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Karilynn Rockhill 4/21/2014

The effects of prepregnancy body mass index and gestational weight gain on fetal macrosomia among American Indian/Alaskan Native women

By

Karilynn Rockhill
Master of Public Health

Department of Epidemiology

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Dr. Carol Hogue
Faculty Thesis Advisor

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Karilynn Rockhill

BS, Ithaca College, 2010

Faculty Thesis Advisor: Dr. Carol Hogue, PhD, MPH

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ABSTRACT

The effects of prepregnancy body mass index and gestational weight gain on fetal macrosomia among American Indian/Alaskan Native women

By Karilynn Rockhill

Background: The American Indian/Alaskan Native (AI/AN) population is at high health risk across many health indicators, including obesity. Fetal macrosomia can result in obstetric and long-term maternal and child complications. We investigated the effects of prepregnancy body mass index (BMI) and gestational weight gain (GWG) on macrosomia among AI/ANs.

Methods: Data came from the Pregnancy Risk Assessment Monitoring System in eight states from 2004-2011 for adult AI/ANs who delivered a live, singleton birth. Macrosomia (birthweight ≥4,000 grams) and the World Health Organization's BMI categories were used. GWG enumerated the pounds women deviated from the Institute of Medicine guidelines for pregnancy weight gain. Prevalence of macrosomia by select characteristics was estimated. Multivariable logistic regression calculated adjusted odds ratios (aOR) for effects of BMI and GWG, controlling for other factors.

Results: About 30% of women were obese, and approximately 50% had excess GWG. Prevalence of macrosomia varied from 8.00-18.83% (Utah/Alaska). Characteristics with significantly high prevalence of macrosomia were obesity (16.67%), excess GWG (16.32%), multiparity (13.46%), diabetes (17.93%), no smoking (13.54%), no nausea (13.37%), post-term delivery (18.36%), and male infant (14.98%). There were significant independent effects of prepregnancy obesity [aOR:1.63; 95%Confidence Interval

(CI):1.29,2.07] and excess GWG [aOR:1.16; 95%CI:1.12,1.20 per five pounds gained beyond appropriate] for macrosomia but no significant joint effects.

Conclusions: Obesity and excess GWG are independent factors for macrosomia among AI/ANs. Culturally appropriate interventions need to address these factors. Providers should target all women when counseling about GWG, emphasizing the increased risk associated with every additional pound above recommended weight gain.

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LIST OF ABBREVIATIONS

The following is a list of all abbreviations used as they appear in the text:

AI/AN	American Indian/Alaskan Native
GWG	Gestational weight gain
ACOG	American College of Obstetricians and Gynecologists
LGA	Large for gestational age
BMI	Body Mass Index
WHO	World Health Organizations
IOM	Institute of Medicine
aOR	Adjusted Odds Ratio
CI	Confidence Interval
OR	Odds Ratio
GDM	Gestational Diabetes Mellitus
RR	Risk Ratio
IHS	Indian Health Service
PRAMS	Pregnancy Risk Assessment Monitoring System
CDC	Centers for Disease Control and Prevention
std	Standard Deviation
IRB	Institutional Review Board
DAG	Direct Acyclic Graph

CHAPTER 1: INTRODUCTION/BACKGROUND

It is well established that the United States displays many racial disparities among general health indicators and adverse pregnancy outcomes. The American Indian/Alaskan Native (AI/AN) population is unique to the United States and is a high-risk group across many health indicators.[1] Research is necessary to investigate risk factors and help drive the programs and interventions needed to target this high-risk population, particularly pregnant women.

Macrosomia is a term used to describe infants who are born large as measured by birth weight or size for gestational age. Fetal macrosomia comes with many risks, including obstetric complications for the mother, immediate health concerns or injuries to the infant during delivery, and long-term health problems for the child. This study investigates macrosomia among AI/AN's. In particular, this analysis will look at the individual and joint effects of prepregnancy maternal weight and excess gestational weight gain (GWG) on the risk of macrosomia.

Definitions

Macrosomia characterizes infants who have excessive intrauterine growth. Since there are no internationally established definitions for macrosomia, it has been classified multiple ways. It is usually defined in the literature by birth weight with varying cut-off points. The most common definition of macrosomia is birth weight greater than 4,000 grams, or 8 lbs., 14 ounces, irrespective of gestational age. This weight corresponds to the 90th percentile of birth weight for a full term infant of 40 weeks gestation.[2] By this definition, the reported prevalence of macrosomia across the world ranges from five to 20%, with Nordic countries having the highest prevalence.[3]

There are other common cut-offs. For example, the American College of Obstetricians and Gynecologists (ACOG) uses 4,500 grams, or 9 lbs., 15 ounces, which marks increased maternal and neonatal complication rates.[4,5] Given that gestational age is the strongest predictor of birth weight, fetal growth can also be classified by percentage of birth weight based on gestational age. Infants who weigh either more than the 90th percentile, or above two standard deviations of weight for gestational age are identified as large for gestational age (LGA).[2,3] Neither of these definitions of large infants actually discriminates between normal and abnormal fetal body composition.[6] Therefore, other measures have been created to classify infant size at birth. The Ponderal Index, for example, describes fetal body proportions and is defined as body weight divided by the third power of length.[3]

Macrosomia is diagnosed retrospectively after delivery, since prenatal diagnostic measures that predict and estimate fetal weight in utero are imprecise. Therefore, measures such as LGA estimation are more useful clinically for predicting potential obstetric risks for complications and determining the course of action for the delivery.[7] For research purposes, the research aims typically determine the choice of definition for classifying large infants. Studies investigating the effects of infant size and pregnancy outcomes are more likely to look at macrosomia based on birth weight. Studies investigating biological plausibility of intrauterine fetal growth and fat distribution tend to use LGA as their measurement tool.[2,6]

Body Mass Index (BMI) is a simple index that classifies weight-for-height in adults but does not take into account body composition. The World Health Organization (WHO) established a universal equation and classification scheme for BMI. It is

calculated as weight in kilograms divided by the square of height in meters (kg/m^2). BMI is classified into four main categories: underweight (<18.5), normal range (18.50–24.99), overweight (25.00–29.99), and obese (≥30.00). Obese is further broken down into three classes: Obese Class I (30.00–34.99), Obese Class II (35.00–39.99), and Obese Class III (≥40.00).[8]

In 1990, the Institute of Medicine (IOM) established guidelines for recommended ranges of acceptable GWG during pregnancy based on maternal prepregnancy BMI. These guidelines were updated in 2009 to reflect the growing diversity of the current American female population, characterized by increases in obesity, multiple births, and women having children later in life.[9] There were two major changes made to the GWG guidelines. First, the prepregnancy BMI categories were changed to match the WHO classification scheme instead of the Metropolitan Life Insurance tables. Second, the range of appropriate weight gain for obese women is now more narrow and capped compared to the open-ended weight gain range previously considered acceptable.[9] Recommended ranges of acceptable GWG during pregnancy are outlined in Figure 1 of the Appendix. The IOM also identified research gaps and called for research including the effect of weight gain during pregnancy on maternal and infant health outcomes.[9]

Risk Factors for Macrosomia

Factors that affect excessive intrauterine growth leading to macrosomia and LGA infants are both genetic and environmental in nature. According to the ACOG committee opinion, the risk factors, excluding preexisting diabetes mellitus, for

> "fetal macrosomia in decreasing order of importance are as follows: a history of macrosomia, maternal prepregnancy weight, weight gain during pregnancy, multiparity, male fetus, gestational age more than 40 weeks, ethnicity, maternal birth weight, maternal height, maternal age younger than 17 years and a positive

> 50-g glucose screen with a negative result on the three-hour glucose tolerance test."[5]

This list includes both modifiable and non-modifiable factors. Modifiable risk factors for fetal macrosomia include mainly maternal physical characteristics such as BMI, GWG, glucose metabolism control, smoking status, nutritional intake, and physical activity.[3,6,7,10,11] Non-modifiable risk factors are mainly situational and genetic such as gestational age at delivery, parity, history of previous macrosomic delivery, maternal age, maternal height, and Type 1 and 2 diabetes.[3,6]

The strongest risk factor for fetal macrosomia is a previous macrosomic delivery, probably reflecting both genetic and environmental risk factors.[3,7] Studies have shown the odds ratios for delivering a macrosomic infant are as high as 15.8 with a history of a previous macrosomic birth. Reoccurrence rates were shown to be 32% after the first macrosomic delivery compared to 0.3% in those that delivered a previous normal birth weight baby. In women who have had multiple macrosomic infants, the risk is even greater.[6]

Genetic Risk Factors

Some of the genetic risk factors of fetal macrosomia include fetal sex, ethnicity, and gene regulation of insulin production. Estimates of overall contribution of genetics on fetal birth weight vary greatly, ranging between 25-80%.[3] This variation is mostly due to the inconclusive evidence surrounding many genetic interactions with in utero environment. However, some genetic contributions are well established. A male fetus is more likely to be macrosomic, with an average fetal weight gain rate of 0.5 gram per day greater than for a female fetus.[3,6,7,12] Ethnicity may also be related to fetal macrosomia, with the Caucasian race having the highest risk.[7] Differences among ethnicities related to

reproductive anatomy and body type can also increase risk of maternal complications associated with macrosomia, such as perineal tears.[13] Genes influencing insulin production, and insulin-like growth factor and their receptors, are also possible candidates for influencing fetal growth.[3] New research on epigenetic regulation has indicated that nutrition and other intrauterine factors may modify long-term fetal expression of genes.[3] For example, the paternal gene for insulin-like growth factor II is imprinted, which seems to be an important factor in placental growth and nutrient transfer.[3] Another example of interaction between nutrients and gene expression may be maternal glucose metabolism affecting gene expression.[3] However more research needs to be done in this area, and evidence of epigenetic regulation on fetal growth is unresolved.[3]

Environmental Risk Factors

Many situational risk factors surrounding the pregnancy and risk factors associated with the intrauterine environment can affect excess fetal growth. For instance, birth weight is directly related to gestational age of the fetus. Gestational age greater than 40 weeks, or post-term delivery, is a main predictor of macrosomia by birth weight.[7] Some evidence suggests that intrauterine growth displays a curvilinear fetal weight gain pattern between 37 and 42 weeks of gestation, with growth rates peaking during this time and declining afterwards.[6] Multiparity is another non-modifiable environmental risk factor for macrosomia.[3,14] Parity over four has been shown to be a strong risk factor for macrosomia defined by birth weight.[2] Maternal age at delivery is a risk factor independent of parity.[3] Two international studies researched this risk associated with maternal age. One 2003 study determined maternal age to be associated with increased

risk of fetal macrosomia defined as LGA- measured by 90th percentile- but not when measured as birth weight. The authors hypothesized that this could have been attributed to a greater number of older women delivering earlier in the pregnancy, or before full term. However, increased maternal age may promote higher growth velocities in infants due to the slowing of maternal metabolism with age.[2] In another study, infants of mothers of normal BMI who were over 35 years old were associated with an adjusted odds ratio (aOR) for macrosomia of 1.79 (95% Confidence Interval (CI): 1.17-2.74) compared to mothers under 25 years old.[12] Maternal height is also an independent risk factor for fetal macrosomia, and consequently shorter women with a macrosomic infant are at higher risk for birth complications.[3,6]

In contrast to genetics and situational factors, many of the environmental risk factors are modifiable. Most notably, prepregnancy maternal BMI, particularly obesity at conception, has been shown to be a strong risk factor for macrosomia by birth weight. This association is independent of diabetes, glucose intolerance, and GWG, which are often comorbid conditions.[2,3,6,15-17] A meta-analysis assessing the association of infant birth weight to maternal BMI at conception showed overweight and obese women had positive associations with macrosomia defined as birth weight ≥4,000 grams in 12 studies (Odds Ratio (OR): 1.53; 95% CI: 1.44-1.63 and OR: 2.00; 95% CI: 1.84-2.18 respectively); had a positive association with macrosomia defined as birth weight ≥4,500 grams in 10 studies (OR: 1.67; 95% CI: 1.42-1.97 and OR: 3.23; 95% CI: 2.39-4.37 respectively); and had a positive association with LGA in 21 studies (OR: 1.53; 95% CI: 1.44-1.63 and OR: 2.08; 95% CI: 1.95-2.23 respectively).[17] Some studies, however, do

not show a significant relationship between overweight at conception and macrosomia once adjusted for other risk factors (aOR: 1.1; 95% CI: 0.9-1.3).[16]

As well, risk for macrosomia increases as obesity increases. One study in Ireland showed that maternal BMI was associated with macrosomia, ≥4,000 grams, with the underweight group least likely to deliver a macrosomic infant and the overweight and obese classes 1, 2, and 3 being 1.5, 1.9, 2.1, and 3.2 times as likely to deliver a macrosomic infant, respectively, after adjusting for infant gender and gestational age.[18] It is hypothesized that additional metabolic factors related to maternal weight will influence both fetal growth and fetal body proportions.[3] In addition, there is evidence to show that interconception weight gain can increase the risk of having a subsequent large baby and that this risk decreases with interconception weight loss.[3]

Once pregnancy begins, maternal BMI at conception is not modifiable, but weight gain during pregnancy can be managed clinically and "controlled weight gain" programs are available from specialists.[3] Independent of maternal prepregnancy BMI, excess weight gain above the IOM guidelines for each BMI category is associated with increased risk of excess fetal growth, though the combination of the two can lead to even greater risk of macrosomia.[3,16,19] While obesity, diabetes, and excess weight gain often can occur simultaneously, this association has even been seen in non-diabetic mothers with normal prepregnancy BMI who experienced excess weight gain during pregnancy. Additionally, many studies exclude or restrict diabetic pregnancies to control for potential confounding since diabetes is also a risk factor for macrosomia. One study in Italy showed independent effects of prepregnancy BMI and GWG on macrosomia, with women who gained in excess of the IOM recommendations having almost twice the odds

of macrosomia defined as ≥4,000 grams (aOR: 1.9; 95% CI: 1.6-2.2).[16] A study of only mothers with gestational diabetes mellitus (GDM) showed that, for every BMI category, women exceeding IOM weight gain recommendations had a higher risk of having a macrosomic infant independent of having a history of a previous macrosomic birth.[20] In the United Kingdom, Egan et. al. found that the odds for LGA and macrosomia increased in diabetic women who experience excess GWG. This was further compounded by beginning insulin therapy for women with GDM, with the combined effect greater than either individual contribution of both variables.[21]

Studies have also looked at the risk for gestational weight loss during pregnancy, particularly the third trimester. For example, studies of obese women with GDM looked at gestational weight loss to see if there was a reduced risk for adverse pregnancy and perinatal outcomes. In a study by Yee et. al., obese American women with GDM who lost weight during their third trimester were less likely to have macrosomic infants (aOR: 0.66; 95% CI: 0.53-0.83) and LGA infants (aOR: 0.63; 95% CI: 0.52-0.77) compared to similar women who did not lose weight.[22]

Prepregnancy BMI and GWG are independent risk factors for macrosomia and large infants and their biological metabolic pathways to excess infant growth differ. Prepregnancy BMI is caused by many factors like maternal age, physical activity level, and nutritional status prior to conception, whereas, GWG is attributable to fetal-maternal physiological changes from both environmental and genetic factors. It is estimated that 30-40% of GWG is comprised of fetal contributions such as fetal weight, placental weight, and the amniotic fluid. The remaining 60-70% of GWG is comprised of maternal contributions such as breast and uterine growth and fat deposits.[16]

Diabetes, both prepregnancy and gestational, is associated with increased fetal growth.[3,7,10] Historically, diabetic pregnancies have been the main concern regarding maternal and infant adverse outcomes caused from deliveries of large fetuses.[3] GDM is defined as any glucose intolerance during pregnancy in a woman who was never diagnosed with diabetes before pregnancy.[23] The American Diabetes Association estimates that GDM affects about 7% of pregnancies.[24] Up to 35% of infants born to diabetic mothers have birth weights above the 95th percentile, although the majority of macrosomic infants are born to non-diabetic mothers.[6]

Clinically, maternal glucose control is one of the most modifiable risk factors for macrosomia during pregnancy. Continuous glucose monitoring, especially during the third trimester when fetal growth rates peak, is associated with lower birth weight and reduced risk of macrosomia.[6] The risk of macrosomia can be as high as 20% if GDM is left undiagnosed or untreated.[5] Glucose intolerance is extremely relevant to infant weight since, biologically, glucose is the main energy source the fetus uses for growth. Glucose intolerance is seen as a continuum.[6] Therefore, some mothers who are not diagnosed as diabetic, since they do not reach specific thresholds, may have some increased risk of fetal macrosomia.[3] This can be explained by the Pedersen hypothesis, which states that fetal growth is stimulated by elevated glucose levels in the fetus caused by overstimulation of the fetal pancreas due to maternal hyperglycemia. Insulin can have growth promoting properties, particularly in the third trimester.[25] The fetus is receiving more energy than it needs for growth and development so the excess energy is stored in adipose tissue.[23] Legardeur et. al. found elevated blood glucose levels to be a major independent risk factor of macrosomia and LGA infants.[10] The odds of macrosomia,

≥4,000grams, was greater in mothers with GDM compared to mothers without diabetes (aOR: 1.72; 95% CI: 1.23-2.40).[10]

Diabetes is also associated with changes in fetal growth profiles, even if the infant is not diagnosed as LGA or as fetal macrosomia. A study on fetal growth profiles between macrosomic and non-macrosomic infants with regards to mothers with gestational, Type 1, and Type 2 diabetes found that head circumference and femur length of fetuses did not differ between any types of diabetic pregnancies and controls. However, abdominal circumference did differ between the types of diabetes and controls. Macrosomic infants of mothers with Type 1 diabetes had the largest increase over time, and the increase was significantly higher than mothers with gestational diabetes and controls. As expected, the disproportionate growth in pregnancies complicated by GDM did not become significant compared to controls until later in the pregnancy, corresponding to when GDM is often diagnosed. Overall, there was a disproportionate fetal growth profile and fat distribution among pregnancies complicated by all three types of diabetes.[26] Some studies have shown that GDM is associated with delivery < 40 weeks gestation; in those pregnancies, maternal diabetes may be associated with LGA but not always macrosomia by birth weight.[27]

In general, though, maternal BMI may contribute more attributable risk for macrosomia than diabetes on a population level since the prevalence of overweight and obese mothers is much higher than the prevalence of diabetes in the population.[3] For example, a study in Florida to determine the population-attributable fractions for BMI, excess GWG, and diabetes for LGA stratified by race found that GDM contributed the least to the fraction of LGA, ranging from 2.0% in Whites to 8.0% in Blacks and GWG

contributed the most, ranging from 33.3% in Hispanics to 37.7% in Asian/Pacific Islanders. The contributions of BMI for overweight or obese women ranged from 9.5% in Asian/Pacific Islanders to 22.4% in Blacks.[19] Unfortunately, this study did not include AI/AN as a race category and therefore data on this population are still missing.

