.684	0.000



Heterogeneity Measured: Q=19.7, p=0.001, I^2=80
Heterogeneity Self-Report: Q=280.1, p=0.00, I^2=98
Heterogeneity Overall: Q=421.5, p=0.00, I^2=97

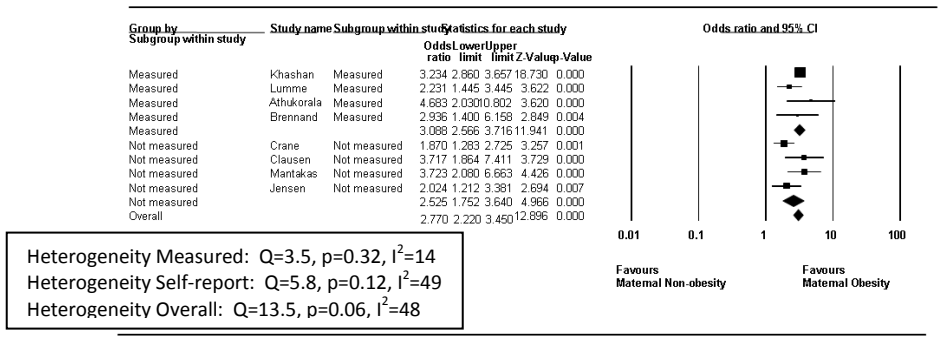
Figure 3.9 Forest Plot for Macrosomia (>/= 4000g) Analysis by Assessment of Weight and Height

Group by Subgroup within study	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Measured	Bhattacharya	Measured	2.168	1.886	2.493	10.875	0.000
Measured	El-Gilany	Measured	7.060	1.532	32.545	2.507	0.012
Measured	Brennand	Measured	3.756	2.340	6.027	5.483	0.000
Measured	Van Wooten	Measured	4.722	0.901	24.751	1.837	0.066
Measured			3.082	1.882	5.047	4.474	0.000
Not measured	Mantakas	Not measured	2.204	1.739	2.793	6.537	0.000
Not measured	Le Thai	Not measured	23.885	3.088	184.716	3.040	0.002
Not measured	Crane	Not measured	1.861	1.469	2.359	5.143	0.000
Not measured	Sukalich	Not measured	1.785	1.295	2.460	3.538	0.000
Not measured	Jensen	Not measured	1.432	1.148	1.786	3.181	0.001
Not measured	Baeten	Not measured	1.951	1.841	2.067	22.570	0.000
Not measured	Driul	Not measured	2.576	1.073	6.187	2.117	0.034
Not measured	Roman	Not measured	3.106	2.284	4.223	7.225	0.000
Not measured	Sahu	Not measured	25.576	1.019	642.214	1.971	0.049
Not measured	Rode	Not measured	1.881	1.525	2.319	5.909	0.000
Not measured	Langer	Not measured	1.893	1.431	2.503	4.474	0.000
Not measured	Stepan	Not measured	2.861	2.276	3.597	9.004	0.000
Not measured			2.078	1.812	2.382	10.476	0.000
Overall			2.171	1.920	2.449	11.291	0.000



Heterogeneity Measured: Q=7.6, p=0.055, I^2=61
Heterogeneity Self-report: Q=36.9, p=0.00, I^2=70
Heterogeneity Overall: Q=48.8, p=0.00, I^2=69

Figure 3.10 Forest Plot for Macrosomia (>/=4500g), Analysis by Assessment of Weight and Height



Heterogeneity Measured: Q=3.5, p=0.32, I^2=14
Heterogeneity Self-report: Q=5.8, p=0.12, I^2=49
Heterogeneity Overall: Q=13.5, p=0.06, I^2=48

Figure 4.1 Description of the Derivation of the Cohorts

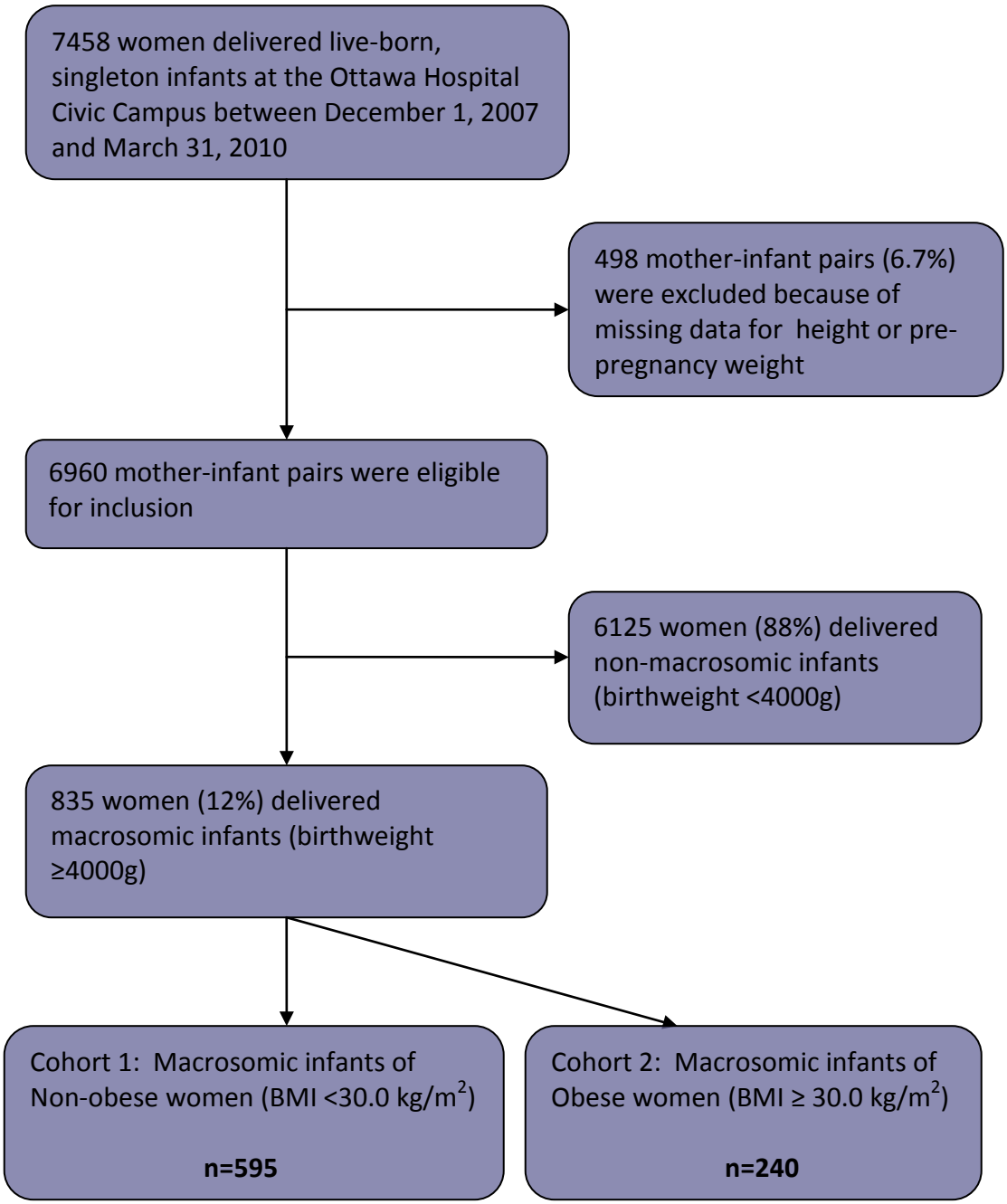


Table 4.1: Study Cohort Definition

Cohort A	**Cohort B**
Non-obese Mother Pre-pregnancy BMI <30 kg/m^2 Macrosomic Infant Birthweight ≥ 4000g	Obese Mother Pre-pregnancy BMI ≥ 30 kg/m^2 Macrosomic Infant Birthweight ≥ 4000g

Table 4.2 Proportion of Missing Data for Individual Variables for Mothers Delivering Singleton Infants at the Ottawa Hospital Civic Campus between December 1, 2007 and March 31, 2010

Variable	Proportion of Data Missing (%)
Maternal obesity	6.7
Macrosomia (birthweight ≥ 4000g)	0
Cesarean section for any indiction	0
Induction of labour	0
Induction of labour for LGA	0.1
Augmentation with oxytocin	22.2
Prolonged second stage (>3 hours)	40.3
Cesarean section for failure to progress/descend	0
Cesarean section for non-reassuring fetal heart rate	0
Cesarean section for breech presentation	0
Cesarean section for maternal indications	0
Vacuum assisted vaginal delivery	0
Vacuum or forceps assisted vaginal delivery	0
Regional anesthesia	0
Intrapartum auscultation	0.1
Internal fetal monitoring	0.1
External fetal monitoring	0.1
Meconium	0
Cord artery base excess >12.0	3.4
No resuscitation required	0
Free flow oxygen	0
Positive pressure ventilation	0
Intubation	0
Stillbirth	0
Early neonatal mortality	0
Late neonatal mortality	0
Perinatal mortality	0
Maternal age	0
Parity	0
Gestational age at delivery	0
Smoking	0.1
Infant sex	0
Gestational diabetes	0.4
Gestational hypertension	0.4

BMI Class	Number	Percent

Underweight (BMI <18.50 kg/m^2)	286	4.11
Normal weight (BMI 18.50-24.99 kg/m^2)	3698	53.13
Overweight (BMI 25.00-29.99 kg/m^2)	1648	23.68
Obese (BMI ≥ 30 kg/m^2)	1328	19.08

Table 4.3: Description of Maternal BMI Among Women Who Delivered Live-born, Singleton Infants at the Ottawa Hospital Civic Campus between December 1, 2007 and March 31, 2010

Table 4.4: Baseline Characteristics of Women With and Without Complete Data to Allow Calculation of Maternal BMI, Singleton Infants at the Ottawa Hospital Civic Campus between December 1, 2007 and March 31, 2010

Characteristics	Subjects With Data Needed to Calculate BMI n=6960	Subjects with Missing Data Needed to Calculate BMI n=498	p-value
	n (%)	n (%)	
Maternal age (y)			
<30	2355 (33.84)	185 (37.15)	0.13
30-39	4221 (60.65)	289 (58.03)	0.25
>=40	384 (5.52)	24 (4.82)	0.51
Nulliparity	3097 (44.50)	213 (42.77)	0.45
Gestational age at delivery (mean±SD)	38.63±1.92	38.60±2.07	0.77
Body mass index prepregnancy (kg/m^2)	NA	NA	NA
Height (cm)	NA	NA	NA
Pre-pregnancy weight (kg)	NA	NA	NA
Gestational diabetes	311 (4.48)	20 (4.20)	0.78
Gestational hypertension	248 (3.57)	6 (1.26)	0.0073‡
Eclampsia	NA	NA	NA
Smoking in pregnancy	489 (7.04)	33 (6.63)	0.73
Birthweight (g) (mean±SD)	3369±579.91	3373±599.77	0.89
Large for gestational age (>90%ile)	862 (12.39)	74 (14.89)	0.10
Macrosomia I (≥4000g)	835 (12.00)	64 (12.85)	0.57
Macrosomia II (≥4500g)	154 (2.21)	10 (2.01)	0.76
Infant sex male	3546 (50.96)	263 (52.81)	0.42

‡Statistically significant

Table 4.5: Description of Maternal BMI Among Non-Macrosomic and Macrosomic Live-born, Singleton Infants at the Ottawa Hospital Civic Campus between December 1, 2007 and March 31, 2010

	Maternal BMI Class	Number	Percent
Non-macrosomic Infants	Underweight	272	4.4
	Normal weight	3336	54.5
	Overweight	1429	23.3
	Obese	1088	17.8
Macrosomic Infants	Underweight	14	1.7
	Normal weight	362	43.4
	Overweight	219	26.2
	Obese	240	28.7

Table 4.6: Baseline Characteristics of Women Delivering Non-Macrosomic and Macrosomic Live-born, Singleton Infants at the Ottawa Hospital Civic Campus between December 1, 2007 and March 31, 2010

Characteristics	**Macrosomic Infant Non-obese Mother* n=595**	**Macrosomic Infant, Obese Mother n=240**	**p-value**
	n (%)	**n (%)**	
Maternal age (y)			
<30	178 (29.92)	84 (35.00)	0.16
30-39	377 (63.36)	140 (58.33)	0.18
>40	40 (6.72)	16 (6.67)	1.00
Nulliparity	229 (38.49)	91 (37.92)	0.94
Gestational age at delivery (mean)	39.87 (1.05)	39.33 (1.25)	<0.001‡
Body mass index prepregnancy (kg/m^2)	24.06 (3.06)	36.46 (6.52)	<0.001‡
Height (cm)	164.21 (6.84)	165.87 (7.90)	0.003‡
Pre-pregnancy weight (kg)	67.54 (9.96)	100.68 (21.48)	<0.001‡
Gestational diabetes	16 (2.70)	28 (11.72)	<0.001‡
Gestational hypertension	15 (2.53)	13 (5.44)	0.05‡
Eclampsia	0 (0)	0 (0)	1.00
Smoking in pregnancy	16 (2.69)	15 (6.25)	0.02‡
Birthweight (g) (mean)	4268 (233.15)	4328 (276.44)	0.002‡
Large for gestational age (>90%ile)	407 (68.40)	202 (84.17)	<0.001‡
Macrosomia I (≥4000g)	595 (100.0)	240 (100.0)	1.00
Macrosomia II (≥4500g)	94 (15.80)	60 (25.00)	0.003‡

‡Statistically significant

Table 4.7: Crude and Adjusted Relations Between Macrosomic Infants Exposed to Maternal Obesity and Adverse Maternal Outcomes, Live-born, Singleton Infants at the Ottawa Hospital Civic Campus between December 1, 2007 and March 31, 2010

	Macrosomic Infant of Non-obese Mother n=595	Macrosomic Infant of Obese Mother n=240				
Maternal Outcome Measure	**n (%)**	**n (%)**	**Crude OR**	**95% CI**	**Adjusted OR[¥]**	**95% CI**
Induction of labour	198 (33.28)	88 (36.67)	1.16	0.85-1.59	1.42[‡]	1.10-1.98
Induction of labour for LGA	53 (10.41)	27 (14.84)	1.50	0.91-2.47	0.83	0.45-1.56
Labour augmentation with oxytocin	145 (46.77)	43 (46.24)	0.98	0.62-1.56	0.99	0.59-1.65
Prolonged second stage (>3h)	52 (13.79)	16 (13.22)	0.95	0.52-1.74	1.11	0.55-2.22
Cesarean section delivery						
All indications	215 (36.20)	119 (49.58)	1.73	1.28-2.35	1.45[‡]	1.04-2.01
Failure to progress/descend	84 (39.07)	33 (27.73)	0.60	0.37-0.97	0.75	0.41-1.37
Non-reassuring fetal heart rate	33 (15.35)	14 (11.76)	0.74	0.38-1.44	0.90	0.44-1.83
Breech presentation	12 (5.58)	7 (5.88)	1.06	0.41-2.76	0.78	0.28-2.14
Maternal indication	8 (3.72)	15 (12.61)	3.73	1.53-9.09	3.70[‡]	1.47-9.34
Operative vaginal delivery						
Vacuum assisted vaginal delivery	40 (6.72)	13 (5.42)	0.80	0.42-1.51	0.85	0.43-1.65
Vacuum or forceps assisted	43(7.22)	14 (5.84)	0.80	0.43-1.48	0.86	0.45-1.63
Anesthesia						
Regional	504 (84.71)	206 (85.83)	1.06	0.70-1.60	0.88	0.57-1.37

*Non-obese = BMI <30.0 kg/m^2, Obese = BMI ≥ 30.0 kg/m^2

OR, odds ratio; CI, confidence interval

[¥]Adjusted for maternal age, parity (0 vs ≥1), gestational age at delivery (continuous), smoking (yes vs no), infant sex (male vs female), gestational diabetes (yes vs no) and gestational hypertension (yes vs no)

[‡]Statistically significant

Table 4.8: Crude and Adjusted Relations Between Macrosomic Infants Exposed to Maternal Obesity and Adverse Neonatal Outcomes, Live-born, Singleton Infants at the Ottawa Hospital Civic Campus between December 1, 2007 and March 31, 2010