Obesity, diabetes, hypertension, and dyslipidemia are all factors associated with metabolic syndrome. There is evidence that maternal dyslipidemia is associated with increased risk of fetal macrosomia, independent of the other metabolic syndrome factors. Maternal serum lipid levels increase during mid to late pregnancy to maintain an energy source to the fetus.[28] A Norwegian cohort study in 2005 included blood parameters from 17-19 weeks gestation in the regression model for macrosomia and found that non-high density lipoprotein-cholesterol and low levels of L-cholesterol were independent risk factors apart from maternal BMI, weight gain, and GDM.[15] These blood parameters are characteristic of metabolic syndrome often associated with obesity, but during early pregnancy can account for independent increased risks to macrosomia. Other international studies have found that later in pregnancy, but not early in pregnancy, high triglyceride levels have been independently associated with increased risk of LGA.[28]

In addition, a negative smoking history is also a risk factor for macrosomia.[7] However, the benefits associated with not smoking during pregnancy far outweigh the increased risk for macrosomia. Smoking during pregnancy can cause adverse infant outcomes such as preterm delivery and restricted fetal growth.[29] High rates of smoking among the AI/AN populations may impact rates of macrosomia, leading to more low-birth weight infants instead of high-birth weight infants. Smoking cessation however, is known to cause weight gain in both pregnant and non-pregnant women. In one Danish

study of smoking quits during pregnancy, adjusted GWG at 37 weeks was 2.0 kg (95% CI: 1.5-2.6) higher in quitters than in non-smoking women. This corresponded to an aOR of 1.9 (95% CI: 1.5-2.4) for excess weight gain, defined by the 2009 IOM guidelines, adjusted for gestational age and preeclampsia.[30] Accordingly, smoking status can have direct effect on macrosomia in addition to impacting other related risk factors.

Physical activity can also affect pregnancy outcomes and is a modifiable risk factor. Studies on physical activity in relation to macrosomia specifically are inconclusive. Nevertheless, in one study in Canada, women with higher physical activity scores during pregnancy were less likely to deliver a macrosomic infant, with further analysis adjustment for GWG not changing this association.[31] Also, physical activity has been shown to reduce the risk of many other obstetric outcomes as well.[3,31] For instance, physical activity during pregnancy has been shown to help control glucose levels in diabetic pregnancies.[3]

Maternal diet is another modifiable risk factor for macrosomia, but evidence linking diet to macrosomia is inconclusive. Like with diabetic pregnancies, there is evidence showing an association between maternal glucose levels and fetal growth, even when blood glucose levels are within normal range. Maternal diets with high glycemic index carbohydrates influence maternal blood glucose levels. High blood glucose levels in turn can lead to weight gain and fetal-placental overgrowth, both of which are predispositions to macrosomia. Nevertheless, evidence surrounding maternal diet interventions during pregnancy is inconclusive.[6]

Complications

The ACOG guidelines on fetal macrosomia have identified the most common and most severe complications linked with macrosomia. Increased risk of cesarean delivery is the primary maternal risk, because of concern about both maternal and infant complications associated with disproportion between fetal size and pelvic size. ACOG identified shoulder dystocia in infants as the most serious complication, even though the condition is rare, and infant clavicle fracture and brachial plexus nerve damage as the most common fetal injuries associated with macrosomia.[5] In 2012, King et. al. found the risk of composite maternal and neonatal complications increased 2.29 times for infants weighing between 4,000-4,499 grams and 6.27 times for infants weighing between 4,500-4,999 grams compared to infants with birth weights below 4,000 grams. This increased risk held true for both diabetic and non-diabetic pregnancies.[32]

Maternal Complications

Short-term complications for the mother are usually a result of the actual large physical size of the fetus. Correspondingly, the number one concern regarding fetal macrosomia is the risk associated with a vaginal birth and therefore potential cesarean section.[5,7] There are multiple neonatal and maternal complications that are associated with suspected fetal macrosomia that can occur simultaneously, so clinically the "overall risk" of vaginal delivery of a macrosomic infant is uncertain.[32]

Common short-term maternal concerns include risks of longer first and second stages of labor, instrumental vaginal delivery, emergency cesarean sections, perineal trauma, and postpartum hemorrhage (Table A).[2,3,7,32,33] Postpartum hemorrhage was also associated with macrosomia, most likely due to perineal trauma and greater uterine distension.[2] Mothers of macrosomic infants were also more likely to have longer hospital

stays, which is an indicator of overall increased maternal morbidity.[2] Specific associations between maternal short-term complications across several studies can be seen in the tables below.

Interestingly, one study from 2005 to 2008 in France showed that multiparous women who had a previous vaginal delivery of a macrosomic infant had a decreased risk of maternal complications with the subsequent macrosomic birth. It is thought that the perineal tissues, which have already experienced a macrosomic birth, handle subsequent births with fewer adverse events.[13]

Since macrosomia can only be diagnosed retrospectively, estimated fetal weight is used to predict potential risk. Elective caesarean section is used to prevent complications from predicted fetal macrosomia, such as maternal lacerations and infant brachial plexus injuries. However, in the general population the number of elective caesarean sections needed to prevent one of these cases makes most experts believe that elective caesarean section based on estimated fetal weight alone is unjustifiable.[3] There has also been evidence that inducing labor early for women with suspected fetal macrosomia does not decrease rates of emergency cesarean sections or perinatal morbidity.[3]

Some long-term complications for the mother that have been associated with a macrosomic infant include diabetes, persistent perineal defects, and anal dysfunction.[3] The Nurses' Health Study showed having a macrosomic baby, defined as greater than 10-lbs, could be predictive of future Type 2 diabetes in mothers. Women who gave birth to a macrosomic baby had a 1.61 (95% CI: 1.24-2.08) times the risk of developing Type 2 diabetes, showing significance between six and 20 years after the first birth. When restricting the analysis to women who had no history of GDM or hypertension during

pregnancy, the association strengthened to a hazard ratio of 2.22 (95% CI: 1.50-3.28). This could be indicative of maternal hyperglycemia that did not meet clinical definitions of GDM.[34]

In addition, other factors that are risks for macrosomia, like GWG, can have long-term effects. One meta-analysis showed that women with excess GWG are more likely to have an increased risk of becoming overweight and obese postpartum, which could affect subsequent pregnancies, which was shown elsewhere to be true for both primiparous and nulliparous women.[35,36]

Table A: Maternal Short-term Complications

	Jolly et. al.[2]		Najafian et. al.[14]
Population	350,311 pregnancies from the North West Thames Region, St. Mary's Maternity Information System Database		201,102 pregnancies at Obstetrics and Gynecology Department, in Ahvaz city, Iran
Type of Study	Retrospective Cohort		Nested Case Control
Date	1988-1997		2007-2011
Outcome of Interest	Macrosomia: >4,000 grams	Macrosomia: >90th percentile (LGA)	Macrosomia: >4,000 grams
Short-term Complications			
Longer 1st/2nd Stage Labor	1st stage: aOR: 1.57 (99% CI: 1.51-1.63) 2nd stage: aOR: 2.03 (99% CI: 1.88-2.19)	1st stage: aOR: 1.21 (99% CI: 1.16-1.27) 2nd stage: aOR: 1.70 (99% CI: 1.54-1.83)	-
Instrumental Vaginal Delivery	aOR: 1.76 (99% CI: 1.68-1.85)	aOR:1.34 (99% CI: 1.27-1.42)	-
Cesarean Section	aOR:1.84 (99% CI: 1.75-1.93)	aOR: 1.41 (99% CI: 1.34-1.49)	89% Cases vs. 28.5% Controls; p=0.32
Perineal Trauma	2nd degree tear: aOR: 1.44 (99% CI: 1.39-1.49) 3rd degree tear: aOR: 2.73 (99% CI: 2.30-3.23)	2nd degree tear: aOR: 1.29 (99% CI: 1.24-1.34) 3rd degree tear: aOR: 1.88 (99% CI: 1.54-2.31)	4.9% Cases vs. 0.2% Controls; p=0.0001
Postpartum Hemorrhage	aOR: 2.01 (99% CI: 1.93-2.10)	aOR: 1.63 (99% CI: 1.56-1.71)	-
Placenta Previa	aOR: 0.46, (99% CI: 0.30-0.71)	aOR: 1.67 (99% CI: 1.32-2.12)	-
Longer Hospital Stay	-	-	-

Table A: Maternal Short-term Complications

	King et. al.[32]		
Population	14,406 women from Los Angeles County, University of Southern CA Medical Center delivering singleton, full term infants		
Type of Study	Retrospective Cohort		
Date	1995-2004		
Outcome of Interest	Macrosomia: 4,000-4,499 grams	Macrosomia: 4,500-4,999 grams	Macrosomia: ≥5,000 grams
Short-term Complications			
Longer 1st/2nd Stage Labor	-	-	-
Instrumental Vaginal Delivery	-	-	-
Cesarean Section	aOR: 2.82 (95% CI: 2.39-3.32)	aOR: 8.28 (95% CI: 5.85-11.73)	aOR: 6.91 (95% CI: 3.17-15.07)
Perineal Trauma	aOR: 1.70 (95% CI: 1.32-2.19)	aOR: 2.46 (95% CI: 1.36-4.43)	aOR: 2.00 (95% CI: 0.46-8.68)
Postpartum Hemorrhage	aOR: 3.18 (95% CI: 2.47-4.10)	aOR: 7.59 (95% CI: 4.79-12.03)	aOR: 8.60 (95% CI: 3.22-22.98)
Placenta Previa	-	-	-
Longer Hospital Stay	aOR: 2.18 (95% CI: 1.76-2.71)	aOR: 2.13 (95% CI: 1.21-3.72)	aOR: 3.80 (95% CI: 1.36-10.59)

Table A: Maternal Short-term Complications

	Boulet et. al.[33]		
Population	8,264,308 pregnancies from the National Center for Health Statistics linked live birth/death files for term, singleton births		
Type of Study	Cross Sectional		
Date	1995-1997		
Outcome of Interest	Macrosomia: 4,000-4,499 grams	Macrosomia: 4,500-4,999 grams	Macrosomia: ≥5,000 grams
Short-term Complications			
Longer 1st/2nd Stage Labor	aOR: 1.38 (95% CI: 1.35-1.41)	aOR: 1.55 (95% CI: 1.48-1.62)	aOR: 1.76 (95% CI: 1.55-1.99)
Instrumental Vaginal Delivery	-	-	-
Cesarean Section	aOR: 1.62 (95% CI: 1.61-1.63)	aOR: 2.61 (95% CI: 2.58-2.64)	aOR: 4.68 (95% CI: 4.54-4.83)
Perineal Trauma	-	-	-
Postpartum Hemorrhage	-	-	-
Placenta Previa	-	-	-
Longer Hospital Stay	-	-	-

Neonatal Complications

Neonatal complications of macrosomia include increased risk of shoulder dystocia, clavicle fracture, death, admissions to the neonatal unit, and newborn metabolic problems like hyperglycemia (Table B).[7,14,32,33,37] Most notably, macrosomia by birth weight has been shown to increase risk of intrauterine death by two or three times. This is mainly due to prolonged labor, operative deliveries, shoulder dystocia, and hypoxia.[3] Shoulder dystocia is therefore one of the key reasons for delivery interventions involving fetal macrosomia. However, 48% of shoulder dystocia cases occur in non-macrosomic infants, and the majority of macrosomic infants do not have shoulder dystocia.[7] The major concern with shoulder dystocia is risk of permanent nerve palsy. The Ponderal Index and infant body proportions can also be indicators of increased risk for shoulder dystocia, along with body weight and size.[3] Maternal diabetes is independently associated with higher risk of shoulder dystocia at any given birth weight compared to non-diabetic mothers.[3] For macrosomic infants above 4,500 grams, the risk of shoulder dystocia among non-diabetic pregnancies is increased between 9.2-24% and 19.9-50% among diabetic pregnancies. However, shoulder dystocia can occur unpredictably in normal weight infants as well.[5] Evidence indicating when a diabetic mother with suspected fetal macrosomia should undergo elective caesarean section to prevent shoulder dystocia is insufficient.[3]

The most common neonatal complication influenced by macrosomia is clavicle fracture, with risks increasing approximately ten-fold in macrosomic infants compared to normal birth weight infants.[5] Brachial plexus injuries are associated with clavicle fractures and shoulder dystocia. Such injuries are rare, but the risk for them increases

almost 20 times with fetal weight above 4,500 grams.[5,14] Other short-term risks that are increased with high fetal weight include hypoglycemia, hyperbilirubinemia, and longer stay in the neonatal intensive care unit.[3]

Long-term risks to the offspring associated with macrosomia include diabetes, overweight/obesity, metabolic syndrome, asthma, persistent plexus injuries, and some cancers (Table C).[3,6,21,38,39] An recent study in the New England Journal of Medicine showed that the prevalence of being overweight among children who were macrosomic, ≥4,000 grams, at was statistically higher and consistently increased compared non-macrosomic births, ranging from 22.5% in kindergarten to 31.2% in eighth grade. In addition, these children had the largest difference in risk, with children being 5.1 times as likely to be overweight in the next nine years after age five compared to children non-macrosomic at birth (Risk Ratio (RR): 5.11; 95% CI: 2.92-8.94).[39] A study among American Indian children in Wisconsin found that macrosomia, defined as over 4,500 grams, and excess GWG both increased the odds that the child would be overweight or obese at ages one and five to eight years old, even when mothers had no diagnosis of GDM.[40] Increased risk of breast cancer has also been reported in several studies, with odds three times as high in women who were born macrosomic, ≥4,500 grams, than woman who were not heavy at birth.[41,42] Specific study associations for long-term and short-term neonatal complications can be seen in the tables below.

Table B: Neonatal Short-term Complications

	Jolly et. al.[2]		Najafian et. al.[14]
Population	350,311 pregnancies from the North West Thames Region, St. Mary's Maternity Information System Database		201,102 pregnancies at Obstetrics and Gynecology Department, in Ahvaz city, Iran
Type of Study	Retrospective Cohort		Nested Case Control in Cohort
Date	1988-1997		2007-2011
Outcome of Interest	Macrosomia: >4,000 grams	Macrosomia: >90th percentile (LGA)	Macrosomia: >4,000 grams
Short-term Complications			
Neonatal Death	-	-	-
Stillbirth	aOR: 0.76, (99% CI: 0.52-1.12)	aOR: 1.00 (99% CI: 0.76-1.32)	-
Admission to Neonatal Intensive Care Unit	aOR: 1.51 (99% CI: 1.38-1.66)	aOR: 1.24 (99% CI: 1.14-1.34)	-
Shoulder Dystocia	-	-	11% Cases vs. 0.5% Controls; p=0.0001
Clavicle Fracture	-	-	0.6% Cases vs. 0.1% Controls; p=0.0001
Brachial Plexus Injuries	-	-	1.9% vs. 0.1% Controls; p=0.0001

Table B: Neonatal Short-term Complications

	King et. al.[32]		
Population	14,406 women from Los Angeles County, University of Southern CA Medical Center delivering singleton, full term infants		
Type of Study	Retrospective Cohort		
Date	1995-2004		
Outcome of Interest	Macrosomia: 4,000-4,499 grams	Macrosomia: 4,500-4,999 grams	Macrosomia: ≥5,000 grams
Short-term Complications			
Neonatal Death	-	-	-
Stillbirth	-	-	-
Admission to Neonatal Intensive Care Unit	aOR: 1.71 (95% CI: 1.47-1.98)	aOR: 3.88 (95% CI: 2.79-5.38)	aOR: 3.53 (95% CI: 1.67-7.43)
Shoulder Dystocia	aOR: 7.10 (95% CI: 5.18-9.72)	aOR: 20.45 (95% CI: 12.60-33.18)	aOR: 22.69 (95% CI: 8.45-60.90)
Clavicle Fracture	-	-	-
Brachial Plexus Injuries	aOR: 6.61 (95% CI: 4.16-10.50)	aOR: 11.53 (95% CI: 5.08-26.15)	aOR: 8.59 (95% CI: 1.14-14.65)

Table B: Neonatal Short-term Complications

	Boulet et. al.[33]		
Population	8,264,308 pregnancies from the National Center for Health Statistics linked live birth/death files for term, singleton births		
Type of Study	Cross Sectional		
Date	1995-1997		
Outcome of Interest	Macrosomia: 4,000-4,499 grams	Macrosomia: 4,500-4,999 grams	Macrosomia: ≥5,000 grams
Short-term Complications			
Neonatal Death	aOR: 0.87 (95 %CI: 0.80-0.96)	aOR: 1.00 (95% CI: 0.83-1.21)	aOR: 2.69 (95% CI: 1.91-3.80)
Stillbirth	-	-	-
Admission to Neonatal Intensive Care Unit	-	-	-
Shoulder Dystocia	-	-	-
Clavicle Fracture	-	-	-
Brachial Plexus Injuries	-	-	-
Hypoglycemia	-	-	-

Table C: Neonatal Long-term Complications

	Harder et. al.[38]	Innes et. al.[42]	Lindberg et. al.[40]	Cunningham et. al.[39]
Population	Meta-analysis from 9 studies for high birth weight	484 cases and 2,870 controls combination from vital records and cancer registries from New York State.	471 American Indian children, subset of WINGS cohort in Wisconsin	7,738 children/50,396 person-years in the United States, Early Childhood Longitudinal Study
Type of Study	Meta-analysis	Matched Case Control	Retrospective Cohort	Retrospective Cohort
Date	1989-2005	1978-1995	2012	1998-1999 Cohort
Outcome of Interest	Macrosomia: >4,000 grams	Macrosomia: >4,500 grams	Macrosomia: >4,500 grams	Macrosomia: ≥4,000 grams
Long-term Complications				
Diabetes	aOR: 1.26 (95% CI: 1.12-1.42)	-	-	-
Overweight/Obesity	-	-	At age 1: aOR: 4.38 (95% CI: 1.25-15.38) At age 5-8: aOR: 4.38 (95% CI: 1.59-12.10)	RR: 5.11 (95% CI: 2.92-8.94) for overweight after 5 years old for next 9 years
Cancers	-	Breast Cancer: aOR: 3.10 (95% CI: 1.18-7.97)	-	-

In addition, studies have shown associations with prepregnancy BMI and excess GWG with childhood overweight and obesity later in life. One meta-analysis for prepregnancy overweight or obese mothers showed an increased risk of offspring being overweight/obese compared to normal weight mothers at conception (aOR: 1.95; 95% CI: 1.77-2.13 and aOR: 3.06; 95% CI: 2.68-3.49 respectively).[17] Another meta-analysis of all prospective studies showed that excess gestational weight gained compared to adequate weight gain resulted in increased relative risk of obesity later in life 40% overall (RR: 1.40; 95% CI: 1.23-1.59). This risk remained significantly elevated throughout life although the association decreased over time. This meta-analysis showed the relative risk of obesity for under five years old was 1.91 (95% CI: 1.21-3.02), for children five to 18 years old was 1.32 (95% CI: 1.14-1.53), and for long term as adults over 18 years old was 1.47 (95% CI: 1.21-1.77).[43] There potentially could be a circular pattern with conditions such as prepregnancy obesity and gestational weight gain that are reinforced from generation to generation.[3]

Studies on both maternal and infant complications from macrosomia typically only look at birth weight or LGA. Often body composition and body proportions increase the risk for complications as well even if the infants do not fall into macrosomia classifications.[3]

Diagnosis of Macrosomia

Most studies that investigate macrosomia-related risk factors and maternal and neonatal complications have to use birth weight measurements after the delivery. The main reason for trying to identify fetal macrosomia is to prepare for shoulder dystocia in

the infant.[3] The amount of possible risk reduction through early diagnosis of suspected fetal macrosomia based on the above recognizable risk factors is essentially unknown due to inaccuracy of fetal weight measurements.[2]

Fetal weight prediction can be made by clinical assessment, ultrasound, or maternal prediction. Clinical measurements can include abdominal palpation and symphysis-fundal height measurement. Palpation can be compromised by maternal obesity or polyhydramnios (excess amniotic fluid in the amniotic sac), but has been shown in some studies to be as sensitive as ultrasound techniques.[6,7] Abdominal circumference is the most useful single ultrasound predictor of fetal size during the third trimester. Many formulas exist to predict fetal weight from ultrasound techniques during the third trimester, with the most common being those from Hadlock and Shephard.[4,7] Sonographic measurements have shown to be slightly more accurate, but a combination of clinical assessment and ultrasound appears to be best.[6,32] According to one report in 2007 and a meta-analysis completed in 2008, the sensitivity of determining fetal macrosomia across diabetic and non-diabetic pregnancies is between 50-60%, with about 8-10% error in estimated weight.[3,7] The mean absolute error in birth weight across most studies is approximately 250-500 grams. Both sonographic and clinical measurements have false positives and false negatives, which can impact clinical care.[3] Maternal assessment of fetal weight has also been shown to be almost as accurate as clinical measures, although nulliparous women are less accurate than multiparous women.[7] Magnetic resonance imaging may become an additional tool to assess body composition and fetal weight in the future, but its clinical usefulness still needs more research.[3] Fetal growth can essentially only be tracked across consecutive measurements over the course

of the pregnancy to detect the possibility of a LGA or macrosomic infant and identify high-risk pregnancies.[4] Repeated ultrasounds for diabetic pregnancies are used to detect accelerated fetal growth, which is associated with worse outcomes.[7] Incorrect diagnoses of fetal macrosomia may lead to increased elective caesarian deliveries, which may not actually reduce or prevent infant morbidities.[2]

Management of fetal macrosomia is best through prevention.[3] Reducing prepregnancy weight and increasing physical activity are regarded as tools for preventing metabolic syndrome, obesity, and diabetes, all of which can have effects on birth outcomes.[3] After conception, clinical care is directed more at the management and control of macrosomia risk factors, like tight glucose control and weight gain, than preventing excessive intrauterine growth.

Cultural Context

Traditional Beliefs

AI/ANs have many cultural practices surrounding health and wellbeing, including pregnancy. AI/AN culture and traditional practices can differ by tribe, but, there are some overarching beliefs among AI/ANs. In contrast to individualistic western culture, AI/AN culture includes characteristics such as conformity, respect for authority figures, and spirituality.[44] However, over time, due to acculturation and migration to urban areas, many of the traditional teachings surrounding medicine and healing techniques are being abandoned[45]. There are many factors that play into the abandonment of traditional cultural practices among AI/ANs: federal policies in the 1950's impacting tribal reservations, Indian boarding schools prohibiting native languages and customs, and racism and discrimination to name a few.[45]

There are some universal beliefs surrounding childbearing as well. In general, AI/AN children are considered gifts and are honored and cherished.[44] Qualitative studies in northwest AI/ANs showed:

> "cultural beliefs and values about childbearing said that pregnancy was a normal event not requiring biomedical intervention. In fact attending prenatal care was perceived by some as a pampering the mother."[45]

Pregnancy in traditional culture is not seen as a condition a woman needs to see a doctor to treat. However, pregnancy is seen as a normal and natural event for which care for the child really begins in-utero, so women are encouraged to quit smoking and drinking during pregnancy.[45] Another qualitative study in Oregon found that a major theme affecting prenatal care is the disturbance of traditional indigenous women's role as primary transmitters of information through oral traditions and as typically being the birth attendants.[45] This breakdown resulted in Western models of prenatal care being culturally inappropriate. In this Oregon community, the traditional practices of learning from older women about pregnancy and birth were unavailable, so there was a greater dependency on community resources.[45] However, women were reluctant to accept interventions that do not consider their social and cultural contexts.[46]

Health Disparities

According to the 2010 U.S. Census, there are approximately 5.2 million AI/ANs comprising about 1.7% of the U.S. total population.[47] This is a very diverse group consisting of 566 federally recognized tribes, with 229 being found in Alaska and the rest across 33 states.[48] Disparities between AI/AN and other races have been shown to have existed for 500 years, beginning with infectious disease disparities during colonization.[46,49] The most recently published National Vital Statistics Report in 2011

showed that AI/AN women had a higher percentage of macrosomic births, ≥4,000 grams, than the national average across all races (9.8% versus 7.8%, respectively).[50] Other birth profiles among AI/AN women compared to other races include higher rates of diabetes during pregnancy (7.5% compared to 5.5%, respectively), lower rates of caesarean delivery (28.4% versus 32.8%, respectively), higher rates of certified midwife deliveries (16.7% versus 7.8%, respectively), and higher rates of late term births (9.6% versus 8.3%, respectively).[50] In 2010, the prevalence of smoking was also highest among AI/AN women compared to other racial groups, with 55% smoking before pregnancy, and 26% continuing to smoking during pregnancy.[29] Other maternal characteristics include higher drinking rates, having their first birth about three years younger than women of other races, and being more likely to be unmarried at delivery.[50,51] As a population, AI/ANs also have higher rates of mental disorders, substance abuse, suicidal behaviors, and behavioral and relationship problems.[46] Overall, some have reported the "health statistics among AI/ANs are sometimes closer to those found in lower- and middle-income countries."[52]

To address many of the health disparities among this unique population, the Indian Health Service (IHS) was created in 1955, designed mostly to treat infectious diseases.[53] Currently it is estimated to serve approximately 1.6 million AI/AN across 36 states.[53] Although the creation of IHS helped bring much needed health services to AI/ANs, it did come with some limitations. For those that do receive care from the IHS, the per capita funding is less than half of what is provided to Medicaid or incarcerated populations.[52]

The AI/AN population has also mostly migrated off traditional lands since the creation of the IHS. Since the 1970's, more AI/ANs are moving to more urban areas from the rural and reservation communities. Census data showed that the proportion of AI/ANs living in urban areas rose from 38% in 1970 to 61% in 2000.[54] Residential shifts can be attributed to federal relocation policies from the 1950's, along with increased opportunities in urban areas for education, employment, and housing. This residential shift has been accompanied by loss of access to healthcare provided by the IHS.[54] To address the growing urban population, IHS funded 34 metropolitan urban Indian health organizations. Despite over 60 % of the AI/AN population living in urban areas off reservations, only 1% of the total IHS budget is allocated to these urban organizations, which are only accessible to about 44% of the urban population.[52,54] Clearly, access to healthcare services is a problem among the AI/AN population.

Education, income, and unemployment rates are consistent factors in the literature explaining the health disparities for AI/AN populations.[46,47,52,54-56] The American Community Survey was used to assess disparities in health insurance among 27 different races found in the United States. AI/ANs were found to have the second highest unemployment rate (14.29%), second highest adult poverty rates (23.78%), third highest child poverty rate (32.45%), and fourth lowest per capita income ($23,721). [55] Other issues include inadequate housing, food insecurities on reservations, and poor nutrition. After adjusting for socio-economic differences, AI/AN still had 3.5 times higher odds for children and 2.2 times higher odds for adults of being uninsured compared to Whites.[55] The 2010 Census estimated 29.2% of AI/ANs lacked health insurance.[47] Research has

shown uninsured individuals are more likely to delay or forego medical care.[55] Many of these factors are compounded by geographic isolation on reservations.[52]

There is conflicting data on whether urban or rural AI/AN populations have higher rates of inadequate prenatal care. AI/AN women in rural areas or reservations may have inadequate care due to poor proximity to providers and lack of transportation.[57] On the other hand, studies have found poor access to care for urban AI/ANs since children are not eligible or have no access to services provided by the IHS or tribal health programs. [56] Overall, AI/ANs are more than 3.6 times as likely to enter prenatal care in the third trimester or to receive no prenatal care at all compared to non-Hispanic whites.[57] AI/ANs have been shown to have consistently the highest rates of inadequate care compared to other races, which takes into account both timing of entry into prenatal care and number of prenatal visits throughout pregnancy.[57] One study found 57% of AI/AN infants compared to 79% of non-Hispanic white infants had mothers who received adequate prenatal care.[57]

Focus groups have identified cultural barriers to utilization and access, which account for some of these differences. As mentioned earlier, traditionally females act as the birth attendants, whereas doctors within the IHS were typically white males. Domestic violence and substance abuse were also identified as major barriers along with typical access barriers such as transportation and competing life priorities.[45]

Geographic Differences

According to the 2010 Census, approximately 40.7% of the AI/AN population resides in the West, 32.7% in the South, 16.8% in the Midwest, and 9.7% in the Northwest.[58] Moreover, about 77% of the people that reside on traditional Indian lands do

not identify as AI/AN.[58] There are regional and tribal differences across the United States for risk factors and adverse infant outcomes among AI/AN women. The Midwest region, compared to the South/Northeast and West regions, has the highest risk of infant mortality, mainly driven by higher birth weights and gestational age-specific mortality rates in that area.[51] In addition, rates of late or no prenatal care differ among AI/ANs geographically. For example, from 1995-1997, late entry or no prenatal care ranged from 9.0% below the U.S. AI/AN national rate in Alaska, to 12.6% above the national rate in New Mexico.[57] Patterns for state-level disparities between races vary widely. Whereas some states are shrinking the disparities in prenatal care utilization, in other states the disparities are increasing. The Midwest in general has the widest disparities for indicators, late entry and inadequate prenatal care.[57]

Geographical differences also include tribal differences in both genetic lineage and cultural beliefs. Alaska consists of 228 federally recognized tribes. Eskimos are the most prevalent, consisting of both the Yupik and Inuit tribes. There are nine total federally recognized tribes in Minnesota, with the largest being the Sioux and Chippewa tribes. Nebraska also has a large Sioux population, along with six federally recognized tribes. New Mexico is home to the largest federally recognized tribe, the Navajo and 21 other federally recognized tribes. Utah is also predominantly Navajo, with eight total federally recognized tribes. Both Oklahoma and Oregon are mostly Cherokee. There are 38 federally recognized tribes in Oklahoma, and ten in Oregon. There are 29 federally recognized tribes in Washington, with the greatest population bring the Puget Salish.[59]

Research Aims

The IOM revised guidelines include a call for increased research surrounding GWG. AI/AN women are a unique population to the United States with high rates of maternal obesity and diabetes. There needs to be more research surrounding the effects of prepregnancy BMI and GWG during pregnancy and subsequent pregnancy outcomes to help guide clinical management of high-risk pregnancies among AI/AN women. The primary objective of this study is to investigate the individual and joint effects of high prepregnancy BMI and excess GWG on fetal macrosomia using a retrospective cohort study of AI/AN women. A sub-analysis of only non-diabetic women will be conducted to account for the possible confounding of diabetes. The secondary aim of this analysis is to display the associations of macrosomia with these two main exposures for each individual state to look at possible geographic differences.

CHAPTER 2: EXTENDED METHODS

This retrospective cohort study was conducted among women who delivered a live, singleton birth between 2004 and 2011 and participated in the Pregnancy Risk Assessment Monitoring System (PRAMS) in the United States.

PRAMS is a population-based survey on maternal attitudes and experiences before, during, and after pregnancy that is jointly led by the Centers for Disease Control and Prevention (CDC) and by state health departments. This survey, which expanded from six states 1987 to 40 states in 2013, is administered through the mail to a sample of all mothers who have given birth to a live infant within the participating states. Once a mother returns the survey, the self-report questionnaire data are then linked to the infant's birth certificate. If the mother fails to respond to the first mail survey, one more mailing is sent, followed by a telephone contact. All attempts to contact the mother end nine months after delivery. Between 1,300 and 3,400 women are systematically sampled from each state per year from the birth certificate registries. The PRAMS methodology is standardized across all participating states, allowing single or multi-state data comparisons. Reponses are weighted to represent the entire state, adjusting for sample design, non-response, and non-coverage. A more detailed explanation of the PRAMS methodology can be found elsewhere.[60]

The PRAMS questionnaire is updated periodically, and this analysis includes Phase 5 (2004-2008) and Phase 6 (2009-2011). To be included in this analysis, a state had to have reported that at least five percent of all live births are to AI/AN women, which limited the analysis to: Alaska (2004-2010), Minnesota (2004-2011), Nebraska (2004-2011), New Mexico (2004-2005, 2011), Oklahoma (2004-2011), Oregon (2004-

2011), Utah (2004-2011), and Washington (2004-2011).[1] All states must have had a ≥70% response rate from 2004-2006 and ≥65% response rate from 2007-2011 to be included. Some states, such as Arizona, Montana, North Dakota, and South Dakota, also have high percentages of births to AI/AN women but either do not participate in PRAMS or did not participate during the phases included.

This study was designed as a retrospective cohort study using the PRAMS questionnaires to obtain exposure data and birth certificate data to confirm birth outcomes. The total sample contained 95,428 women. The main analysis was limited to AI/AN women who delivered a live singleton birth (n=12,420). AI/AN women under 20 years old (n=2,055) were also excluded from the analysis because teenagers follow different BMI categorizations based on age and sex that are not comparable with the adult WHO BMI categories.[61] The final analytic sample consisted of 10,363 woman-infant pairs.

Variable Definitions

Variable information that was extracted from the birth certificate included: maternal race, maternal age, infant birth weight, clinical infant gestational age, infant sex, GWG, diabetes, birth plurality, number of previous live births, marital status, and maternal educational level. Variable information that was collected from the mother's self report on the PRAMS questionnaire included: prepregnancy BMI, diabetes, hypertension, smoking status during pregnancy, nausea, entry into prenatal care, pregnancy intention, and federal poverty level. Women were included as AI/AN if they identified as being single race American Indian or Alaskan Native, or reported being mixed race with any indication of being partially AI/AN.