	Macrosomic Infant of Non-obese Mother n=595	Macrosomic Infant of Obese Mother n=240				
	n (%)	n (%)	Crude OR	95% CI	Adjusted OR[¥]	95% CI
Intrapartum monitoring						
Auscultation	458 (76.97)	198 (82.85)	1.44	0.98-2.13	1.32	0.89-1.97
Internal FM	34 (5.71)	18 (7.53)	0.75	0.54-1.04	0.90	0.62-1.30
External FM	448 (75.29)	166 (69.46)	1.34	0.74-2.43	1.55	0.84-2.88
Meconium	101 (16.97)	39 (16.25)	0.95	0.63-1.42	1.21	0.79-1.86
Cord artery base excess >12.0	48 (8.38)	10 (4.27)	0.49	0.24-0.98	0.48	0.23-1.00
Delivery room resuscitation required						
No resuscitation	502 (84.37)	189 (78.75)	0.69	0.47-1.00	0.64[‡]	0.43-0.95
Free flow oxygen	75 (12.61)	42 (17.50)	1.47	0.98-2.22	1.57[‡]	1.03-2.42
Positive pressure ventilation	42 (7.06)	24 (10.0)	1.46	0.87-2.48	1.57	0.91-2.71
Intubation	20 (3.36)	11 (7.58)	1.38	0.65-2.93	1.68	0.77-3.65
Stillbirth	0 (0)	0 (0)	N/A	N/A	N/A	N/A
Neonatal mortality						
Early (<7 days)	0 (0)	0 (0)	N/A	N/A	N/A	N/A
Late (7-28 days)	0 (0)	0 (0)	N/A	N/A	N/A	N/A
Perinatal mortality						
Stillbirth + neonatal death	0 (0)	0 (0)	N/A	N/A	N/A	N/A

*Non-obese = BMI <30.0 kg/m^2, Obese = BMI≥30.0 kg/m^2
OR, odds ratio; CI, confidence interval
[¥]Adjusted for maternal age, parity (0 vs ≥1), gestational age at delivery (continuous), smoking (yes vs no), infant sex (male vs female), gestational diabetes (yes vs no) and gestational hypertension (yes vs no)
[‡]Statistically significant

Table 4.9: Crude and Adjusted Relations Between Macrosomic Infants Exposed to Varying Maternal Weight Classes versus Obese Weight Class and Adverse Maternal Outcomes, Live-born, Singleton Infants at the Ottawa Hospital Civic Campus between December 1, 2007 and March 31, 2010

Maternal Outcome Measure	Control Group (Maternal BMI Class)	Macrosomic Infant of Control Group proportion (%)[#]	Macrosomic Infant of Obese Mother (BMI ≥ 30kg/m^2) proporation (%)	Crude OR*	95% CI	Adjusted OR*	95% CI
Induction of Labour	Underweight	N/A	N/A	N/A	N/A	N/A	N/A
	Normal weight	122/362 (33.70)	88/240 (36.67)	1.14	0.81-1.60	1.31	0.89-1.93
	Overweight	71/219 (32.42)	88/240 (36.67)	1.21	0.82-1.78	1.37	0.89-2.09
Induction of labour for LGA	Underweight	N/A	N/A	N/A	N/A	N/A	N/A
	Normal weight	29/314 (9.24)	27/182 (14.84)	1.71	0.98-3.00	1.57	0.88-2.82
	Overweight	23/184 (12.50)	27/182 (14.84)	1.22	0.67-2.22	1.16	0.63-2.16
Labour augmentation with oxytocin	Underweight	N/A	N/A	N/A	N/A	N/A	N/A
	Normal weight	89/191 (46.60)	43/93 (46.24)	0.99	0.60-1.62	1.19	0.68-2.08
	Overweight	55/113 (48.67)	43/93 (46.24)	0.91	0.52-1.57	0.83	0.45-1.53
Prolonged second stage (>3 hours)	Underweight	N/A	N/A	N/A	N/A	N/A	N/A
	Normal weight	32/238 (13.45)	16/121 (13.22)	0.98	0.52-1.87	1.20	0.57-2.55
	Overweight	19/130 (14.62)	16/121 (13.22)	0.89	0.44-1.82	1.04	0.45-2.27
Cesarean section delivery – all indications	Underweight	N/A	N/A	N/A	N/A	N/A	N/A
	Normal weight	122/362 (33.70)	119/240 (49.58)	1.93	1.38-2.69	1.96	1.37-2.81
	Overweight	88/219 (40.18)	119/240 (49.58)	1.46	1.01-2.12	1.53[‡]	1.03-2.27
Cesarean section delivery – failure to progress/descend	Underweight	N/A	N/A	N/A	N/A	N/A	N/A
	Normal weight	48/122 (39.34)	33/119 (27.73)	0.59	0.34-1.02	0.88	0.45-1.72
	Overweight	35/88 (39.77)	33/119 (27.73)	0.58	0.32-1.04	0.52	0.26-1.05
Cesarean section delivery – non-reassuring fetal heart rate	Underweight	N/A	N/A	N/A	N/A	N/A	N/A
	Normal weight	22/122 (18.03)	14/119 (11.76)	0.61	0.29-1.25	0.59	0.27-1.31??
	Overweight	11/122 (12.50)	14/119 (11.76)	0.93	0.40-2.17	0.96	0.40-2.29
Cesarean section delivery – breech presentation	Underweight	N/A	N/A	N/A	N/A	N/A	N/A
	Normal weight	6/122 (4.92)	7/119 (5.88)	1.21	0.39-3.71	0.85	0.25-2.88
	Overweight	N/A	N/A	N/A	N/A	N/A	N/A
Cesarean section delivery – maternal indication	Underweight	N/A	N/A	N/A	N/A	N/A	N/A
	Normal weight	N/A	N/A	N/A	N/A	N/A	N/A
	Overweight	N/A	N/A	N/A	N/A	N/A	N/A
Vacuum assisted vaginal delivery	Underweight	N/A	N/A	N/A	N/A	N/A	N/A
	Normal weight	26/362 (7.18)	13/240 (5.42)	0.74	0.37-1.47	0.85	0.42-1.73
	Overweight	12/219 (5.48)	13/240 (5.42)	0.99	0.44-2.21	1.06	0.47-2.42
Vacuum or forceps assisted vaginal delivery	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Normal weight	28/362 (7.73)	14/240 (5.83)	0.74	0.38-1.44	0.79	0.39-1.59
	Overweight	13/219 (5.94)	14/240 (5.83)	0.98	0.45-2.14	0.97	0.43-2.19
Regional anesthesia	Underweight	12/14 (85.71)	203/240 (84.85)	0.91	0.20-4.25	0.43	0.07-2.55

	Normal weight	300/362 (82.87)	203/240 (84.85)	1.13	0.73-1.77	1.12	0.69-1.83
	Overweight	187/219 (85.39)	203/240 (84.85)	0.94	0.56-1.57	0.96	0.55-1.67

[#] proportion of patients with available data for each variable

* OR, odds ratio; CI, confidence interval

[¥]Adjusted for maternal age, parity (0 vs ≥1), gestational age at delivery (continuous), smoking (yes vs no), infant sex (male vs female), gestational diabetes (yes vs no) and gestational hypertension (yes vs no)

[‡]Statistically significant

N/A: Data suppressed due to risk of re-identification

Table 4.10: Crude and Adjusted Relations Between Macrosomic Infants Exposed to Varying Maternal Weight Classes Versus Obese Weight Class and Adverse Fetal or Neonatal Outcomes, Live-born Singleton Infants at the Ottawa Hospital Civic Campus between December 1, 2007 and March 31, 2010