Macrosomia was defined by three classifications. Birth weight definitions included weight from the birth certificate ≥4,000 grams, most commonly found in the literature, and ≥4,500 grams, as defined by ACOG. LGA was defined as ≥90th percentile of weight for gestational age. In this analysis, fetal macrosomia will be defined as birth weight ≥4,000 grams, which is consistent with other literature.[16,17,37]

The two main exposures were maternal prepregnancy BMI and GWG. To determine prepregnancy weight, women were asked: "Just before you got pregnant with your baby, how much did you weigh?" Maternal prepregnancy BMI was calculated by each woman's self-report of height and weight before pregnancy and classified by the WHO guidelines as underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), or obese (≥30.0 kg/m^2). BMI's that were less than 13 kg/m^2 or greater than 70 kg/m^2 were considered implausible and were excluded from the analysis under recommendation from the PRAMS team at the CDC.[62]

GWG was extracted from the birth certificate and was classified by two methods. First, GWG was categorized as inadequate, appropriate, or excess based on the updated 2009 IOM guidelines. Second, a continuous variable for GWG was created that counted the number of pounds the women fluctuated above or below their recommended appropriate GWG. Women within the appropriate GWG recommended range for their BMI were coded as having zero pounds over appropriate weight gain. The specific ranges of acceptable GWG by BMI category can be seen in Figure 1 of the Appendix. The 2009 IOM guidelines were chosen over the 1990 guidelines because the ranges were updated to better represent the American population and provide finite ranges based on the WHO BMI categories.

The federal poverty level of the women was calculated by taking into account the self-reported household income and number of dependents from the questionnaire. The PRAMS questionnaire asked the mothers for the total gross household income during the 12 months prior to the birth of this most recent infant. The questionnaire also asked: "During the 12 months before your new baby was born, how many people, including yourself, depended on this income?" The federal poverty level was calculated using an algorithm developed by the CDC. This algorithm uses the reported number of dependents and adds one dependent for the new infant in the house. Any report of greater than 13 dependents was collapsed into ≥13 dependents. This algorithm then uses the federal poverty guidelines from the year before the infants' births and the reported gross household income to determine federal poverty level. This takes into account the yearly differences in federal poverty guidelines and the differences in poverty cut-points between Alaska and the continental United States. Federal poverty annual income cut-points were found on external websites.[63]

Other clinical and maternal characteristics variables were defined as follows. A positive diabetes status was defined as any report of diabetes, either gestational or prepregnancy diabetes, listed on the birth certificate or reported by the mother on the PRAMS questionnaire. Hypertension, including both prepregnancy hypertension and hypertension during the pregnancy, as well as reported nausea were identified using the question: "Did you have any of the following problems during your most recent pregnancy?" Two questions were used to define pregnancy intention. First, the women were asked: "Thinking back to right before you got pregnant with your new baby, how did you feel about becoming pregnant?" The options for answers were: "I wanted to

become pregnancy sooner," "later," "then," and "I didn't want to become pregnant then or at any time in the future." The women were then asked: "When you got pregnant with your baby, were you trying to become pregnant?" The pregnancies were defined as intended pregnancies if the women answered "Yes" to trying to become pregnant or if they answered that they wanted to become pregnant "sooner" or "then." The pregnancies were defined as unintended pregnancies if they answered "No" to trying to become pregnant or if they answered that they wanted to become pregnant "later" or "never."

Ascertainment of smoking changed between Phase 5 and Phase 6 in PRAMS with a variation in the smoking filter question. During Phase 5, women were asked: "Have you smoked at least 100 cigarettes in the past 2 years?" During Phase 6, the filter question changed to: "Have you smoked any cigarettes in the past 2 years?" If women answered "Yes" to these questions, they were then asked a series of smoking related questions addressing activity before, during, and after pregnancy. For this analysis, the women were classified as smoking during pregnancy if they smoked during the last three months of their pregnancy. In other reports, the change in filter question did have a significant effect on the prevalence of women who reported smoking before pregnancy but did not have a significant effect on the number of women who smoked during pregnancy or after delivery.[29]

Data Analysis

Descriptive statistics were completed on the total analytic sample. Univariate analysis was conducted to determine the prevalence estimates with 95% confidence intervals and chi square tests for macrosomia using all three definitions. Descriptive statistics were conducted for the outcome by select maternal demographic characteristics

(maternal AI/AN race, maternal age, maternal education level, marital status, and federal poverty level) and pregnancy characteristics (maternal prepregnancy BMI, GWG, parity, pregnancy intention, entry into prenatal care, any diabetes, hypertension, maternal smoking, reported nausea, gestational age, and infant gender).

Summary statistics for the continuous variables for maternal prepregnancy BMI and absolute number of pounds gained during pregnancy were calculated among macrosomic and non-macrosomic deliveries. Pairwise comparisons of the macrosomia stratified means for BMI and absolute number of pounds gained were conducted.

The mean and standard deviation (std) of the mean for BMI were calculated overall in addition to each BMI category and through stratification by weight gain categories (inadequate, appropriate, excess) and macrosomia. Pairwise comparisons were conducted between mean BMI for each weight gain category for macrosomic deliveries to the mean BMI for non-macrosomic deliveries.

The mean number of pounds gained from the appropriate range was also calculated overall and for each BMI category stratified by macrosomia. Pairwise comparisons were calculated between mean number of pounds gained for each BMI category for macrosomic deliveries and the mean number of pounds gained for non-macrosomic deliveries. All pairwise comparisons used Bonferroni's method to determine the statistically significant alpha value ($p=0.004$ for BMI and $p=0.006$ for GWG).

Among AI/AN women, crude odds ratios for macrosomia (≥4,000 grams) were calculated with 95% confidence intervals for all the demographic and pregnancy characteristics using logistic regression. Reference groups were chosen either by standard of practice (i.e. normal for BMI, or appropriate for GWG), or, in the case where there

was no standard reference group, by the level of the categorical variable that had the lowest prevalence of macrosomia (i.e. female for infant gender). American Indian and Alaskan Native populations have well established differential health indicators and should be treated as separate ethnicities; therefore, mixed race individuals were chosen as the referent category. Factors having a significant crude association with outcome were then tested for crude associations with both of the main exposures.

Polytamous logistic regression was used to assess the association of covariates with maternal prepregnancy BMI using normal weight as the reference category. Polytamous regression was chosen over ordinal regression to allow for a dose-response effect to be seen, as it was thought that the BMI categories are not inherently ordinal in nature. The least square means with continuous GWG was tested using linear regression. All the above associations, along with information based on the potential causal relationships guided the creation of the multivariable logistic regression model.

This multivariable logistic regression model was built to quantify the association between macrosomia and the two main exposures adjusted for all possible confounders: race, maternal age, parity, history of any type of diabetes, smoking during pregnancy, reported nausea, gestational age, and infant sex. Four interaction terms were considered in the original model: prepregnancy BMI and weight gain, prepregnancy BMI and diabetes, prepregnancy BMI and parity, and GWG and smoking during pregnancy. The interaction term for BMI and GWG was included to assess the joint effects of the two main exposures in addition to the independent effects of these exposures.

Interaction assessment and confounding assessment were conducted to determine the final regression model used in the analysis. After the evaluation of interaction terms,

an assessment of confounding was conducted on the resulting model adjusted for all possible covariates. The criteria for confounding included any set of variables that changed the adjusted estimated beta estimates of the main exposures more than 10%. All possible models with different sets of confounding variables that did not display confounding effects were compared by precision of the confidence interval. The final regression model chosen was the fully adjusted model, which included no interaction terms and the following variables: maternal age, parity, diabetes, smoking during pregnancy, reported nausea, gestational age, and infant sex. The reported OR's examined the association between macrosomia and prepregnancy BMI and GWG using normal weight/appropriate GWG as the reference group.

The secondary aim of the study was addressed by conducting descriptive statistics and regression analysis stratifying the analytic dataset by state of residence. The proportion of macrosomia, maternal prepregnancy BMI, and GWG were calculated individually for each state along with 95% CI's. In addition, adjusted OR's and 95% CI's for macrosomia were conducted for each state. Regression models to look at state effects included the same covariates as above.

A sub-analysis was conducted on all AI/AN women who had no report of diabetes before pregnancy or gestational diabetes to control for all confounding of excess growth from diabetes. The same regression model included for the main analysis was used on the sub-sample of all women who reported no diabetes (n=8,931). The reported OR's looked at the association between macrosomia and prepregnancy BMI and GWG using normal weight/appropriate GWG as the reference group.

Statistical significance was defined as p-values ≤0.05. All analyses were performed using SAS 9.3 and SUDAAN Version 11 to accommodate the complex survey design of the PRAMS (Cary, NC, USA). Through Emory University's Institutional Review Board (IRB) on November 11, 2013 this study was determined to not require IRB review since it does not involve "human subjects."

CHAPTER 3: MANUSCRIPT

The effects of prepregnancy body mass index and gestational weight gain on fetal macrosomia among American Indian/Alaskan Native women

Author: Karilynn Rockhill

Abstract: (250 words)

Background: The American Indian/Alaskan Native (AI/AN) population is at high health risk across many health indicators, including obesity. Fetal macrosomia can result in obstetric and long-term maternal and child complications. We investigated the effects of prepregnancy body mass index (BMI) and gestational weight gain (GWG) on macrosomia among AI/ANs.

Methods: Data came from the Pregnancy Risk Assessment Monitoring System in eight states from 2004-2011 for adult AI/ANs who delivered a live, singleton birth. Macrosomia (birthweight ≥4,000 grams) and the World Health Organization's BMI categories were used. GWG enumerated the pounds women deviated from the Institute of Medicine guidelines for pregnancy weight gain. Prevalence of macrosomia by select characteristics was estimated. Multivariable logistic regression calculated adjusted odds ratios (aOR) for effects of BMI and GWG, controlling for other factors.

Results: About 30% of women were obese, and approximately 50% had excess GWG. Prevalence of macrosomia varied from 8.00-18.83% (Utah/Alaska). Characteristics with significantly high prevalence of macrosomia were obesity (16.67%), excess GWG (16.32%), multiparity (13.46%), diabetes (17.93%), no smoking (13.54%), no nausea (13.37%), post-term delivery (18.36%), and male infant (14.98%). There were significant

independent effects of prepregnancy obesity [aOR:1.63; 95%Confidence Interval (CI):1.29,2.07] and excess GWG [aOR:1.16; 95%CI:1.12,1.20 per five pounds gained beyond appropriate] for macrosomia but no significant joint effects.

Conclusions: Obesity and excess GWG are independent factors for macrosomia among AI/ANs. Culturally appropriate interventions need to address these factors. Providers should target all women when counseling about GWG, emphasizing the increased risk associated with every additional pound above recommended weight gain.

Background:

The American Indian/Alaskan Native (AI/AN) population is unique to the United States and is a high-risk group across many health indicators.[1] The maternal AI/AN population is characterized by having significantly higher levels of obesity, diabetes, smoking, and alcohol use than other racial groups in the United States.[29,51,64] Education, income, and unemployment rates are consistent factors in the literature explaining the health disparities for AI/AN populations.[46,52,54,55] Over the last 30 years, the AI/AN population has migrated to be predominately in urban areas compared to traditional reservations.[54] Access and healthcare utilizations disparities between AI/ANs and other races are mixtures of systematic barriers such as lack of transportation along with medical care conflicting with cultural beliefs and practices.[45]

In 2011, AI/AN women had 2% more macrosomic births than the national average across all races.[50] Macrosomia characterizes infants who have excessive intrauterine growth, resulting in infants being born large as measured by birthweight or large for gestational age (LGA). Fetal macrosomia comes with many risks, including

obstetric complications for the mother, immediate health concerns or injuries to the infant during delivery, and long-term health problems for the child. One study in 2012 estimated composite maternal and neonatal complications risk for fetal macrosomia increased 2.29 times for infants weighing between 4,000-4,499 grams and 6.27 times for infants weighing between 4,500-4,999 grams compared to infants with birth weights below 4,000 grams.[32] Some common short-term maternal concerns as a result of large infant size at delivery include risks of longer first and second stages of labor, instrumental vaginal delivery, emergency cesarean sections, perineal trauma, and postpartum hemorrhage.[2,3,32,33] Neonatal complications from macrosomia at time of delivery include increased risk of shoulder dystocia, clavicle fracture, brachial plexus injuries, admissions to the neonatal unit, and death.[2,14,32,33,37] Long-term risks for the child associated with macrosomia include diabetes, overweight/obesity during childhood, asthma, persistent plexus injuries, and some cancers.[3,6,38-40,42]

Macrosomia is diagnosed retrospectively after delivery, since prenatal diagnostic measures that predict and estimate fetal weight in utero are imprecise.[3] However, predicting fetal weight is clinically useful to prepare for potential obstetric risks for complications and determining the course of action for the delivery.[7] Therefore, addressing possible risk factors to reduce the likelihood of fetal macrosomia is important before and during pregnancy.

Macrosomia is influenced by both genetic and environmental factors. In contrast to genetic and situational factors, many of the environmental risk factors are modifiable, such as prepregnancy body mass index (BMI) and gestational weight gain (GWG). High prepregnancy BMI, excess GWG, and diabetes are all well established risk factors for

macrosomia and are prevalent among the AI/AN population.[2,3,6,16,17,19] The increase in prevalence of macrosomia in recent years can be mostly attributed to increases in the prevalence of environmental exposures such as these.[16]

Different biological metabolic pathways are responsible for increased maternal prepregnancy BMI and GWG. Prepregnancy BMI is influenced by lifestyle behaviors and nutritional status of the mother before conception, whereas, GWG is influenced by fetal-maternal physiological changes in addition to genetic and nutritional factors throughout pregnancy. Thirty to 40% of GWG can be attributed to fetal contributions such as fetal weight while the additional 60-70% can be attributed to maternal factors.[16]

Population-attributable fractions for BMI, excess GWG, and diabetes for LGA infants stratified by race in Florida showed GWG contributed the most, ranging from 33.3% in Hispanics to 37.7% in Asian/Pacific Islanders and BMI contributions for overweight or obese women ranged from 9.5% in Asian/Pacific Islanders to 22.4% in Blacks.[19] Unfortunately, this study did not include AI/AN as a race category, and data on this population are still missing.

The Institute of Medicine (IOM) called for more research surrounding the effects of prepregnancy BMI and GWG during pregnancy to help guide clinical management of high-risk pregnancies, and this is particularly needed for AI/AN women. The primary objective of this study was to investigate the individual and joint effects of high prepregnancy BMI and excess GWG on fetal macrosomia among adult AI/AN women in the United States. The secondary aim of this analysis is to display the associations of macrosomia with these two main exposures for each individual state to see possible geographic differences.

Methods:

This retrospective cohort study was conducted among adult women who delivered a live, singleton birth between 2004 and 2011 and participated in the Pregnancy Risk Assessment Monitoring System (PRAMS) in the United States. PRAMS is a population-based survey on maternal attitudes and experiences before, during, and after pregnancy. To be included in this analysis, a state had to have reported that at least five percent of all live births are to AI/AN women, which limited the analysis to: Alaska (2004-2010), Minnesota (2004-2011), Nebraska (2004-2011), New Mexico (2004-2005, 2011), Oklahoma (2004-2011), Oregon (2004-2011), Utah (2004-2011), and Washington (2004-2011).[1] Some states, such as Arizona, Montana, North Dakota, and South Dakota, also have high percentages of births to AI/AN women but either do not participate in PRAMS or did not participate during the phases included. A more detailed explanation of the PRAMS methodology can be found elsewhere.[60]

Only AI/AN women were included, defined by women identifying as being single race American Indian or Alaskan Native, or women who reported being mixed race with any indication of being partially AI/AN. Only women who delivered a live singleton birth (n=12,420) were included. Women under 20 years old (n=2,055) were also excluded from the analysis since teenagers have separate BMI classification schemes.[61] The final analytic sample consisted of 10,363 woman-infant pairs.

Consistent with other studies, macrosomia was defined from the birth certificate as birth weight greater than or equal to 4,000 grams.[16,17] The two main exposures for this analysis were prepregnancy BMI and GWG. The World Health Organization established a universal equation and classification scheme for BMI calculated as weight in kilograms

divided by the square of height in meters (kg/m^2). Prepregnancy BMI was calculated from the mothers' self report of weight and height from the PRAMS questionnaire and was classified into four main categories: underweight (<18.5), normal range (18.50–24.99), overweight (25.00–29.99), and obese (≥30.00).[8] BMI's less than 13 kg/m^2 or greater than 70 kg/m^2 were considered implausible and were excluded from the analysis.

Based on BMI, the IOM established guidelines in 2009 for recommended GWG to minimize maternal and perinatal risks. For underweight women the IOM recommends GWG of 28-40lbs.; for normal weight women, 25-35 lbs.; for overweight women, 15-25 lbs.; and for obese women, 11-20 lbs.[9] GWG was extracted from the birth certificate and was classified by two methods. First, GWG was categorized as inadequate, appropriate, or excess based on the 2009 IOM guidelines. Second, a continuous variable for GWG was created that counted the number of pounds the women fluctuated above or below their recommended appropriate GWG. Women within the appropriate GWG recommended range for their BMI were coded as having zero pounds over appropriate weight gain.

Possible covariate information about each mother-infant pair was taken from the infant's birth certificate or the mothers' self report on the PRAMS questionnaire. A positive diabetes status was defined as any report of diabetes, either gestational or prepregnancy diabetes, listed on the birth certificate or PRAMS questionnaire. Women were classified as smokers during pregnancy if they reported smoking during the last three months of their pregnancy.

Descriptive statistics were completed on the total analytic sample. Univariate analysis was conducted to determine the prevalence estimates with 95% confidence

intervals (CI) and chi squares tests for macrosomia stratified by select demographic and pregnancy characteristics.

A pairwise comparison of the means for BMI between women who delivered a macrosomic and non-macrosomic infant was calculated. The mean number of pounds gained from the appropriate range was also calculated for each BMI category stratified by macrosomia. Pairwise comparisons were calculated between mean number of pounds gained for each BMI category for macrosomic deliveries and non-macrosomic deliveries. All pairwise comparisons for GWG used Bonferroni's method to determine the statistically significant alpha value of $p=0.006$.

Potential confounders considered for the multivariable logistic regression were chosen from the crude associations and potential causal variables from the literature. Reference groups were chosen either by standard of practice (i.e. normal for BMI, or appropriate for GWG), or, in the case where there was no standard reference group, by the level of the categorical variable that had the lowest prevalence of macrosomia (i.e. female for infant gender). American Indian and Alaskan Native populations have well established differential health indicators and should be treated as separate ethnicities; therefore, mixed race individuals were chosen as the referent category.

A multivariable logistic regression model was built to quantify the association between macrosomia and the two main exposures adjusted for all possible confounders. An interaction term for BMI and GWG was included to assess the joint effects of the two main exposures. The criteria for confounding included any set of variables that changed the adjusted estimated beta estimates of the main exposures more than 10%. The final regression model chosen included no interaction terms and the following variables:

maternal age, parity, diabetes, smoking during pregnancy, reported nausea, gestational age, and infant sex. The reported adjusted Odds Ratios (aOR) examined the association between macrosomia and prepregnancy BMI and GWG using normal weight/appropriate GWG as the reference group.

The secondary aim of the study was addressed by conducting descriptive statistics and regression analysis stratifying by state of residence. Regression models to look at state effects included the same covariates as above.

Statistical significance was defined as p-values ≤ 0.05. All analyses were performed using SAS 9.3 and SUDAAN Version 11 to accommodate the complex survey design of the PRAMS (Cary, NC, USA).

Results:

The total PRAMS sample contained 95,428 women across the eight states. Approximately 13.38% of the sample (n=12,766) identified as AI/AN or mixed race with AI/AN. Approximately 346 AI/AN women had multiple births and were excluded, along with 2,057 women who either had no information on maternal age or were under 20 years old. The final analytic sample included 10,363 women-infant pairs, which comprised 81.18% of all AI/AN women in the sample. Women with missing data on covariates were excluded in the multivariable analysis leaving 8,871 women in the regression analysis.

The average time after delivery that women completed the survey was 122 days, or approximately four months after delivery. Among the total sample, the majority of women were American Indians at 68.01%, with Alaskan Natives comprising 15.34% and mixed race with AI/AN at 16.65% (Table 1). Most of the sample of AI/AN women came from Oklahoma (38.85%), followed by Washington (16.31%) and Alaska (15.59%). All

other states represented less than 10% of the sample. The total sample consisted of mostly normal weight women by BMI (39.83%), followed by approximately equal proportions of overweight and obese women (27.55% and 29.64%, respectively). The average BMI for the sample was in the overweight range at 27.49 kg/m^2. Interestingly, almost half the sample gained an excessive amount of weight during pregnancy (48.33%). Diabetes was also more prevalent in this AI/AN sample at 13.80% compared to the nation's average of 5.5% as of 2011.[50]

Overall, Alaskan Natives had a statistically higher prevalence of macrosomia at 18.90% compared to American Indians at 10.96% and mixed race individuals with any indication of AI/AN at 12.95% (Table1). Prepregnancy BMI showed significantly different prevalence of macrosomia ($p<0.001$) with obese women having the highest prevalence at 16.67%, followed by overweight women at 12.97%, normal weight women at 9.24%, and underweight women at 4.31% (Table 1). In addition, each of the GWG categories also showed statistically different prevalence ($p<0.001$) for macrosomia. Excess weight gain had the highest prevalence of macrosomia with 16.32%, and inadequate and appropriate GWG were similar with 8.48% and 8.45% respectively. The prevalence of macrosomia by state of residence was also significantly different ($p<0.001$) ranging from 8.00% in Utah to 18.83% in Alaska (Table 1).

The highest prevalence of macrosomia was found in women who were ≥30 years old (14.70%), had 12 years of education (13.00%), were married (13.06%), and were living above 138% of the federal poverty line (12.82%) (Table 1). The pregnancy characteristics with the highest prevalence of macrosomia were: multiparous (13.46%), intended pregnancy (13.62%), entry into prenatal care during the first trimester (12.82%),

diabetic pregnancy (17.93%), no report of hypertension (12.64%), non-smoking in pregnancy (13.54%), no report of nausea (13.37%), post-term delivery (18.36%), and male infant (14.98%). Among these characteristics, the categories with statistically significant differences in occurrence of macrosomia were: parity ($p=0.002$), entry into prenatal care ($p=0.003$), diabetes ($p<0.001$), smoking status ($p<0.001$), reported nausea (0.011), gestational age ($p<0.001$), and infant sex ($p<0.001$).

The average BMI among all AI/AN women who delivered a macrosomic infant was significantly higher at 29.26 kg/m^2 (Standard Deviation (std): 0.24, range: 15.18-62.14) compared to an average of 27.24 kg/m^2 (std: 0.15, range: 13.64-69.97) for women delivering non-macrosomic infants ($p<0.001$). There was no significant difference in number of pounds of inadequate weight gain below appropriate between women delivering a macrosomic and non-macrosomic infant (Table 2A). However, women delivering macrosomic and non-macrosomic infants who gained excess amounts of weight gained on average 17.25 pounds more (std: 0.55) and 13.45 pounds more (std: 0.43), respectively, than women in the appropriate weight gain range (Table 2B). Overall, normal weight, overweight, and obese women who delivered a macrosomic infant gained significantly more weight than their non-macrosomic delivery counterparts (Table 2B).

Among the 8,871 women included in the regression, there were 1,514 cases of macrosomia. The final regression model resulted in significant independent effects of both prepregnancy obesity and excess GWG for macrosomia. The interaction between prepregnancy BMI and GWG was non-significant. After controlling for GWG, prepregnancy obesity significantly increased the odds of macrosomia by 63% compared to the odds of macrosomia in normal weight women at conception (aOR: 1.63; 95% CI:

1.29-2.07) (Table 3). Prepregnancy overweight did not independently increase the odds of macrosomia compared to normal weight women at conception (aOR: 1.26; 95% CI: 1.00-1.58). Controlling for prepregnancy BMI, excess GWG did increase the odds of macrosomia compared to appropriate GWG. For every five additional pounds gained over the recommended range for each BMI, the risk for macrosomia increased 16% (aOR: 1.16; 95% CI: 1.12-1.20). This will compound, increasing the odds of macrosomia as the mother gains more weight over the recommended range.

Compared to normal weight women who gained an appropriate amount of weight during pregnancy, the odds of macrosomia increased 90% for obese women for every additional five lbs. gained over the appropriate GWG range (aOR: 1.90; 95% CI: 1.58-2.28) (Table 3). Even women who had inadequate weight gain and were obese had elevated odds of macrosomia (aOR: 1.40; 95% CI: 1.17-1.69). Overweight women only had significantly increased odds of macrosomia when they gained excess amount of weight during pregnancy (aOR: 1.46; 95% CI: 1.20-1.78 for every five lbs. gained over appropriate GWG). Normal weight women had 16% increased odds of macrosomia for every five lbs. over recommended GWG (aOR: 1.16; 95% CI: 1.12-1.20). Inadequate weight gain proved to be statistically protective against macrosomia for underweight and normal weight women (aOR: 0.49; 95% CI: 0.24-0.99 and aOR: 0.86; 95% CI: 0.83-0.89, respectively). Staying within the appropriate weight gain recommendations did not change the odds for macrosomia significantly for any BMI category except obese women as mentioned earlier.

Some state patterns emerged. Alaska, Oregon, and Oklahoma showed significantly increased odds of macrosomia among obese women compared to normal

weight women (Table 4). Only Alaska showed a significant increase in odds of macrosomia among overweight women compared to normal weight women. On the other hand, every five pounds additionally gained beyond appropriate GWG was statistically associated with increased odds of macrosomia in all states except New Mexico and Utah, both of which had a low number of cases of macrosomia (Table 4). Notably, the point estimates for the effect of every five lbs. gained over appropriate were remarkably similar (1.11-1.16) with the exception of Oklahoma (1.22). Utah was missing a disproportionate amount of data compared to other states and therefore the aOR's for the BMI categories are uninformative.

Comments:

Overall, Alaskan Natives had a statistically higher prevalence of macrosomia compared to American Indians and mixed race AI/ANs. The AI/AN population in the United States is known for having higher rates of obesity and diabetes than other races, which held true in this sample.[50]

This analysis showed that both prepregnancy BMI and GWG have independent effects on the odds of macrosomia among adult AI/AN women who have delivered a singleton birth when adjusted for other possible risk factors (AI/AN mixed or single race, maternal age, parity, diabetes, smoking during pregnancy, reported nausea, gestational age, and infant sex). The interaction between prepregnancy BMI and GWG was not significant. In this sample, the average BMI for women who delivered a macrosomic infant was borderline obese at 29.26 kg/m^2, which was significantly higher than for women who did not deliver a macrosomic infant, classified as overweight at 27.24 kg/m^2. In addition, women who delivered a macrosomic infant gained significantly more weight

beyond the recommended range during pregnancy than women who did not deliver a macrosomic infant among normal weight, overweight and obese women.

These results confirm other findings establishing prepregnancy obesity as a risk factor for macrosomia.[16,17] Among adult AI/AN women prepregnancy obesity was significantly associated with macrosomia with 63% increased odds compared to normal weight women at conception. Contrary to some other research, overweight at conception was not significantly associated with increased odds of macrosomia among adult AI/AN women in this sample after controlling for other factors such as diabetes and GWG.[17] One possible explanation for this is that in overweight AI/AN women, the effect of excess GWG is a more dominant risk factor for macrosomia.

Excess GWG is also a well established risk factor for increased fetal growth independent of both diabetes and prepregnancy BMI.[16] This analysis extended prior findings examining the association of GWG with macrosomia for every additional pound gained beyond the recommended amount during pregnancy. For every five pounds a woman gained beyond the appropriate GWG recommendations, her odds of macrosomia increased 16%. The effects of excess GWG will compound and increase as a woman gains weight beyond the recommended guidelines. The average number of pounds gained beyond the appropriate weight range among women who had a macrosomic infant was 17.25 lbs. in this sample. With these findings, a woman matching this average excess GWG increased her odds of a macrosomic infant by 68% compared to if she had gained an appropriate amount of weight during her pregnancy (aOR: 1.68; 95% CI: 1.49-1.89).

Increased prepregnancy BMI and excess GWG are important independent risk factors for fetal macrosomia, which should be clinically addressed to help reduce the risk

of adverse pregnancy outcomes among AI/AN women. Although both exposures are modifiable, the timing of interventions to address prepregnancy BMI and GWG will differ. The healthcare provider who will deliver care will also differ between BMI and GWG. A survey in 2004 found that only one in six obstetricians/gynecologists or family physicians provided both preconception care and prenatal care to the majority of the woman they serve.[65] Many of the risk factors that can cause adverse pregnancy outcomes occur early in gestation, possibly even before the woman knows she is pregnant. Many providers who deliver preconception care, such as primary care physicians, do not focus on pregnancy in particular. However, these providers will be treating women during their preconception period and will need to incorporate regulation of pregnancy-related risk factors into their practice, including weight regulation to control BMI. On the other hand, obstetricians/gynecologists who provide prenatal care would be responsible for counseling and monitoring behaviors to regulate GWG, especially among diabetic pregnancies where glucose control is important.

BMI needs to be addressed before conception to help women enter pregnancy within the normal weight range. Interventions to address prepregnancy obesity during preconception care often involve lifestyle behavioral changes and include combinations of calorie restriction, physical activity, behavioral strategies, and frequent monitoring of weight.[66] Ideally obesity addressed during childhood or adolescences could help reduce the body weight of women to help them enter pregnancy within the normal weight range. Interventions that address multiple pregnancy-related risk factors, such as obesity, smoking, and alcohol misuse, have not been systemically evaluated and are seen less often in clinical practice.[65] Preconception monitoring of body weight is especially

important since entering pregnancy at higher BMI's is also associated with other problems such as increased risk of prematurity, stillbirth, congenital anomalies, and childhood obesity.[67]

Pregnancy can also act as a catalyst for women to enter clinical care and/or possibly switch providers. After conception, GWG becomes more clinically relevant, but clinical approaches to address GWG are similar to those that address obesity in general. Interventions that have shown to be successful in GWG management closely resemble lifestyle programs used for weight management in non-pregnant women, including calorie goals, structured meal plans, frequent weight measurement, behavioral strategies, and ongoing contact with healthcare providers.[66] It is essential that women be counseled on dietary information and healthy eating habits during pregnancy to provide adequate nutrition to the growing fetus while preventing excess GWG. Discussions during the early stages of prenatal care between providers and patients about the appropriate weight gain recommendations should be accompanied by regular weigh-ins and constant monitoring and tracking of GWG throughout pregnancy.[67]

Currently, the ACOG committee opinion states that nutrition consultations should be offered to all overweight or obese women, without mentioning normal weight women.[67] However, this study showed significantly increased odds of macrosomia among normal weight AI/AN women who had excess GWG. Therefore, normal weight AI/AN women need to be included in the recommended nutritional and dietary consultation target population, especially since they accounted for 40% of the entire population. This is consistent with findings recommending that prevention methods for GWG should target women of all BMI categories for Whites, Blacks, Hispanics, and

Asian/Pacific Islanders.[16,19] Although inadequate weight gain showed a significant protective effect for macrosomia, inadequate weight gain has been linked to other adverse pregnancy outcomes such as low birth weight, preterm deliveries, and neonatal intensive care unit admission, and therefore should not be advised.[68]

Notably, among the sample of AI/AN women, obesity represented only about 30% of women whereas excess GWG was seen in almost 50% of women. On a population level, all women need information about macrosomia associated with excess GWG. Every pound above the appropriate weight gain recommended increased the odds of macrosomia in this study. Therefore, weight management counseling should first encourage women to gain within the appropriate range. However, if women are already beyond the normal range, counseling should encourage them to minimize any additional gain to minimalize the risk of macrosomia. Decreasing a woman's risk of delivering a macrosomic infant will also decrease the risk of obstetric complications for both her and her infant.

Among this population, there is the potential for a circular pattern with conditions such as prepregnancy obesity and gestational weight gain that are reinforced from generation to generation.[17,39,43] Although current clinical guidelines suggest when to target women for lifestyle behavioral interventions, in reality such interventions will actually be implemented during the woman's everyday life. Therefore, more research needs to be conducted to adapt and develop interventions that address AI/AN's current attitudes, geographical differences, and socio-economic environment. Potential issues that will need to be addressed for this unique high-risk population include matching literacy levels, improving resources available, incorporating tribal cultural practices,

involving the greater community, and increasing healthcare utilization practices.[44-46] All these aspects need to be in the context of the state in which the women resides. It has been shown that there are severe regional and state level disparities in prenatal care utilization among the AI/AN population.[57] Tackling these clinical and cultural issues to help reduce maternal and infant morbidity will be challenging and requires more research.

This study was able to capture a large sample of AI/AN women using a validated questionnaire to obtain exposure data along with data on many clinical variables. The variety of information the PRAMS questionnaires collect allows data to be captured on many other pregnancy-related behaviors and attitudes that cannot be extracted solely from birth certificates. For example, in this study reported nausea during pregnancy was found to be an important confounder for GWG. In addition, the study was able to include AI/AN women who reside in many different geographic regions across the United States. The PRAMS's sampling methodology allows estimates to represent the entire state and also allows inter-state comparisons.

Although this study had important and clinically relevant findings for AI/AN women, it is not without limitations. Not all the states that have large AI/AN populations, like Arizona and the Dakotas, participate in PRAMS, and PRAMS is only generalizable to the states included in the analysis. In addition, PRAMS only samples women who have had a live birth, so the findings cannot be applied to pregnancies that result in miscarriages or stillbirths.

There are also some limitations surrounding quality of information on variables such as misclassification of prepregnancy BMI and GWG due to post hoc assessment of

prepregnancy weight reported by mothers at the time of the questionnaire. Women may underestimate reported prepregnancy weight, whereas weight at birth is objectively measured. Therefore, pregnancy BMI may be underestimated, and GWG may be slightly overestimated. The largest limitation to this study is the inability to control for history of previous macrosomia, a well-known risk factor for macrosomia reflecting both environmental and genetic factors, since no question on PRAMS captures this information.[3]

Overall, prepregnancy obesity and excess GWG should be considered independent risk factors for delivery of a macrosomic infant among adult AI/AN women. The interventions to address these risk factors need to occur at different times during the reproductive years. Prepregnancy BMI needs to be addressed well before conception so women can enter the pregnancy at a normal weight. Weight management interventions to prevent excess GWG need to begin early in prenatal care and be continued throughout the entire course of pregnancy. It is important that among the AI/AN population excess GWG be considered an independent risk factor for macrosomia among both non-obese and obese women. Weight management programs both before and during pregnancy can help reduce the risks for many adverse outcomes and improve the health of both the mothers and their infants.