Fetal or Neonatal Outcome Measure	Maternal BMI Class	Macrosomic Infant of Control Group proportion (%)[#]	Macrosomic Infant of Obese Mother (BMI ≥ 30kg/m^2) proporation (%)	Crude OR*	95% CI	Adjusted OR*	95% CI
Intrapartum monitoring - auscultation	Underweight	11/14 (78.57)	198/239 (82.85)	1.32	0.35-4.93	1.29	0.32-5.22
	Normal weight	270/362 (74.59)	198/239 (82.85)	1.65	1.09-2.48	1.49	0.97-2.29
	Overweight	177/219 (80.82)	198/239 (82.85)	1.15	0.71-1.84	1.09	0.67-1.77
Intrapartum monitoring – internal fetal monitoring	Underweight	N/A	18/239 (7.53)	N/A	N/A	N/A	N/A
	Normal weight	20/362 (5.52)	18/239 (7.53)	1.39	0.72-2.69	1.49	0.74-2.98
	Overweight	12/219 (5.48)	18/239 (7.53)	1.41	0.66-2.99	1.40	0.64-3.06
Intrapartum monitoring – external fetal monitoring	Underweight	9/14 (64.29)	166/239 (69.46)	1.26	0.41-3.90	1.05	0.29-3.86
	Normal weight	277/362 (76.52)	166/239 (69.46)	0.70	0.48-1.01	0.74	0.49-1.12
	Overweight	162/219 (73.97)	166/239 (69.46)	0.80	0.53-1.20	0.78	0.50-1.22
Meconium	Underweight	N/A	39/240 (16.25)	N/A	N/A	N/A	N/A
	Normal weight	62/362 (17.13)	39/240 (16.25)	0.94	0.61-1.46	1.03	0.64-1.67
	Overweight	37/219 (16.89)	39/240 (16.25)	0.95	0.58-1.56	0.95	0.57-1.57
Cord artery base excess <-12.0	Underweight	N/A	10/234 (4.27)	N/A	N/A	N/A	N/A
	Normal weight	27/347 (7.78)	10/234 (4.27)	0.53	0.25-1.12	0.57	0.26-1.23
	Overweight	19/213 (8.92)	10/234 (4.27)	0.46	0.21-1.00	0.45	0.20-1.04
Delivery room resuscitation – none needed	Underweight	13/14 (92.86)	189/240 (78.75)	0.29	0.04-2.23	0.32	0.04-2.61
	Normal weight	310/362 (85.64)	189/240 (78.75)	0.62	0.41-0.95	0.61[‡]	0.39-0.96
	Overweight	179/219 (81.74)	189/240 (78.75)	0.83	0.52-1.31	0.86	0.53-1.38
Delivery room resuscitation – free flow oxygen	Underweight	N/A	42/240 (17.5)	N/A	N/A	N/A	N/A
	Normal weight	45/362 (12.43)	42/240 (17.5)	1.49	0.95-2.36	1.51	0.93-2.45
	Overweight	30/219 (13.70)	42/240 (17.5)	1.34	0.80-2.22	1.33	0.78-2.84
Delivery room resuscitation – positive pressure ventilation	Underweight	N/A	24/240 (10.00)	N/A	N/A	N/A	N/A
	Normal weight	25/362 (6.91)	24/240 (10.00)	1.50	0.83-2.69	1.51	0.80-2.83
	Overweight	16/219 (7.31)	24/240 (10.00)	1.41	0.73-2.73	1.42	0.72-2.84
Delivery room resuscitation – intubation	Underweight	N/A	11/240 (4.58)	N/A	N/A	N/A	N/A
	Normal weight	9/362 (2.49)	11/240 (4.58)	1.88	0.77-4.62	2.03	0.79-5.23
	Overweight	10/219 (4.57)	11/240 (4.58)	1.00	0.42-2.41	1.02	0.42-2.51
Stillbirth	Underweight	N/A	N/A	N/A	N/A	N/A	N/A
	Normal weight	N/A	N/A	N/A	N/A	N/A	N/A
	Overweight	N/A	N/A	N/A	N/A	N/A	N/A
Neonatal mortality – early (<7 days)	Underweight	N/A	N/A	N/A	N/A	N/A	N/A
	Normal weight	N/A	N/A	N/A	N/A	N/A	N/A
	Overweight	N/A	N/A	N/A	N/A	N/A	N/A

Neonatal mortality – late (7-28 days)	Underweight	N/A	N/A	N/A	N/A	N/A	N/A
	Normal weight	N/A	N/A	N/A	N/A	N/A	N/A
	Overweight	N/A	N/A	N/A	N/A	N/A	N/A
Perinatal mortality (stillbirth + neonatal death)	Underweight	N/A	N/A	N/A	N/A	N/A	N/A
	Normal weight	N/A	N/A	N/A	N/A	N/A	N/A
	Overweight	N/A	N/A	N/A	N/A	N/A	N/A

[#] proportion of patients with available data for each variable

* OR, odds ratio; CI, confidence interval

[¥]Adjusted for maternal age, parity (0 vs ≥1), gestational age at delivery (continuous), smoking (yes vs no), infant sex (male vs female), gestational diabetes (yes vs no) and gestational hypertension (yes vs no)

[‡]Statistically significant

N/A: Data suppressed due to risk of re-identification

Table 4.11: Crude and Adjusted Relations Between Macrosomic Infants Exposed to Maternal Obesity and Relative Strength of Association Compared to Confounding Variables, Live-born, Singleton Infants at the Ottawa Hospital Civic Campus between December 1, 2007 and March 31, 2010

Outcome Variable of Interest	Exposure Variable of Interest	n (%)	Crude OR	95% CI	Adjusted OR[x]	95% CI
Induction of Labour	Obesity	88/240 (36.67)	1.16	0.85-1.29	1.33	0.94-1.90
	Non-obesity	198/535 (33.28)	Reference			
	Maternal age <30	98/262 (37.40)	1.18	0.86-1.61	0.83	0.58-1.20
	Maternal age 30-39	174/517 (33.66)	Reference			
	Maternal age ≥40	14/56 (25.00)	0.66	0.35-1.24	0.55	0.28-1.10
	Parity ≥ 1	137/515 (26.60)	0.42	0.31-0.56	0.54	0.39-0.76*
	Parity 0	149/320 (46.56)	Reference			
	Smoking	8/31 (25.81)	0.66	0.29-1.49	0.42	0.17-1.04
	Non-smoking	278/803 (34.62)	Reference			
	Male Infant	177/503 (35.19)	1.11	0.83-1.49	1.28	0.93-1.77)
	Female Infant	109/332 (32.3)	Reference			
	Gestational diabetes	17/44 (38.64)	1.22	0.65-2.27	1.46	0.71-3.00
	No gestational diabetes	269/788 (34.14)	Reference			
	Gestational hypertension	24/28 (85.71)	12.41	4.26-36.14	19.24	6.36-58.22*
	No gestational hypertension	262/804 (32.59)	Reference			
	Gestational age ≥ 41 weeks	138/254 (54.26)	3.56	2.61-4.85	4.11	2.93-5.76*
	Gestational age <41 weeks	148/583 (25.39)	Reference			
Induction of Labour for LGA	Obesity	27/182 (14.84)	1.50	0.91-2.47	1.40	0.83-2.34
	Non-obesity	53/509 (10.41)	Reference			
	Maternal age <30	27/252 (11.16)	0.88	0.54-1.45	0.85	0.50-1.43
	Maternal age 30-39	51/409 (12.47)	Reference			
	Maternal age ≥40	S	0.37	0.09-1.58	0.35	0.08-1.51
	Parity ≥ 1	44/398 (11.06)	0.89	0.56-1.42	0.86	0.52-1.43
	Parity 0	36/293 (12.29)	Reference			
	Smoking	S	0.67	0.16-2.97	0.62	0.14-2.77
	Non-smoking	78/666 (11.71)	Reference			
	Male Infant	46/416 (11.06)	0.88	0.55-1.41	0.91	0.56-1.46
	Female Infant	34/275 (12.36)	Reference			
	Gestational diabetes	8/35 (22.86)	2.39	1.05-5.46	2.20	0.92-5.25
	No gestational diabetes	72/653 (11.03)	Reference			
	Gestational hypertension	S	1.78	0.65-4.83	1.47	0.52-4.18
	No gestational hypertension	75/661 (11.35)	Reference			
	Gestational age ≥ 41 weeks	27/246 (10.98)	0.91	0.56-1.49	1.02	0.60-1.71
	Gestational age <41 weeks	53/445 (11.91)	Reference			
Labour Augmentation with Oxytocin	Obesity	43/93 (46.24)	0.98	0.62-1.56	1.06	0.63-1.78
	Non-obesity	145/310 (46.77)	Reference			
	Maternal age <30	83/143 (58.04)	1.85	1.22-2.83	1.32	0.82-2.11
	Maternal age 30-39	100/234 (42.74)	Reference			
	Maternal age ≥40	S	0.32	0.12-0.88	0.35	0.12-1.00
	Parity ≥ 1	90/258 (34.88)	0.26	0.17-0.40	0.29*	0.18-0.46
	Parity 0	98/145 (67.59)	Reference			
	Smoking	11/15 (73.33)	3.30	1.03-10.45	2.09	0.60-7.31
	Non-smoking	176/386 (45.58)	Reference			
	Male Infant	106/239 (44.35)	0.80	0.54-1.19	0.72	0.47-1.12
	Female Infant	82/164 (50.00)	Reference			
	Gestational diabetes	S	0.34	0.11-1.06	0.34	0.10-1.16
	No gestational diabetes	182/383 (47.52)	Reference			
	Gestational hypertension	S	0.57	0.05-6.37	0.82	0.05-12.91
	No gestational hypertension	185/397 (46.60)	Reference			
	Gestational age ≥ 41 weeks	61/108 (56.48)	1.72	1.10-2.68	1.51	0.93-2.46
	Gestational age <41 weeks	127/295 (43.05)	Reference			
Prolonged Second	Obesity	16/121 (13.22)	0.95	0.52-1.74	1.15	0.58-2.31

Stage (>3h)	Non-obesity	52/377 (13.79)	Reference			
	Maternal age <30	36/170 (21.18)	2.42	1.43-4.10	1.08	0.58-2.01
	Maternal age 30-39	30/300 (10.00)	Reference			
	Maternal age ≥40	S	0.69	0.16-3.06	1.68	0.31-9.26
	Parity ≥ 1	9/337 (2.67)	0.05	0.02-0.10	0.05*	0.02-0.10
	Parity 0	59/161 (36.65)	Reference			
	Smoking	S	0.78	0.18-3.48	0.48	0.09-2.47
	Non-smoking	66/479 (13.78)	Reference			
	Male Infant	42/300 (14.00)	1.08	0.64-1.82	0.95	0.52-1.75
	Female Infant	26/198 (13.13)	Reference			
	Gestational diabetes	S	0.26	0.04-1.97	0.40	0.05-3.45
	No gestational diabetes	67/471 (14.23)	Reference			
	Gestational hypertension	S	0.83	0.19-3.72	0.78	0.14-4.25
	No gestational hypertension	66/478 (13.81)	Reference			
	Gestational age ≥ 41 weeks	28/166 (16.87)	1.48	0.88-2.50	1.07	0.58-1.96
	Gestational age <41 weeks	40/332 (12.05)	Reference			
Cesarean Delivery for Any Indication	Obesity	119/240 (49.58)	1.73	1.28-2.35	1.76	1.28-2.43
	Non-obesity	215/594 (36.20)	Reference			
	Maternal age <30	91/261 (34.87)	0.75	0.55-1.02	0.53	0.38-0.75*
	Maternal age 30-39	215/517 (41.59)	Reference			
	Maternal age ≥40	28/56 (50.00)	1.41	0.81-2.44	1.60	0.89-2.86
	Parity ≥ 1	175/514 (34.05)	0.52	0.39-0.70	0.36	0.26-0.50*
	Parity 0	159/320 (49.69)	Reference			
	Smoking	13/31 (41.94)	1.08	0.52-2.24	1.24	0.57-2.66
	Non-smoking	321/802 (40.02)	Reference			
	Male Infant	201/502 (40.04)	1.00	0.75-1.33	0.99	0.74-1.33
	Female Infant	133/332 (40.06)	Reference			
	Gestational diabetes	20/44 (45.45)	1.26	0.68-2.31	0.97	0.51-1.87
	No gestational diabetes	314/787 (39.90)	Reference			
	Gestational hypertension	11/28 (39.29)	0.96	0.45-2.08	0.63	0.28-1.42
	No gestational hypertension	323/803 (40.22)	Reference			
	Gestational age ≥ 41 weeks	85/251 (33.86)	0.69	0.05-0.94	0.56*	0.40-0.78
	Gestational age <41 weeks	249/583 (42.71)	Reference			
Cesarean Delivery for Failure to Progress/Descend	Obesity	33/119 (27.73)	0.60	0.37-0.97	0.66	0.36-1.20
	Non-obesity	84/215 (39.07)	Reference			
	Maternal age <30	48/91 (52.75)	2.75	1.66-4.57	1.60	0.86-2.97
	Maternal age 30-39	62/215 (28.84)	Reference			
	Maternal age ≥40	7/28 (25.00)	0.82	0.33-2.03	0.84	0.28-2.45
	Parity ≥ 1	21/175 (12.00)	0.09	0.05-0.16	0.16*	0.08-0.30
	Parity 0	96/159 (60.38)	Reference			
	Smoking	S	0.55	0.15-2.02	0.42	0.08-2.21
	Non-smoking	114/321(35.51)	Reference			
	Male Infant	69/201 (34.33)	0.93	0.59-1.46	1.05	0.60-1.86
	Female Infant	48/133 (36.09)	Reference			
	Gestational diabetes	S	0.45	0.15-1.36	0.64	0.17-2.35
	No gestational diabetes	113/314 (35.99)	Reference			
	Gestational hypertension	S	1.57	0.47-5.26	1.13	0.30-4.24
	No gestational hypertension	112/323 (34.67)	Reference			
	Gestational age ≥ 41 weeks	61/85 (71.76)	8.67	5.01-15.31	4.10*	2.15-7.81
	Gestational age <41 weeks	56/249 (22.49)	Reference			
Cesarean Delivery for Non-reassuring Fetal Status	Obesity	14/119 (11.76)	0.74	0.38-1.44	0.80	0.39-1.64
	Non-obesity	33/215 (15.35)	Reference			
	Maternal age <30	12/91 (13.19)	0.84	0.41-1.71	0.60	0.28-1.27
	Maternal age 30-39	33/215 (15.35)	Reference			
	Maternal age ≥40	S	0.42	0.10-1.87	0.42	0.09-1.93
	Parity ≥ 1	14/175 (8.00)	0.33	0.17-0.65	0.28*	0.13-0.61
	Parity 0	33/159 (20.75)	Reference			
	Smoking	S	0.50	0.06-3.92	0.56	0.07-4.77
	Non-smoking	46/321 (14.33)	Reference			
	Male Infant	31/201 (15.42)	1.33	0.70-2.55	1.41	0.72-2.76

	Female Infant	16/133 (12.03)	Reference			
	Gestational diabetes	S	0.66	0.15-2.96	0.98	0.20-4.73
	No gestational diabetes	45/314 (14.33)	Reference			
	Gestational hypertension	S	0.60	0.08-4.82	0.40	0.05-334
	No gestational hypertension	46/323 (14.24)	Reference			
	Gestational age ≥ 41 weeks	17/85 (20.00)	1.83	0.95-3.51	1.03	0.48-2.20
	Gestational age <41 weeks	30/249 (12.05)	Reference			
Cesarean Delivery for Breech Presentation	Obesity	7/119 (5.88)	1.06	0.41-2.76	0.76	0.27-2.12
	Non-obesity	12/215 (5.58)	Reference			
	Maternal age <30	S	0.98	0.34-2.88	0.87	0.27-2.80
	Maternal age 30-39	12/215 (5.58)	Reference			
	Maternal age ≥40	S	1.30	0.28-6.14	1.23	0.25-6.10
	Parity ≥ 1	9/175 (5.14)	0.81	0.32-2.04	0.43	0.15-1.24
	Parity 0	10/159 (6.29)	Reference			
	Smoking	S	1.40	0.17-11.40	1.87	0.20-17.51
	Non-smoking	18/321 (5.61)	Reference			
	Male Infant	10/201 (4.98)	0.72	0.29-1.83	0.76	0.29-1.99
	Female Infant	9/133 (6.77)	Reference			
	Gestational diabetes	S	3.29	0.87-12.38	3.06	0.73-12.92
	No gestational diabetes	16 (314 (5.10)	Reference			
	Gestational hypertension	S	1.69	0.21-13.98	0.84	0.09-7.42
	No gestational hypertension	18/323 (5.57)	Reference			
	Gestational age ≥ 41 weeks	S	0.15	0.02-1.16	0.10*	0.01-0.83
	Gestational age <41 weeks	18/249 (7.23)	Reference			
Cesarean Delivery for Maternal Indications	Obesity	15/119 (12.61)	3.73	1.53-9.09	3.35*	1.30-8.64
	Non-obesity	8/215 (3.72)	Reference			
	Maternal age <30	7/91 (7.69)	1.11	0.44-2.82	0.83	0.29-2.38
	Maternal age 30-39	15/215 (6.98)	Reference			
	Maternal age ≥40	S	0.49	0.06-3.89	0.44	0.05-3.66
	Parity ≥ 1	9/175 (5.14)	0.56	0.24-1.34	0.46	0.16-1.32
	Parity 0	14/159 (8.81)	Reference			
	Smoking	S	1.13	0.14-9.12	1.05	0.12-9.52
	Non-smoking	22/321 (6.85)	Reference			
	Male Infant	12/201 (5.97)	0.70	0.30-1.65	0.67	0.28-1.64
	Female Infant	11/133 (8.27)	Reference			
	Gestational diabetes	S	3.88	1.18-12.76	2.34	0.64-8.55
	No gestational diabetes	19/314 (6.05)	Reference			
	Gestational hypertension	S	5.68	1.40-23.09	3.17	0.66-15.29
	No gestational hypertension	20/323 (6.19)	Reference			
	Gestational age ≥ 41 weeks	S	0.60	0.20-1.81	0.60	0.17-2.10
	Gestational age <41 weeks	19/249 (7.63)	Reference			
Vacuum Assisted Vaginal Delivery	Obesity	13/240 (5.42)	0.80	0.42-1.51	0.88	0.45-1.71
	Non-obesity	40/595 (6.72)	Reference			
	Maternal age <30	23/262 (8.78)	1.75	0.98-3.11	1.16	0.63-2.14
	Maternal age 30-39	27/519 (5.22)	Reference			
	Maternal age ≥40	S	1.03	0.30-3.50	1.24	0.35-4.38
	Parity ≥ 1	15/515 (2.91)	0.22	0.12-0.41	0.23*	0.12-0.45
	Parity 0	38/320 (11.88)	Reference			
	Smoking	S	0.48	0.06-3.60	0.47	0.06-3.65
	Non-smoking	52/802 (6.48)	Reference			
	Male Infant	34/503 (6.76)	1.19	0.67-2.13	1.15	0.63-2.08
	Female Infant	19/332 (5.72)	Reference			
	Gestational diabetes	S	N/A	N/A	N/A	N/A
	No gestational diabetes	53/788 (6.73)	Reference			
	Gestational hypertension	S	0.54	0.07-4.20	0.46	0.06-3.64
	No gestational hypertension	52/804 (6.47)	Reference			
	Gestational age ≥ 41 weeks	21/252 (8.33)	1.57	0.88-2.77	1.02	0.56-1.87
	Gestational age <41 weeks	32/ (5.49)	Reference			
Vacuum or	Obesity	14/240 (5.83)	0.80	0.43-1.48	0.82	0.43-1.59