Table 1: Population and prevalence of macrosomia by demographic and pregnancy characteristics among American Indian/Alaskan Native women

	Total Sample		Prevalence of Macrosomia		
	unweighted n=10,363		Birth weight ≥4,000 grams		
	n[a]	%† (95% CI)[b]	n[a]	%† (95% CI)[c]	p-value[d]
Total Sample			1,736	12.51† (11.66-13.41)	-
DEMOGRAPHIC FACTORS					
AI/AN	10,363		1,736		<0.001[e]
American Indian		68.01† (66.29-69.67)		10.96† (10.12-11.87)	
Alaskan Native		15.34† (14.74-15.95)		18.90† (17.51-20.38)	
Mixed-AI/AN with other		16.65† (15.03-18.42)		12.95† (9.85-16.83)	
State of Residence	10,363				<0.001[e]
Alaska		15.59† (14.98-16.22)		18.83† (17.43-20.31)	
Minnesota		7.47† (6.74-8.27)		13.88† (10.72-17.78)	
Nebraska		3.58† (3.39-3.79)		13.66† (11.35-16.35)	
New Mexico		7.12† (6.55-7.73)		9.92† (7.38-13.20)	
Oklahoma		38.85† (36.79-40.95)		9.27† (8.29-10.35)	
Oregon		7.22† (6.88-7.57)		13.38† (11.95-14.96)	
Utah		3.86† (3.20-4.65)		8.00† (4.44-14.01)	
Washington		16.31† (14.99-17.72)		15.13† (11.98-18.94)	
Maternal Age (years)	10,363		1,736		0.409
20-24		41.57† (39.62-43.56)		11.63† (10.32-13.09)	
25-29		32.35† (30.51-34.24)		11.87† (10.55-13.32)	
30-34		18.07† (16.62-19.61)		14.70† (12.40-17.35)	
≥35		8.01† (7.11-9.02)		14.70† (12.23-17.58)	
Education (years)	10,234		1,713		0.212
>12		18.46† (17.04-19.97)		11.02† (9.42-12.86)	
12		42.95† (40.97-44.95)		13.00† (11.70-14.42)	
<12		38.59† (36.67-40.55)		12.54† (11.10-14.14)	
Marital Status	10,353		1,734		0.286
Married		44.24† (42.27-46.22)		13.06† (11.71-14.55)	
Not Married		55.76† (53.78-57.73)		12.07† (11.01-13.23)	

Table 1: Continued

	Total Sample		Prevalence of Macrosomia		
	unweighted n=10,363		Birthweight ≥4,000 grams		
	n[a]	% (95% CI)[b]	n[a]	% (95% CI)[c]	p-value[d]
Federal Poverty Level[f]	9,592		1,616		0.552
≤138% FPL		68.47 (66.54-70.34)		12.24 (11.15-13.44)	
>138% FPL		31.53 (29.66-33.46)		12.82 (11.38-14.42)	
PREGNANCY CHARACTERISTICS					
Prepregnancy BMI (kg/m²)	9,921		1,661		<0.001[e]
<18.5 Underweight		2.98 (2.31-3.85)		4.31 (2.62-7.01)	
18.5-24.9 Normal		39.83 (37.83-41.87)		9.24 (7.90-10.78)	
25.0-29.9 Overweight		27.55 (25.80-29.37)		12.97 (11.51-14.59)	
≥30.0 Obese		29.64 (27.86-31.48)		16.67 (15.00-18.48)	
Weight Gain During Pregnancy[g]	9,242		1,562		<0.001[e]
Inadequate		22.17 (20.45-23.98)		8.48 (7.01-10.23)	
Appropriate		29.50 (27.59-31.49)		8.45 (7.15-9.96)	
Excess		48.33 (46.22-50.45)		16.32 (14.92-17.83)	
Parity	10,314		1,731		0.002[e]
First Birth		30.19 (28.36-32.09)		10.38 (8.92-12.04)	
Second or Later Birth		69.81 (67.91-71.64)		13.46 (12.42-14.57)	
Pregnancy Intention	10,321		1,730		0.061
Intended		38.57 (36.67-40.52)		13.62 (12.19-15.19)	
Unintended		61.43 (59.48-63.33)		11.85 (10.80-12.98)	
Entry into Prenatal Care	9,963		1,679		0.003[e]
1st Trimester		81.88 (80.29-83.37)		12.82 (11.84-13.86)	
2nd Trimester		15.02 (13.65-16.50)		11.99 (9.93-14.41)	
3rd Trimester or no PNC		3.10 (2.47-3.87)		6.38 (4.15-9.70)	
Any Reported Diabetes[h]	10,361		1,736		<0.001[e]
Yes		13.80 (12.52-15.18)		17.93 (15.59-20.53)	
No		86.20 (84.82-87.48)		11.64 (10.73-12.62)	
Hypertension	10,240		1,720		0.757
Yes		8.36 (7.37-9.48)		12.07 (9.02-15.98)	
No		91.64 (90.52-92.63)		12.64 (11.75-13.58)	

Table 1: Continued

	Total Sample		Prevalence of Macrosomia		
	unweighted n=10,363		Birth weight ≥4,000 grams		
	n[a]	% (95% CI)[b]	n[a]	% (95% CI)[c]	p-value[d]
Smoking During Pregnancy[i]	10,138		1,702		<0.001[e]
Yes		22.82 (21.18-24.54)		9.00 (7.44-10.85)	
No		77.18 (75.46-78.82)		13.54 (12.53-14.61)	
Reported Nausea	10,239		1,718		0.011[e]
Yes		34.04 (32.14-35.99)		10.89 (9.45-12.51)	
No		65.96 (64.01-67.86)		13.37 (12.31-14.49)	
Gestational Age[j]	10,255		1,724		<0.001[e]
Preterm		9.18 (8.29-10.16)		2.39 (1.64-3.48)	
Term		90.46 (89.48-91.36)		13.52 (12.58-14.52)	
Post-term		0.36 (0.29-0.44)		18.36 (11.27-28046)	
Infant Gender	10,362		1,736		<0.001[e]
Male		49.02 (47.04-51.00)		14.98 (13.67-16.39)	
Female		50.98 (49.00-52.96)		10.13 (9.06-11.32)	

Stratified sample sizes may not match total due to missing information

[a] unweighted n

[b] Prevalence (95% CI: Confidence Interval)

[c] Prevalence of macrosomia seen within each stratum (95% CI: Confidence Interval)

[d] χ^2 p-value

[e] Statistically significant, P 0.05

[f] Federal Poverty Level determined by maternal self report of income and number of dependents from the year previous to infant's birth

[g] Weight gain categories determined by 2009 IOM guidelines by each BMI category

[h] Any diabetes includes diagnosis of either prepregnancy diabetes or gestational diabetes

[i] Maternal self-report of any smoking during the last trimester

[j] Preterm: < 37 weeks, Term: 37-42 weeks, Post-term: > 42 weeks gestation

Table 2A: Average weight gained by prepregnancy body mass index category among American Indian/ Alaskan Native women who gained an inadequate amount of weight[a]

	Macrosomia	No Macrosomia	
	mean[b] (std)[c]	mean[b] (std)[c]	p-value[d]
Prepregnancy BMI (kg/m^2)			
Total	-7.27 (0.51)	-8.02 (0.33)	0.221
<18.5 Underweight	-7.14 (3.59)	-11.03 (2.34)	0.363
18.5-24.9 Normal	-9.24 (0.71)	-8.68 (0.47)	0.506
25.0-29.9 Overweight	-6.93 (0.70)	-7.45 (0.50)	0.545
≥30.0 Obese	-6.02 (0.74)	-6.17 (0.40)	0.852

Table 2B: Average weight gained by prepregnancy body mass index category among American Indian/ Alaskan Native women who gained an excess amount of weight[a]

	Macrosomia	No Macrosomia	
	mean[b] (std)[c]	mean[b] (std)[c]	p-value[d]
Prepregnancy BMI (kg/m^2)			
Total	17.25 (0.55)	13.45 (0.43)	<0.001[e]
<18.5 Underweight	9.60 (1.56)	15.94 (6.13)	0.316
18.5-24.9 Normal	14.85 (0.99)	11.19 (0.56)	0.001[e]
25.0-29.9 Overweight	18.84 (0.99)	14.69 (0.93)	0.002[e]
≥30.0 Obese	17.62 (0.83)	14.24 (0.59)	0.001[e]

[a] Categorization of gestational weight gain according to the IOM 2009 guidelines

[b] Mean (lbs.), continuous variable representing the number of pounds gained from the appropriate range of weight gain recommended for each BMI category recommended by the IOM 2009 guidelines

[c] Standard deviation of mean

[d] Chi-square p-values for mean pairwise comparisons of average number of pounds gained outside of the recommended amount stratified by BMI between macrosomic and non-macrosomic infants

[e] Bonferonii adjusted statistically significant, alpha = 0.006

Table 3: Adjusted odds ratios of prepregnancy body mass index and gestational weight gain for macrosomia among American Indian/Alaskan Native women

	Gestational Weight Gain		
	Every 5 lbs. Under Appropriate[a]	Appropriate	Every 5 lbs. Over Appropriate[a]
	aOR (95% CI)[b]	aOR (95% CI)[b]	aOR (95% CI)[b]
Prepregnancy BMI (kg/m^2)			
<18.5 Underweight	0.49 (0.24-0.99)[c]	0.57 (0.28-1.15)	0.66 (0.33-1.34)
18.5-24.9 Normal	0.86 (0.83-0.89)[c]	1.00	1.16 (1.12-1.20)[c]
25.0-29.9 Overweight	1.08 (0.89-1.32)	1.26 (1.00-1.58)	1.46 (1.20-1.78)[c]
≥30.0 Obese	1.40 (1.17-1.69)[c]	1.63 (1.29-2.07)[c]	1.90 (1.58-2.28)[c]

8,871 women were included in analysis due to missing information on covariates

[a] Gestational weight gain above and below the recommended appropriate range by 5 lb. intervals

[b] Adjusted Odds Ratios (95% CI: Confidence Intervals) determined by multivariable logistic regression, controlled for: AI/AN race, maternal age, parity, any diabetes, smoking during pregnancy, reported nausea, gestational age of infant, and infant sex

[c] Statistically significant aOR, alpha=0.05

Table 4: Adjusted odds ratios for independent effects of prepregnancy body mass index and gestational weight gain on macrosomia among American Indian/Alaskan Native women by state of residence

	Alaska	Minnesota	Nebraska	New Mexico
	aOR (95%CI)[a]	aOR (95%CI)[a]	aOR (95%CI)[a]	aOR (95%CI)[a]
Cases of Macrosomia	392	124	112	36
Prepregnancy BMI (kg/m^2)				
<18.5 Underweight vs. 18.5-24.9 Normal	0.59 (0.16-2.21)	0.98 (0.22-4.41)	0.49 (0.15-1.60)	-[b]
25.0-29.9 Overweight vs. 18.5-24.9 Normal	1.45 (1.09-1.92)[c]	1.31 (0.67-2.56)	1.25 (0.66-2.37)	1.55 (0.60-4.02)
≥30.0 Obese vs. 18.5-24.9 Normal	1.92 (1.44-2.55)[c]	1.63 (0.63-4.24)	1.63 (0.99-2.68)	1.82 (0.63-5.25)
Gestational Weight Gain[d]				
Every 5 lbs. under appropriate	0.86 (0.82-0.90)[c]	0.86 (0.79-0.94)[c]	0.86 (0.79-0.94)[c]	0.86 (0.74-1.00)
Every 5 lbs. gained over appropriate	1.16 (1.11-1.22)[c]	1.16 (1.06-1.27)[c]	1.16 (1.07-1.26)[c]	1.16 (1.00-1.35)

	Oklahoma	Oregon	Utah	Washington
	aOR (95%CI)[a]	aOR (95%CI)[a]	aOR (95%CI)[a]	aOR (95%CI)[a]
Cases of Macrosomia	429	243	10	168
Prepregnancy BMI (kg/m^2)				
<18.5 Underweight vs. 18.5-24.9 Normal	0.92 (0.38-2.25)	1.08 (0.45-2.60)	-[b]	0.24 (0.03-2.21)
25.0-29.9 Overweight vs. 18.5-24.9 Normal	1.07 (0.72-1.60)	1.35 (0.92-1.99)	8.08 (0.48-134.88)	1.08 (0.57-2.05)
≥30.0 Obese vs. 18.5-24.9 Normal	1.60 (1.09-2.35)[c]	1.95 (1.39-2.74)[c]	4.81 (0.65-35.58)	1.22 (0.68-2.20)
Gestational Weight Gain[d]				
Every 5 lbs. under appropriate	0.82 (0.77-0.88)[c]	0.90 (0.86-0.95)[c]	0.86 (0.71-1.05)	0.90 (0.84-0.97)[c]
Every 5 lbs. gained over appropriate	1.22 (1.14-1.41)[c]	1.11 (1.06-1.16)[c]	1.16 (0.96-1.41)	1.11 (1.03-1.19)[c]

[a] Adjusted Odds Ratios (95% CI: Confidence Intervals) determined by multivariable logistic regression, controlled for: AI/AN race, maternal age, parity, any diabetes, smoking during pregnancy, reported nausea, gestational age of infant, and infant sex

[b] No cases of macrosomia within stratum

[c] Statistically significant aOR, alpha=0.05

[d] Gestational weight gain above and below appropriate weight gain recommended by 5 lb. intervals

Chapter 4: Extended Analysis

The entire sample from the PRAMS across all races and states included 95,428 women. There were 1,003 women who had no information on race, comprising 1.05% of the total sample. Approximately 13.38% of the sample (n=12,766) identified as AI/AN or mixed race with AI/AN. Approximately 2.70% of AI/AN women had multiple births and were therefore were excluded from the analysis, along with one woman with no information on plurality (n=346). In addition, 2,057 women were excluded who either had no information on maternal age or were under 20 years old. The final analytic sample included 10,363 women-infant pairs, which comprised 10.86% of the original sample and 81.18% of all AI/AN women. Women with missing data on covariates were excluded in the multivariable analysis leaving 8,871 women in the regression analysis. The sub-analysis of only non-diabetic AI/AN included 8,931 women-infant pairs, which represents 86.18% of the analytic sample and 69.95% of all AI/AN women. Again, missing data in covariates left 7,662 women in the regression analysis. A flowchart of inclusion/exclusion criteria can be found in Figure 1.

The average time after delivery that women completed the survey was 122 days (std: 0.78) or approximately four months after delivery. Among the total sample, the majority of women were American Indians at 68.01%, with Alaskan Natives comprising 15.34% and mixed race with AI/AN at 16.65% (Table 2). The total sample consisted of mostly normal weight women by BMI (39.83%), followed by approximately equal proportions of overweight and obese women (27.55% and 29.64%, respectively). The distribution of BMI across the sample can be seen in Figure 2. The overall average BMI for the sample was overweight at 27.49 kg/m^2. Interestingly, almost half the sample

gained an excessive amount of weight during pregnancy (48.33%). Diabetes was also more prevalent in this AI/AN sample at 13.80% compared to the nation's average of 5.5% as most recently published in the National Vital Statistics Report in 2011. Infants were about evenly split between male and female (49.02% and 50.98% respectively).

Among various definitions of macrosomia, macrosomia by LGA (90^{th} percentile) was the most common, with a prevalence of 13.55% (95% CI: 12.49-14.68) among all births in the sample. Macrosomia defined as birth weight ≥4,000 grams was second most prevalent at 12.51% (95% CI: 11.66-13.41), and, lastly, macrosomia defined as birth weight ≥4,500 grams showed a prevalence of 2.26% (95% CI: 1.99-2.57) (Table 3). The distribution of birth weight for the entire sample can be seen in Figure 3.

The prevalence of each type of macrosomia by demographic and pregnancy characteristics can be found in Table 3. The prevalence of macrosomia by all three definitions varied between American Indians, Alaskan Natives, and mixed race individuals, and this difference was statistically significantly ($p<0.001$). Alaskan Natives showed the highest prevalence of macrosomia, defined as birth weight ≥4,000 grams, at 18.90% (95% CI: 17.51-20.38), followed by mixed race individuals at 12.95% (95% CI: 9.85-16.83), and American Indians at 10.96% (95% CI: 10.12-11.87) (Table 3 and Figure 3).

Prepregnancy BMI showed significantly different prevalence of macrosomia ($p<0.001$) with obese women having the highest prevalence at 16.67% (95% CI: 15.00-18.48) followed by overweight women at 12.97% (95% CI: 11.51-14.59), normal weight women at 9.24% (95% CI: 7.90-10.78), and underweight women at 4.31% (95% CI: 2.62-7.01). Figure 4 shows the proportion of each BMI category in the sample stratified

by macrosomia. Approximately 4% of the analytic sample had missing data on BMI. In addition, each of the GWG categories also showed statistically different prevalence ($p<0.001$) for macrosomia. Excess weight gain had the highest prevalence of macrosomia with 16.32% (95% CI: 14.92-17.83), and inadequate and appropriate GWG were similar with 8.48% (95% CI: 7.01-10.23) and 8.45% (95% CI: 7.15-9.96) respectively. Figure 5 displays the proportion of the weight gain categories in the sample stratified by presence of fetal macrosomia. Approximately 11% of the analytic sample was missing data on GWG, which included every person with missing BMI information.

The highest prevalence of macrosomia was found in women who were ≥30 years old (14.70%), had 12 years of education (13.00%), were married (13.06%), and were living above 138% of the federal poverty line (12.82%) (Table 3). The pregnancy characteristics with the highest prevalence of macrosomia were: multiparous (13.46%), intended pregnancy (13.62%), entry into prenatal care during the first trimester (12.82%), diabetic pregnancy (17.93%), no report of hypertension (12.64%), non-smoking pregnancy (13.54%), no report of nausea (13.37%), post-term delivery (18.36%), and male infant (14.98%). Among these characteristics, the categories with statistically significant differences in occurrence of macrosomia were: parity ($p=0.002$), entry into prenatal care ($p=0.003$), diabetes ($p<0.001$), smoking status ($p<0.001$), reported nausea (0.011), gestational age ($p<0.001$), and infant sex ($p<0.001$).