Forceps Assisted Vaginal Delivery	Non-obesity	43/535 (7.23)	Reference			
	Maternal age <30	24/262 (9.16)	1.64	0.94-2.86	1.12	0.62-2.04
	Maternal age 30-39	30/517 (5.80)	Reference			
	Maternal age ≥40	S	0.92	0.27-3.11	1.11	0.31-3.91
	Parity ≥ 1	17/515 (3.30)	0.24	0.13-0.43	0.24*	0.13-0.46
	Parity 0	40/320 (12.50)	Reference			
	Smoking	S	0.45	0.06-3.32	0.43	0.06-3.33
	Non-smoking	56/803 (6.97)	Reference			
	Male Infant	37/503 (7.36)	1.24	0.71-2.17	1.29	0.71-2.31
	Female Infant	20/332 (6.02)	Reference			
	Gestational diabetes	S	N/A	N/A	N/A	N/A
	No gestational diabetes	56/788 (7.11)	Reference			
	Gestational hypertension	S	N/A	N/A	N/A	N/A
	No gestational hypertension	55/804 (6.84)	Reference			
	Gestational age ≥ 41 weeks	24/252 (9.52)	1.75	1.01-3.04	1.21	0.67-2.17
	Gestational age <41 weeks	33/583 (5.66)	Reference			
Regional Analgesia	Obesity	203/240 (84.58)	1.06	0.70-1.60	1.05	0.67-1.64
	Non-obesity	499/595 (83.87)	Reference			
	Maternal age <30	226/308 (86.26)	1.18	0.78-1.81	0.79	0.50-1.26
	Maternal age 30-39	435/517 (84.14)	Reference			
	Maternal age ≥40	41/56 (73.21)	0.52	0.27-0.97	0.63	0.32-1.22
	Parity ≥ 1	404/515 (78.45)	0.27	0.17-0.44	0.22	0.13-0.37
	Parity 0	298/320 (93.13)	Reference			
	Smoking	27/31 (87.10)	1.29	0.45-3.75	1.37	0.45-4.14
	Non-smoking	674/803 (83.94)	Reference			
	Male Infant	426/503 (84.69)	1.12	0.77-1.64	1.10	0.75-1.63
	Female Infant	276/332 (83.13)	Reference			
	Gestational diabetes	32/44 (72.73)	0.48	0.24-0.97	0.48	0.23-1.02
	No gestational diabetes	667/788 (84.64)	Reference			
	Gestational hypertension	25/28 (89.29)	1.61	0.48-5.40	1.22	0.33-4.43
	No gestational hypertension	674/804 (83.83)	Reference			
	Gestational age ≥ 41 weeks	204/252 (80.95)	0.73	0.49-1.07	0.51	0.33-0.79
	Gestational age <41 weeks	498/583 (85.42)	Reference			

* Statistically significant

S: data suppressed due to cell size <6

Table 4.12: Crude and Adjusted Relations Between Macrosomic Infants Exposed to Maternal Obesity and Relative Strength of Association Compared to Confounding Variables (Fetal/Neonatal Outcomes), Live-born, Singleton Infants at the Ottawa Hospital Civic Campus between December 1, 2007 and March 31, 2010

Outcome Variable of Interest	Exposure Variable of Interest	n (%)	Crude OR	95% CI	Adjusted OR[x]	95% CI
Intrapartum Monitoring - Ausculation	Obesity	198 (82.85)	1.44	0.98 – 2.13	1.31	0.88 – 1.95
	Non-obesity	458 (76.97)	Reference			
	Maternal age <30	209 (80.08)	1.19	0.82 – 1.72	1.47	0.99 – 2.18
	Maternal age 30-39	399 (77.18)	Reference			
	Maternal age ≥40	48 (85.71)	1.77	0.82 – 3.86	1.71	0.78 – 3.76
	Parity ≥ 1	424 (82.49)	1.79	1.28 – 2.50	1.76*	1.22 – 2.54
	Parity 0	232 (72.50)	Reference			
	Smoking	26 (83.87)	1.43	0.54 – 3.78	1.35	0.50 – 3.66
	Non-smoking	629 (78.43)	Reference			
	Male Infant	394 (78.49)	0.98	0.70 – 1.37	0.95	0.67 – 1.34
	Female Infant	262 (78.92)	Reference			
	Gestational diabetes	38 (86.36)	1.76	0.73 – 4.23	1.34	0.54 – 3.32
	No gestational diabetes	616 (78.27)	Reference			
	Gestational hypertension	21 (75.00)	0.81	0.34 – 1.93	0.69	0.28 – 1.70
	No gestational hypertension	633 (78.83)	Reference			
	Gestational age ≥ 41 weeks	181 (71.83)	0.57	0.41 – 0.81	0.63*	0.44 – 0.92
	Gestational age <41 weeks	475 (81.62)	Reference			
Intrapartum Monitoring – Internal Fetal Monitoring	Obesity	18 (7.53)	1.34	0.74 – 2.43	1.44	0.78 – 2.69
	Non-obesity	34 (5.71)	Reference			
	Maternal age <30	18 (6.90)	1.12	0.62 – 2.04	0.73	0.39 – 1.39
	Maternal age 30-39	32 (6.19)	Reference			
	Maternal age ≥40	S	0.56	0.13 – 2.41	0.56	0.13 – 2.47
	Parity ≥ 1	19 (3.70)	0.33	0.19 – 0.60	0.37*	0.20 – 0.70
	Parity 0	33 (10.31)	Reference			
	Smoking	S	1.65	0.48 – 5.61	1.43	0.40 – 5.12
	Non-smoking	49 (6.11)	Reference			
	Male Infant	29 (5.78)	0.82	0.47 – 1.45	0.86	0.48 – 1.53
	Female Infant	23 (6.93)	Reference			
	Gestational diabetes	S	1.10	0.33 – 3.69	1.27	0.36 – 4.51
	No gestational diabetes	49 (6.23)	Reference			
	Gestational hypertension	S	1.85	0.54 – 6.33	1.89	0.52 – 6.90
	No gestational hypertension	49 (6.10)	Reference			
	Gestational age ≥ 41 weeks	25 (9.92)	2.26	1.29 – 3.99	2.02*	1.09 – 3.73
	Gestational age <41 weeks	27 (4.64)	Reference			
Intrapartum Monitoring – External Fetal Monitoring	Obesity	166 (69.46)	0.75	0.54 – 1.04	0.76	0.53 – 1.10
	Non-obesity	448 (75.29)	Reference			
	Maternal age <30	223 (85.44)	2.63	1.78 – 3.89	1.95*	1.27 – 2.98
	Maternal age 30-39	357 (69.05)	Reference			
	Maternal age ≥40	34 (60.71)	0.69	0.39 – 1.22	0.67	0.36 – 1.22
	Parity ≥ 1	331 (64.40)	0.24	0.16 – 0.35	0.34*	0.22 – 0.51
	Parity 0	283 (88.44)	Reference			
	Smoking	23 (74.19)	1.03	0.46 – 2.34	0.79	0.32 – 1.96
	Non-smoking	590 (73.57)	Reference			
	Male Infant	362 (72.11)	0.82	0.60 – 1.13	0.80	0.57 – 1.13
	Female Infant	252 (75.90)	Reference			
	Gestational diabetes	30 (68.18)	0.76	0.40 – 1.46	1.05	0.51 – 2.16
	No gestational diabetes	581 (73.82)	Reference			
	Gestational hypertension	26 (92.86)	4.84	1.14 – 20.58	5.59*	1.26 – 24.69
	No gestational hypertension	585 (72.85)	Reference			
	Gestational age ≥ 41 weeks	223 (88.49)	3.76	2.46 – 5.74	3.13*	2.00 – 4.88
	Gestational age <41 weeks	391 (67.18)	Reference			
Meconium	Obesity	39 (16.25)	0.95	0.63 – 1.42	0.99	0.65 – 1.52