Interestingly, the prevalence of macrosomia was not significantly different by maternal age for either birth weight definitions but was for LGA infants. Statistical significance was also different for entry into prenatal care, with birth weight ≥4,000 grams and LGA both showing significance and birth weight ≥4,500 grams not showing

statistical significance. In addition, reported nausea only showed statistically significant differences in prevalence among macrosomic infants by birth weight and not LGA. Lastly, gestational age was statistically different for macrosomia by birth weight, as expected, with preterm births showing much lower macrosomia than term or post-term births.

Summary statistics for both exposures were conducted as continuous variables, which can be seen in Table 4. The average BMI among all AI/AN women who delivered a macrosomic infant was significantly higher 29.26 kg/m^2 (std: 0.24, range: 15.18-62.14) compared to an average of 27.24 kg/m^2 (std: 0.15, range: 13.64-69.97) for women delivering non-macrosomic infants ($p<0.001$) (Table 4). The average number of pounds gained overall during the pregnancy among all AI/AN women who delivered a macrosomic infant was 33.58 lbs. (std: 0.59) compared to 28.82 lbs. (std: 0.37) for women delivering non-macrosomic infants. The differences between the mean BMI's and mean number of pounds gained overall among these women were both statistically significant (both $p<0.001$).

The average BMI was also calculated for each weight gain category stratified by macrosomia. The mean and standard deviations for all stratums can be seen in Table 5. Two sample t-tests showed that none of the mean BMI's by weight gain category were statistically different between macrosomic and non-macrosomic infants.

For women who were classified as having inadequate or excess weight gain during pregnancy, the mean number of pounds from the appropriate range was calculated for each BMI category stratified by macrosomia. Overall, women delivering macrosomic and non-macrosomic infants who gained inadequate amounts of weight gained on

average 7.27 pounds less (std: 0.51) and 8.02 pounds less (std: 0.33), respectively, than women in the appropriate weight gain range (Table 6A). The differences in the means between women delivering macrosomic and non-macrosomic infants were not statistically significant for any of the inadequate weight gain comparisons overall and within each of the BMI categories. However, women delivering macrosomic and non-macrosomic infants who gained excess amounts of weight gained on average 17.25 pounds more (std: 0.55) and 13.45 pounds more (std: 0.43), respectively, than women in the appropriate weight gain range (Table 6B). The differences in the means between women delivering macrosomic and non-macrosomic infants were statistically significant for all BMI categories except underweight women. Overall, normal weight (14.85 versus 11.19 lbs., respectively, p=0.001), overweight (18.84 versus 14.69 lbs., respectively, p=0.002), and obese (17.62 versus14.24 lbs., respectively, p=0.001) women who delivered a macrosomic infant gained significantly more weight than their non-macrosomic delivery counterparts (Table 6B).

Crude OR's were calculated for macrosomia by all demographic and pregnancy characteristics. The crude OR's and 95% CI's along with chi-square tests for categorical variables can be found in Table 7. The odds of having a macrosomic infant among Alaskan Natives were 1.57 times greater than the odds for those of mixed race (OR:1.57; 95% CI: 1.14-2.16). This association was not significant for American Indian women compared to mixed race women (OR: 0.83; 95% CI: 0.60-1.14). The only demographic factor that showed statistically significant crude associations with macrosomia was maternal age. Both women who were 30-34 years old and who were ≥35 years old had

1.31 times the odds of macrosomia (OR: 1.31; 95% CI: 1.03-1.66 and OR: 1.31; 95% CI: 1.02-1.69 respectively) compared to women who were 20-24 years old.

The pregnancy characteristics that showed statistically significant crude associations with macrosomia include: prepregnancy BMI, continuous GWG, parity, entry into prenatal care, diabetes, smoking status, nausea, gestational age, and infant sex. Overweight women had odds 1.46 times for macrosomia that of normal weight women at conception (OR: 1.46; 95% CI: 1.18-1.82). Obese women had almost twice the odds of macrosomia compared to normal weight women at conception (OR: 1.96; 95% CI: 1.59-2.43). When weight gain was used as a continuous variable, every additional pound of weight gain above the recommended level significantly increased the odds of macrosomia (OR: 1.03; 95% CI: 1.02-1.04).

Women who were multiparous had odds 1.34 times higher for macrosomia than women who were delivering their first child (OR: 1.34; 95% CI: 1.11-1.63). Interestingly, the crude associations between entry into prenatal care and macrosomia seem to show that delayed prenatal care or no prenatal care was actually protective of macrosomia. However, this is likely due to more premature babies being delivered who never entered prenatal care at all. Diabetic women also had statistically significant higher odds of macrosomia compared to non-diabetic women, with 1.66 times the odds (OR: 1.66; 95% CI: 1.37-2.01). Women who report not smoking in their last trimester had 1.58 times higher odds of macrosomia compared to pregnant smokers (OR: 1.58; 95% CI: 1.26-1.99). Mothers who reported on the PRAMS questionnaire that they felt nauseous during their pregnancy had lower odds of macrosomia than women who were not nauseous (OR: 0.79; 95% CI: 0.66-0.95). As expected, delivering preterm lowered the odds of

macrosomia compared to women who delivered term births (OR: 0.16; 95% CI: 0.11-0.23), likely due to less time to reach higher absolute birth weights. However, there was no statistical difference between the odds of macrosomia for those women delivering term and post-term infants. Finally, the gender of the infant raised the odds of macrosomia, with male infants having 1.56 times the odds of macrosomia than female infants (OR: 1.56; 95% CI: 1.33-1.84).

Crude associations between covariates and both exposures were also calculated. Only those covariates that were significantly associated with macrosomia were assessed with the exposures. Polytamous logistic regression showed that the overall variables that had statistically significant associations with prepregnancy maternal BMI include: AI/AN race ($p<0.001$), maternal age ($p<0.001$), continuous GWG ($p<0.001$), parity ($p<0.001$), diabetes ($p<0.001$), smoking before pregnancy ($p=0.008$), and gestational age ($p<0.001$) (Table 8). The variables that were not associated with prepregnancy BMI include: entry into prenatal care ($p=0.099$), reported nausea (0.101), and infant gender ($p=0.858$) (Table 8). Of note, diabetes was associated with both overweight (OR: 1.90; 95% CI: 1.36-2.66) and obese (OR: 4.45; 95% CI: 3.29-6.01). In addition, each additional pound of weight gained beyond the appropriate range showed a significant association with BMI. Both overweight and obese women both had significant associations with excess GWG (OR: 1.04; 95% CI: 1.03-1.05 and OR: 1.04; 95% CI: 1.03-1.05, respectively) (Table 8).

Crude associations with GWG were assessed using linear regression. The continuous GWG variable was used as the outcome. Variables that were linearly associated with GWG include: prepregnancy BMI ($p<0.001$), parity ($p<0.001$), reported nausea ($p<0.001$), and gestational age ($p<0.001$) (Table 9). The covariates that were not

linearly associated with GWG include: AI/AN race (p=0.078), maternal age (p=0.202), entry into prenatal care (p=0.901), diabetes (p=0.337), smoking (p=0.230), and infant sex (p=0.135) (Table 9). Reported nausea was explored further to see if the possible association with macrosomia, seen above, was through the causal pathway of nausea being associated with less weight gain, which then leads to being protective of macrosomia. A logistic regression model between reported nausea and macrosomia controlling for GWG showed that nausea is independently associated with macrosomia in these data. Of note, prepregnancy BMI did not show a dose-response relationship with GWG. The mean number of pounds gained beyond appropriate was highest for those who were overweight (mean: 8.09 lbs., 95% CI: 6.93-9.26), compared to those who were obese (mean: 7.00 lbs.; 95% CI: 6.18-7.82) and normal weight (mean: 1.90 lbs.; 95% CI: 1.20-2.61) (Table 9). Also, those women who reported nausea gained less weight and those who had term and post-term deliveries also gained more weight.

The Directed Acyclic Graph (DAG) drawn provided insights into potential causal pathways between each of the exposures and macrosomia. Assessment for prepregnancy BMI as the main exposure, assuming the DAG drawn is correct (Figure 6), shows a sufficient set to control for all confounding to contain the following variables: GWG, parity, AI/AN race, maternal age, and any report of diabetes. Assessment for GWG as the main exposure showed a sufficient set to control for all confounding to include: prepregnancy BMI, any report of diabetes, smoking status, reported nausea, gestational age, and infant sex. These results, along with the crude associations of covariates with macrosomia, prepregnancy BMI, and GWG, guided the building of the multivariable logistic regression model.

The multivariable logistic regression analysis began including four interaction models. The first interaction term removed was GWG with smoking status (p=0.855), followed by BMI with parity (p=0.817), and BMI with diabetes (p=0.740). Finally, the interaction term, which assessed the joint effects of prepregnancy BMI and GWG, was removed from the model (p=0.181).

After interaction assessment, the final regression model resulted in significant independent effects of both prepregnancy obesity and excess GWG for macrosomia. There were 1,514 cases of macrosomia among 8,871 women used in the final regression due to missing data on covariates. After controlling for GWG, prepregnancy obesity significantly increased the odds of macrosomia by 63% compared to the odds of macrosomia in normal weight women at conception (aOR: 1.63; 95% CI: 1.29-2.07). Prepregnancy overweight did not independently increase the odds of macrosomia compared to normal weight women at conception (aOR: 1.26; 95% CI: 1.00-1.58). Controlling for prepregnancy BMI, excess GWG did increase the odds of macrosomia compared to appropriate GWG. For every five additional pounds gained over the recommended range for each BMI, the risk for macrosomia increased 16% (aOR: 1.16; 95% CI: 1.12-1.20). This will compound, increasing the odds of macrosomia as the mother gains more weight over the recommended range.

Compared to normal weight women who gained an appropriate amount of weight during pregnancy, the odds of macrosomia increased 90% for obese women for every additional five lbs. gained over the appropriate GWG range (aOR: 1.90; 95% CI: 1.58-2.28) (Table 10). Even women who had inadequate weight gain and were obese had elevated odds of macrosomia (aOR: 1.40; 95% CI: 1.17-1.69). Overweight women only

had significantly increased odds of macrosomia when they gained excess amount of weight during pregnancy (aOR: 1.46; 95% CI: 1.20-1.78 for every five lbs. gained over appropriate GWG). Normal weight women had 16% increased odds of macrosomia for every five lbs. over recommended GWG (aOR: 1.16; 95% CI: 1.12-1.20). Inadequate weight gained proved to be statistically protective against macrosomia for underweight and normal weight women (aOR: 0.49; 95% CI: 0.24-0.99 and aOR: 0.86; 95% CI: 0.83-0.89, respectively). Staying within the appropriate weight gain recommendations did not change the odds for macrosomia significantly for any BMI category except obese women as mentioned earlier.

The secondary analysis of geographic differences showed that most of the sample of AI/AN women came from Oklahoma (38.85%), followed by Washington (16.31%) and Alaska (15.59%). All other states represented less than 10% of the sample (Table 11). The prevalence of macrosomia by state of residence was also statistically significantly different ($p<0.001$) ranging from 8.00% (95% CI: 4.44-14.01) in Utah to 18.83% (95% CI: 17.43-20.31) in Alaska (Table 11). The prevalence of women being obese at conception ranged from 27.29% (95% CI: 17.41-36.89) in Utah to 33.01% (95% CI: 30.97-35.11%) in Oregon. Interestingly, excess weight gain during pregnancy was over 40% in all states, with three above 50% and two less than 48%. New Mexico had the lowest prevalence of excess GWG at 40.64% (95% CI: 35.55-45.93) compared to Oregon with the highest prevalence at 54.95% (95% CI: 52.75-57.12) (Table 11).

The multivariable logistic regression showed slightly different patterns for significantly increased odds of macrosomia when stratified by state. Alaska, Oregon, and Oklahoma all showed significantly increased odds of macrosomia among obese women

compared to normal weight women (Table 12). Only Alaska showed a significant increase in odds of macrosomia among overweight women compared to normal weight women. On the other hand, every five pounds additionally gained beyond appropriate GWG was statistically associated with increased odds of macrosomia in all states except New Mexico and Utah, both of which had a low number of cases of macrosomia (Table 12). Notably, the pointe estimates for the effect of every five lbs. gained over appropriate were remarkably similar (1.11-1.16) with the exception of Oklahoma (1.22). Inadequate GWG was statistically significantly protective against macrosomia in most states (Table 12). Utah was missing a disproportionate amount of data compared to other states and therefore the aOR's for the BMI categories are uninformative.

In the sub-analysis of only non-diabetic AI/AN women who delivered singleton births and were older than 20 years of age, slightly different patterns emerged of the independent effects of prepregnancy BMI and GWG. Independent of GWG, overweight and obese women at conception had independent increased odds of macrosomia by 30% and 67%, respectively (aOR: 1.30; 95% CI: 1.01-1.66 and aOR: 1.67; 95% CI: 1.28-2.17) (Table 13). Controlling for prepregnancy BMI, every additional five lbs. gained beyond the appropriate weight gain range resulted in 16% increased odds for macrosomia, which is the observed effect for all women as well. A comparison of odds of macrosomia for all combinations of prepregnancy BMI and GWG can been seen in Table 13.

CHAPTER 5: DISCUSSION

Overall, Alaskan Natives had a statistically higher prevalence of macrosomia compared to American Indians and mixed race AI/ANs. The AI/AN population in the United States is known for having higher rates of obesity and diabetes than other races, which held true in this sample.[50]

This analysis showed that both prepregnancy BMI and GWG have independent effects on the odds of macrosomia among adult AI/AN women who have delivered a singleton birth when adjusted for other possible risk factors (AI/AN race, maternal age, parity, diabetes, smoking during pregnancy, reported nausea, gestational age, and infant sex). The interaction between prepregnancy BMI and GWG was not significant. In this sample, the average prepregnancy BMI for women who delivered a macrosomic infant was borderline obese at 29.26 kg/m^2, which was significantly higher than for women who did not deliver a macrosomic infant, classified as overweight at 27.24 kg/m^2. In addition, women who delivered a macrosomic infant gained statistically more weight beyond the recommended range during pregnancy than women who did not deliver a macrosomic infant among normal weight, overweight and obese women.

These results confirm other findings establishing prepregnancy obesity as a risk factor for macrosomia.[16,17] Among adult AI/AN women prepregnancy obesity was significantly associated with macrosomia with 63% increased odds compared to normal weight women at conception. Contrary to some other research, overweight at conception was not significantly associated with increased odds of macrosomia among adult AI/AN women in this sample after controlling for other factors such as diabetes and GWG.[17]

One possible explanation for this is that in overweight AI/AN women, the effect of excess GWG is a more dominant risk factor for macrosomia.

Excess GWG is also a well established risk factor for increased fetal growth independent of both diabetes and prepregnancy BMI.[16] This analysis extended prior findings by examining the association of GWG with macrosomia for every additional pound gained beyond the recommended amount during pregnancy. For every five pounds a woman gained beyond the appropriate GWG recommendations, her odds of macrosomia increased 16%. The effects of excess GWG will compound and increase as a woman gains weight beyond the recommended guidelines. The average number of pounds gained beyond the appropriate weight range among women who had a macrosomic infant was 17.25 lbs. in this sample. With these findings, a woman matching this average excess GWG increased her odds of a macrosomic infant by 68% compared to if she had gained an appropriate amount of weight during her pregnancy (aOR: 1.68; 95% CI: 1.49-1.89).

Since diabetes has been proven to cause accelerated fetal growth, an analysis of a sub-sample of non-diabetic adult AI/AN women was also conducted.[10,16,26] This resulted in similar findings with both GWG and prepregnancy BMI having independent effects on delivering a macrosomic infant. The only exception was overweight non-diabetic women now had significant increased odds of macrosomia by 30% after controlling for GWG. Obesity at conception still showed a 67% increase in the odds of macrosomia compared to normal weight women after controlling for GWG and other possible risk factors.

Public Health Implications

Increased prepregnancy BMI and excess GWG are important independent risk factors for fetal macrosomia, which should be clinically addressed to help reduce the risk of adverse pregnancy outcomes among AI/AN women. Although both exposures are modifiable, the timing of interventions to address prepregnancy BMI and GWG will differ. The healthcare provider who will deliver care will also differ between BMI and GWG. A survey in 2004 found that only one in six obstetricians/gynecologists or family physicians provided both preconception care and prenatal care to the majority of the woman they serve.[65] Many of the risk factors that can cause adverse pregnancy outcomes occur early in gestation, possibly even before the woman knows she is pregnant. Many providers who deliver preconception care, such as primary care physicians, do not focus on pregnancy in particular. However, these providers will be treating women during their preconception period and need to incorporate regulation of pregnancy-related risk factors into their practice, including weight regulation to control BMI. Other examples of preconception care that require attention include folic acid supplementation to prevent neural tube defects, which is optimal three months prior to conception, and early pregnancy exposures to alcohol, tobacco, and illicit drug use that may lead to fetal developmental problems and pregnancy complications.[65] On the other hand, obstetricians/gynecologists who provide prenatal care would be responsible for counseling and monitoring behaviors to regulate GWG, especially among diabetic pregnancies where glucose control is important.