	Non-obesity	101 (16.97)	Reference			
	Maternal age <30	55 (20.99)	1.54	1.05 – 2.26	1.23	0.81 – 1.86
	Maternal age 30-39	76 (14.70)	Reference			
	Maternal age ≥40	9 (16.07)	1.11	0.52 – 2.36	1.08	0.50 – 2.35
	Parity ≥ 1	62 (12.04)	0.43	0.29 – 0.61	0.49*	0.33 – 0.74
	Parity 0	78 (24.38)	Reference			
	Smoking	S	0.52	0.16 – 1.74	0.42	0.12 – 1.44
	Non-smoking	137 (17.06)	Reference			
	Male Infant	85 (16.90)	1.02	0.71 – 1.49	1.04	0.71 – 1.52
	Female Infant	55 (16.57)	Reference			
	Gestational diabetes	9 (20.45)	1.30	0.61 – 2.77	1.71	0.77 – 3.81
	No gestational diabetes	130 (16.50)	Reference			
	Gestational hypertension	S	1.09	0.41 – 2.91	1.12	0.40 – 3.11
	No gestational hypertension	134 (16.67)	Reference			
	Gestational age ≥ 41 weeks	61 (24.21)	2.04	1.40 – 2.96	1.81*	1.21 – 2.69
	Gestational age <41 weeks	79 (13.55)	Reference			
Cord Artery Base Excess <-12.0	Obesity	10 (4.27)	0.49	0.24 – 0.98	0.48	0.23 – 1.00
	Non-obesity	48 (8.38)	Reference			
	Maternal age <30	20 (7.81)	1.15	0.65 – 2.05	1.14	0.62 – 2.12
	Maternal age 30-39	34 (6.85)	Reference			
	Maternal age ≥40	S	1.07	0.36 – 3.13	0.92	0.31 – 2.75
	Parity ≥ 1	34 (6.80)	0.86	0.50 – 1.48	1.03	0.57 – 1.88
	Parity 0	24 (7.82)	Reference			
	Smoking	S	0.92	0.21 – 3.96	0.84	0.19 – 3.74
	Non-smoking	56 (7.22)	Reference			
	Male Infant	34 (6.97)	0.92	0.54 – 1.58	0.95	0.55 – 1.65
	Female Infant	24 (7.52)	Reference			
	Gestational diabetes	S	1.76	0.66 – 4.65	2.84	1.00 – 8.04
	No gestational diabetes	53 (6.96)	Reference			
	Gestational hypertension	S	0.47	0.06 – 3.50	0.59	0.08 – 4.60
	No gestational hypertension	57 (7.35)	Reference			
	Gestational age ≥ 41 weeks	27 (11.20)	2.18	1.27 – 3.74	2.08*	1.18 – 3.69
	Gestational age <41 weeks	31 (5.48)	Reference			
No Delivery Room Resuscitation Required	Obesity	189 (78.75)	0.69	0.47 – 1.00	0.68	0.46 – 1.02
	Non-obesity	502 (84.37)	Reference			
	Maternal age <30	216 (82.44)	0.94	0.63 – 1.39	1.16	0.76 – 1.77
	Maternal age 30-39	431 (83.37)	Reference			
	Maternal age ≥40	44 (78.57)	0.73	0.37 – 1.44	0.77	0.38 – 1.55
	Parity ≥ 1	444 (86.21)	1.85	1.29 – 2.65	1.89*	1.27 – 2.81
	Parity 0	247 (77.19)	Reference			
	Smoking	27 (87.10)	1.43	0.49 – 4.14	1.59	0.53 – 4.75
	Non-smoking	663 (82.57)	Reference			
	Male Infant	427 (84.89)	1.45	1.01 – 2.08	1.43	0.99 – 2.07
	Female Infant	264 (79.52)	Reference			
	Gestational diabetes	31 (70.45)	0.48	0.24 – 0.93	0.48*	0.24 – 0.99
	No gestational diabetes	657 (83.38)	Reference			
	Gestational hypertension	23 (82.14)	0.96	0.36 – 2.57	1.14	0.41 – 3.16
	No gestational hypertension	665 (82.71)	Reference			
	Gestational age ≥ 41 weeks	198 (78.57)	0.67	0.46 – 0.97	0.72	0.48 – 1.07
	Gestational age <41 weeks	493 (84.56)	Reference			
Free flow oxygen required for resuscitation	Obesity	42 (17.50)	1.47	0.98 – 2.22	1.49	0.97 – 2.30
	Non-obesity	75 (12.61)	Reference			
	Maternal age <30	34 (12.98)	0.94	0.60 – 1.45	0.76	0.48 – 1.22
	Maternal age 30-39	71 (13.73)	Reference			
	Maternal age ≥40	12 (21.43)	1.71	0.86 – 3.40	1.65	0.81 – 3.36
	Parity ≥ 1	58 (11.26)	0.56	0.38 – 0.83	0.52*	0.34 – 0.80
	Parity 0	59 (18.44)	Reference			
	Smoking	S	0.41	0.10 – 1.75	0.39	0.09 – 1.68
	Non-smoking	115 (14.32)	Reference			
	Male Infant	62 (12.33)	0.71	0.48 – 1.05	0.72	0.48 – 1.08

	Female Infant	55 (16.57)	Reference			
	Gestational diabetes	11 (25.00)	2.15	1.05 – 4.37	2.02	0.94 – 4.34
	No gestational diabetes	106 (13.45)	Reference			
	Gestational hypertension	S	1.02	0.35 – 2.99	0.86	0.28 – 2.64
	No gestational hypertension	113 (14.05)	Reference			
	Gestational age ≥ 41 weeks	43 (17.06)	1.42	0.94 – 2.13	1.34	0.86 – 2.08
	Gestational age <41 weeks	74 (12.69)	Reference			
Positive pressure ventilation required for resuscitation	Obesity	24 (10.00)	1.46	0.87 – 2.48	1.47	0.84 – 2.56
	Non-obesity	42 (7.06)	Reference			
	Maternal age <30	16 (6.11)	0.70	0.39 – 1.27	0.50*	0.26 – 0.94
	Maternal age 30-39	44 (8.51)	Reference			
	Maternal age ≥40	6 (10.71)	1.29	0.52 – 3.18	1.19	0.47 – 3.04
	Parity ≥ 1	31 (6.02)	0.52	0.32 – 0.86	0.48*	0.28 – 0.84
	Parity 0	35 (10.94)	Reference			
	Smoking	S	1.26	0.37 – 4.26	1.27	0.36 – 4.44
	Non-smoking	63 (7.85)	Reference			
	Male Infant	37 (7.36)	0.83	0.50 – 1.38	0.88	0.52 – 1.47
	Female Infant	29 (8.73)	Reference			
	Gestational diabetes	7 (15.91)	2.34	1.00 – 5.47	2.30	0.92 – 5.72
	No gestational diabetes	59 (7.49)	Reference			
	Gestational hypertension	S	2.00	0.67 – 5.93	1.95	0.62 – 6.12
	No gestational hypertension	62 (7.71)	Reference			
	Gestational age ≥ 41 weeks	28 (11.11)	1.79	1.07 – 2.99	1.84*	1.05 – 3.22
	Gestational age <41 weeks	38 (6.52)	Reference			
Intubation required for resuscitation	Obesity	11 (4.58)	1.38	0.65 – 2.93	1.46	0.67 – 3.20
	Non-obesity	20 (3.36)	Reference			
	Maternal age <30	10 (3.82)	1.10	0.50 – 2.42	0.74	0.32 – 1.70
	Maternal age 30-39	18 (3.48)	Reference			
	Maternal age ≥40	S	1.57	0.45 – 5.50	1.63	0.45 – 5.97
	Parity ≥ 1	11 (2.14)	0.33	0.16 – 0.69	0.32*	0.14 – 0.72
	Parity 0	20 (6.25)	Reference			
	Smoking	S	0.86	0.11 – 6.51	0.81	0.10 – 6.35
	Non-smoking	30 (3.74)	Reference			
	Male Infant	17 (3.38)	0.80	0.39 – 1.63	0.79	0.38 – 1.65
	Female Infant	14 (4.22)	Reference			
	Gestational diabetes	S	1.25	0.29 – 5.40	1.28	0.27 – 6.02
	No gestational diabetes	29 (3.68)	Reference			
	Gestational hypertension	S	0.96	0.13 – 7.27	0.89	0.11 – 7.13
	No gestational hypertension	30 (3.73)	Reference			
	Gestational age ≥ 41 weeks	14 (5.56)	1.96	0.95 – 4.04	1.59	0.73 – 3.44
	Gestational age <41 weeks	17 (2.92)	Reference			

* Statistically significant

S: data suppressed due to cell size < 6.

Table 4.13 Crude and Adjusted Relations Between Macrosomic Infants Exposed to Maternal Obesity and Gestational Diabetes and Cesarean section, Live-born, Singleton Infants at the Ottawa Hospital Civic Campus between December 1, 2007 and March 31, 2010

	Macrosomic Infant of Obese Mother with Gestational Diabetes (n=28)	**Macrosomic Infant of Obese Mother without Gestational Diabetes (n=211)**				
	n (%)	n (%)	**Crude OR**	**95% CI**	**Adjusted OR***	**95% CI**
Cesarean delivery – any indication	15 (53.57)	104 (49.29)	1.19	0.54 – 2.62	1.20	0.51 – 2.81
Cesarean delivery – maternal indication	4 (26.67)	11 (10.58)	3.08	0.84 – 11.33	2.41	0.58 – 9.92

*[¥]Adjusted for maternal age, parity (0 vs ≥1), gestational age at delivery (continuous), smoking (yes vs no), infant sex (male vs female) and gestational hypertension (yes vs no)

Table 4.14 Crude and Adjusted Relations Between Macrosomic Infants Exposed to Maternal Obesity and Gestational Hypertension and Cesarean section, Live-born, Singleton Infants at the Ottawa Hospital Civic Campus between December 1, 2007 and March 31, 2010

	Macrosomic Infant of Obese Mother with Gestational Hypertension (n=13)	**Macrosomic Infant of Obese Mother without Gestational Hypertension** (n=226)				
	n (%)	n (%)	**Crude OR**	**95% CI**	**Adjusted OR***	**95% CI**
Cesarean delivery – any indication	5 (38.46)	114 (50.44)	0.61	0.20 – 1.93	0.43	0.13 – 1.43
Cesarean delivery – maternal indication	3 (60.00)	12 (10.53)	12.74	1.93 – 84.06	8.63	1.10 – 67.84

*[¥]Adjusted for maternal age, parity (0 vs ≥1), gestational age at delivery (continuous), smoking (yes vs no), infant sex (male vs female) and gestational diabetes (yes vs no)

Appendix 1: Structured Data Abstraction Form

Study Title	
Study citation	
Reviewer	
Notes:	
Date of Review	
Eligibility Assessment	
Does the study define obesity as per the IOM guidelines (obesity = BMI ≥ 30.0 kg/m^2)?	Yes No
Is the obesity measure obtained pre-pregnancy, in the first trimester or at the first prenatal visit?	Yes No (state when obtained) _____
Is the comparison group of underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5 – 24.9 kg/m^2) or underweight + normal weight women (BMI <25.0 kg/m^2)?	Yes No (state comparator used) _____
Is there data present that allows for quantitative measurement of obesity (obesity = BMI ≥ 30.0 kg/m^2)?	Yes No (state obesity measure used) _____
Is there data present that allows for quantitative measurement of risk of macrosomia (≥ 90%ile, ≥ 97%ile, ≥ 4000g, or ≥ 4500g)?	Yes No (state macrosomia measure used) _____
Inclusion Decision	YES NO

Data Abstraction	
What is the study design?	
What is the study setting (ex: clinic, community, etc.)?	
Where was the located (geographic)?	
What is the time period of the study?	
What is the ethnic population in the study?	
What inclusion criteria were used?	
What exclusion criteria were used?	
What was the obesity measure used?	
What is the source of the obesity measure?	
Number of subjects in obese group	
Number of subjects in control group	
How was macrosomia defined?	
What is the source of the macrosomia measure?	
Number of infants with macrosomia in obese group	
Number of infants without macrosomia in obese group	
Number of infants with macrosomia in control group	
Number of infants without macrosomia in control group	
What statistical measures were used?	
Was there adjustment for confounding?	
Were effect modifiers examined?	

Quality Assessment for Cohort Studies

Was the representativeness of the exposed cohort:

a. truly representative of the average obese pregnant woman in the community
b. somewhat representative of the average obese pregnant woman in the community
c. selected group of users (ex: nurses, volunteers)
d. no description of the derivation of the cohort given

Was the non-exposed cohort:

a. drawn from the same community as the exposed cohort
b. drawn from a different source
c. no description of the derivation of the non-exposed cohort given

How was obesity ascertained?

a. secure record (ex: measured weight and height)
b. self-report
c. no description given

Demonstration that the outcome of interest was not present at the start of the study

Not applicable

Are the cohorts comparable for:

a. age: obesity group_____ control group_____
b. parity: obesity group_____ control group_____
c. presence of diabetes: obesity group_____ control group_____
d. presence of hypertension: obesity group_____ control group_____
e. socioeconomic status: obesity group_____ control group_____
f. for race: obesity group_____ control group_____
g. multiple gestation: obesity group_____ control group_____

How was macrosomia assessed?

a. independent blind assessment
b. self-report
c. no description given

Was follow-up long enough for outcomes to occur?

Not applicable

Was the follow-up of the cohorts adequate?

a. all subjects accounted for
b. subjects lost to follow-up unlikely to introduce bias (<5% loss to follow-up and description provided of those lost)
c. loss to follow-up rate >5% or no description of those lost
d. no statement

Quality Assessment for Case-Control Studies
Is the case definition adequate? a. yes, with independent validation b. yes, but not independently validated (eg record linkage or based on self reports) c. no description
Are the cases representative? a. consecutive or obviously representative series of cases b. potential for selection biases or not stated
How were controls selected? a. From community controls b. From hospital controls c. no description
How were controls defined? a. no history of obesity (BMI ≤24.9) b. no description of controls
Are cases and controls comparable for: h. age: cases_____ controls_____ i. parity: cases_____ controls_____ j. presence of diabetes: cases_____ controls_____ k. presence of hypertension: cases_____ controls_____ l. socioeconomic status: cases_____ controls_____ m. for race: cases_____ controls_____ a. multiple gestation: cases_____ controls_____
How was the definition of obesity assigned? a. secure record (ex: measured height and weight) b. self-report c. no description
Was obesity measured the same way in cases and controls? a. yes b. no
Were non-response rates the same for both groups? a. same rate for both groups b. nonrespondents described c. rate difference and nonrespondents not described