BMI needs to be addressed before conception to help women enter pregnancy within the normal weight range. Interventions to address prepregnancy obesity during preconception care often involve lifestyle behavioral changes and include combinations

of calorie restriction, physical activity, behavioral strategies, and frequent monitoring of weight.[66] Ideally obesity addressed during childhood or adolescences could help reduce the body weight of women to help them enter pregnancy within the normal weight range. Interventions that address multiple pregnancy-related risk factors, such as obesity, smoking, and alcohol misuse, have not been systemically evaluated and are seen less often in clinical practice.[65] Preconception monitoring of body weight is especially important since entering pregnancy at higher BMI's is also associated with other problems such as increased risk of prematurity, stillbirth, congenital anomalies, and childhood obesity.[67]

Pregnancy can also act as a catalyst for women to enter clinical care and/or possibly switch providers. After conception GWG becomes more clinically relevant, but clinical approaches to addressing GWG are similar to those that address obesity in general. Interventions that have shown to be successful in GWG management closely resemble lifestyle programs used for weight management in non-pregnant women, including calorie goals, structured meal plans, frequent weight measurement, behavioral strategies, and ongoing contact with healthcare providers.[66] It is essential that women be counseled on dietary information and healthy eating habits during pregnancy to provide adequate nutrition to the growing fetus while preventing excess GWG. Discussions during the early stages of prenatal care between providers and patients about the appropriate weight gain recommendations should be accompanied by regular weigh-ins and constant monitoring and tracking of GWG throughout pregnancy.[67]

Currently, the ACOG committee opinion states that nutrition consultations should be offered to all overweight or obese women, without mentioning normal weight

women.[67] However, this study showed significantly increased odds of macrosomia among normal weight AI/AN women who had excess GWG. Therefore, normal weight AI/AN women need to be included in the recommended nutritional and dietary consultation target population, especially since they accounted for 40% of the entire population. This is consistent with findings recommending that prevention methods for GWG should target women of all BMI categories for Whites, Blacks, Hispanics, and Asian/Pacific Islanders.[16,19] Although inadequate weight gain showed a significant protective effect for macrosomia, inadequate weight gain has been linked to other adverse pregnancy outcomes such as low birth weight, preterm deliveries, and neonatal intensive care unit admission, and therefore should not be advised.[68]

Notably, among the sample of AI/AN women, obesity represented only about 30% of women whereas excess GWG was seen in almost 50% of women. On a population level, all women need information about macrosomia associated with excess GWG. Every pound above the appropriate weight gain recommended increased the odds of macrosomia in this study. Therefore, weight management counseling should first encourage women to gain within the appropriate range. However, if women are already beyond the normal range, counseling should encourage them to minimize any additional gain to minimalize the risk of macrosomia. This study also shows the importance of weight management during pregnancy among both non-diabetic and diabetic AI/AN women. Decreasing a woman's risk of delivering a macrosomic infant will also decrease the risk of obstetric complications for both her and her infant.

Among this population, there is the potential for be a circular pattern with conditions such as prepregnancy obesity and gestational weight gain that are reinforced

from generation to generation.[17,39,43] Although current clinical guidelines suggest when to target women for lifestyle behavioral interventions, in reality such interventions will actually be implemented during the woman's everyday life. Therefore, more research needs to be conducted to adapt and develop interventions that address AI/AN's current attitudes, geographical differences, and socio-economic environment. Potential issues that will need to be addressed for this unique high-risk population include matching literacy levels, improving resources available, incorporating tribal cultural practices, involving the greater community, and increasing healthcare utilization practices.[44-46] All these aspects need to be in the context of the state in which the women resides. It has been shown that there are severe regional and state level disparities in prenatal care utilization among the AI/AN population.[57] Tackling these clinical and cultural issues to help reduce maternal and infant morbidity will be challenging and requires more research.

Strengths and Limitations

This study was able to capture a large sample of AI/AN women using a validated questionnaire to obtain exposure data along with data on many clinical variables. The variety of information the PRAMS questionnaires collect allows data to be captured on many other pregnancy-related behaviors and attitudes that cannot be extracted solely from birth certificates. For example, in this study reported nausea during pregnancy was found to be an important confounder for GWG. In addition, the study was able to include AI/AN women who reside in many geographic regions across the United States. Many states have predominant Native American tribes, which is why state specific estimates for

macrosomia were included. The PRAMS's sampling methodology allows estimates to represent the entire state and also allows inter-state comparisons.

Although this study had important and clinically relevant findings for AI/AN women, it did not come without some limitations. Not all the states that have large AI/AN populations, like Arizona and the Dakotas, participate in PRAMS, and PRAMS is only generalizable to the states included in the analysis. In addition, PRAMS only samples women who have had a live birth, so the findings cannot be applied to pregnancies that result in miscarriages or stillbirths.

There are some limitations surrounding quality of information on variables such as misclassification of prepregnancy BMI and GWG due to post hoc assessment of prepregnancy weight reported by mothers at the time of the questionnaire. Women may underestimate reported prepregnancy weight, whereas weight at birth is objectively measured. Therefore, pregnancy BMI may be underestimated, and GWG may be slightly overestimated. The largest limitation to this study is the inability to control for history of previous macrosomia, a well-known risk factor for macrosomia reflecting both environmental and genetic factors, since no question on PRAMS captures this information.[3]

Conclusions

Overall, prepregnancy obesity and excess GWG should be considered independent risk factors for delivery of a macrosomic infant among adult AI/AN women. The interventions to address these risk factors need to occur at different times during the reproductive years. Prepregnancy BMI needs to be addressed well before conception so women can enter the pregnancy at a normal weight. Weight management interventions to

prevent excess GWG need to begin early in prenatal care and be continued throughout the entire course of pregnancy. It is important that among the AI/AN population excess GWG be considered an independent risk factor for macrosomia among both non-obese and obese women. Weight management programs both before and during pregnancy can help reduce the risks for many adverse outcomes and improve the health of both the mothers and their infants.

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TABLES AND FIGURES

Table 1: Institute of Medicine's weight gain during pregnancy guidelines, 2009

Prepregnancy BMI	Body Mass Index[a] (WHO) (kg/m^2)	Total Weight Gain Range[b] (lbs.)
Underweight	<18.5	28-40
Normal Weight	18.5-24.9	25-35
Overweight	25.0-29.9	15-25
Obese (all classes)	≥30.0	11-20

[a] Body Mass Index based on World Health Organizations categories

[b] Weight gain ranges taken from the Institute of Medicine's revised guidelines[9]

Figure 1: Flowchart for inclusion/exclusion criteria

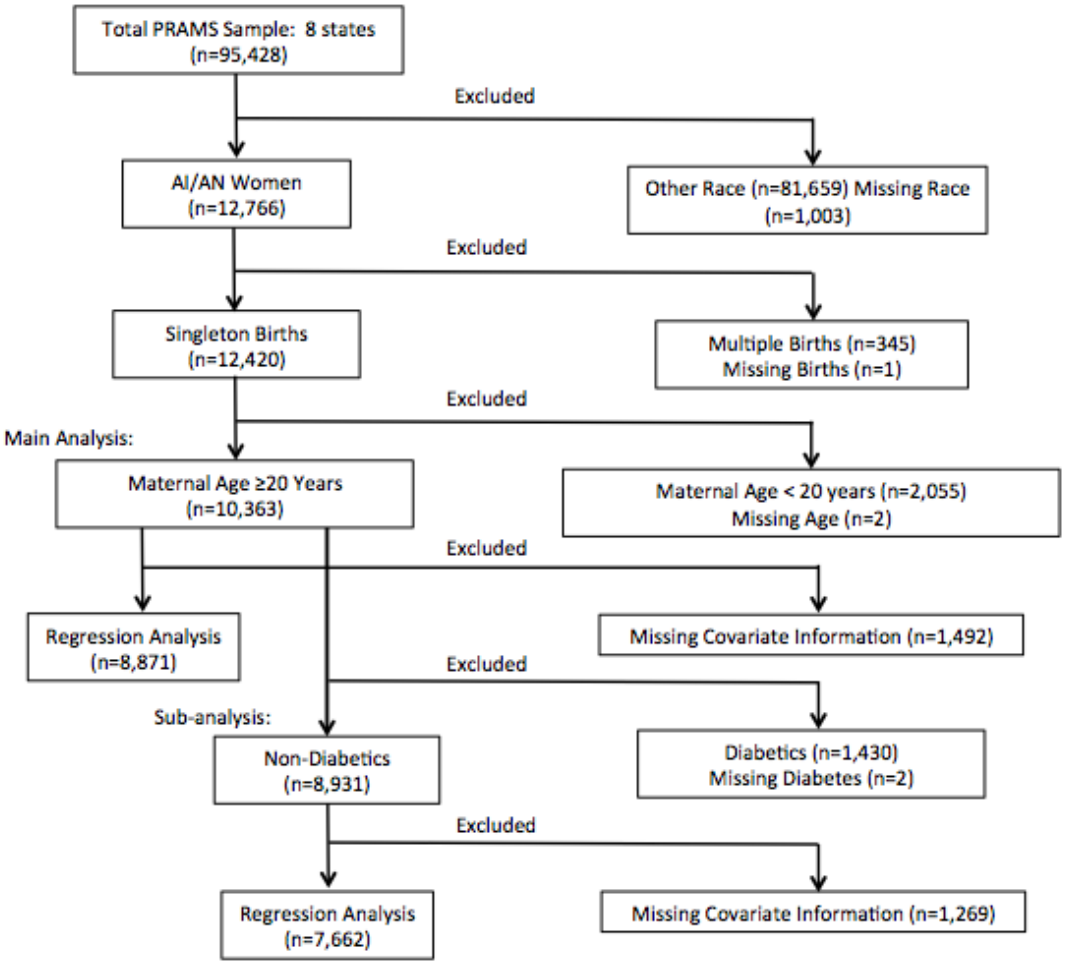

Table 2: Prevalence of demographic and pregnancy characteristics among American Indian/Alaskan Native women

	Total Sample	
	unweighted n=10,363	
	unweighted n	% (95% CI)[a]
DEMOGRAPHIC FACTORS		
AI/AN	10,363	
American Indian		68.01 (66.29-69.67)
Alaskan Native		15.34 (14.74-15.95)
Mixed- AI/AN with other		16.65 (15.03-18.42)
Maternal Age (years)	10,363	
20-24		41.57 (39.62-43.56)
25-29		32.35 (30.51-34.24)
30-34		18.07 (16.62-19.61)
≥35		8.01 (7.11-9.02)
Education (years)	10,234	
>12		18.46 (17.04-19.97)
12		42.95 (40.97-44.95)
<12		38.59 (36.67-40.55)
Marital Status	10,353	
Married		44.24 (42.27-46.22)
Not Married		55.76 (53.78-57.73)
Federal Poverty Level[b]	9,592	
≤138% FPL		68.47 (66.54-70.34)
>138% FPL		31.53 (29.66-33.46)
PREGNANCY CHARACTERISTICS		
Prepregnancy BMI (kg/m^2)	9,921	
<18.5 Underweight		2.98 (2.31-3.85)
18.5-24.9 Normal		39.83 (37.83-41.87)
25.0-29.9 Overweight		27.55 (25.80-29.37)
≥30.0 Obese		29.64 (27.86-31.48)
Weight Gain During Pregnancy[c]	9,242	
Inadequate		22.17 (20.45-23.98)
Appropriate		29.50 (27.59-31.49)
Excess		48.33 (46.22-50.45)
Parity	10,314	
First Birth		30.19 (28.36-32.09)
Second or Later Birth		69.81 (67.91-71.64)
Pregnancy Intention	10,321	
Intended		38.57 (36.67-40.52)
Unintended		61.43 (59.48-63.33)
Entry into Prenatal Care	9,963	
1st Trimester		81.88 (80.29-83.37)
2nd Trimester		15.02 (13.65-16.50)
3rd Trimester or no PNC		3.10 (2.47-3.87)
Any Reported Diabetes[d]	10,361	
Yes		13.80 (12.52-15.18)
No		86.20 (84.82-87.48)

Table 2: Continued

	Total Sample	
	unweighted n=10,363	
	unweighted n	% (95% CI)[a]
Hypertension	10,240	
Yes		8.36 (7.37-9.48)
No		91.64 (90.52-92.63)
Smoking During Pregnancy[e]	10,138	
Yes		22.82 (21.18-24.54)
No		77.18 (75.46-78.82)
Reported Nausea	10,239	
Yes		34.04 (32.14-35.99)
No		65.96 (64.01-67.86)
Gestational Age[f]	10,255	
Preterm		9.18 (8.29-10.16)
Term		90.46 (89.48-91.36)
Post-term		0.36 (0.29-0.44)
Infant Gender	10,362	
Male		49.02 (47.04-51.00)
Female		50.98 (49.00-52.96)

Stratified sample sizes may not match total due to missing information

[a] Prevalence (95% CI: Confidence Interval)

[b] Federal Poverty Level determined by maternal self report of income and number of

[c] Weight gain categories determined by 2009 IOM guidelines for each BMI category

[d] Any diabetes includes diagnosis of either prepregnancy diabetes or gestational diabetes

[e] Maternal self-report of any smoking during the last trimester

[f] Preterm: <37 weeks, Term: 37-42 weeks, Post-term: >42 weeks gestation

Figure 2: Distribution of body mass index across the entire sample of American Indian/Alaskan Native women

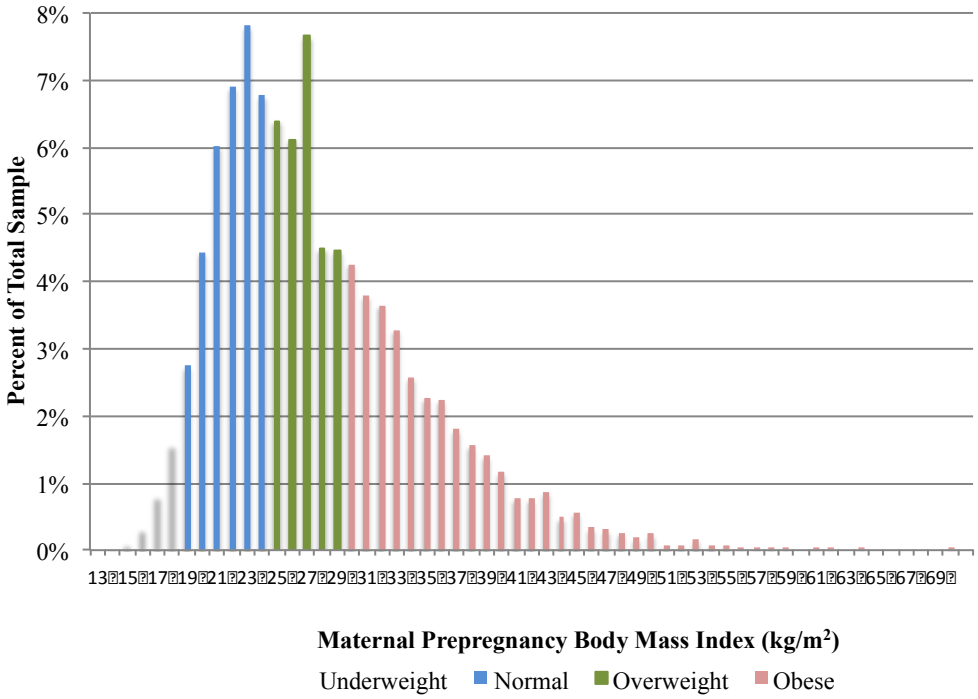

Table 3: Prevalence of macrosomia by selected demographic and pregnancy characteristics among American Indian/Alaskan Native women who delivered a macrosomic infant

	Macrosomia								
	Birth weight ≥4,000 grams			Birth weight ≥4,500 grams			Large for Gestational Age (90th percentile)		
	unweighted n	% (95% CI)[a]	p-value[b]	unweighted n	% (95% CI)[a]	p-value[b]	unweighted n	% (95% CI)[a]	p-value[b]
Total	1,736	12.51 (11.66-13.41)	-	324	2.26 (1.99-2.57)	-	1,680	13.55 (12.49-14.68)	-
DEMOGRAPHIC FACTORS									
AI/AN	1,736		<0.001[c]	324		<0.001[c]	1,680		<0.001[c]
American Indian		10.96 (10.12-11.87)			2.12 (1.79-2.51)			11.81 (10.68-13.18)	
Alaskan Native		18.90 (17.51-20.38)			3.89 (3.23-4.68)			20.59 (19.14-22.13)	
Mixed- AI/AN with other		12.95 (9.85-16.83)			1.35 (0.92-1.98)			13.99 (10.63-18.20)	
Maternal Age (years)	1,736		0.409	324		0.112	1,680		<0.001[c]
20-24		11.63 (10.32-13.09)			1.98 (1.57-2.51)			10.79 (9.43-12.32)	
25-29		11.87 (10.55-13.32)			2.15 (1.76-2.64)			13.29 (11.55-15.25)	
30-34		14.70 (12.40-17.35)			2.68 (2.05-3.49)			18.36 (15.20-22.01)	
≥35		14.70 (12.23-17.58)			3.22 (2.29-4.52)			18.01 (14.53-22.11)	
Education (years)	1,713		0.212	319		0.080	1,655		0.098
>12		11.02 (9.42-12.86)			1.89 (1.41-2.54)			11.31 (9.40-13.55)	
12		13.00 (11.70-14.42)			2.59 (2.16-3.11)			13.54 (11.99-15.25)	
<12		12.54 (11.10-14.14)			1.96 (1.60-2.40)			14.41 (12.54-16.50)	
Marital Status	1,734		0.286	324		0.705	1,678		0.087
Married		13.06 (11.71-14.55)			2.33 (1.96-2.76)			14.64 912.98-16.47)	
Not Married		12.07 (11.01-13.23)			2.22 (1.85-2.66)			12.68 911.34-14.16)	
Federal Poverty Level[d]	1,616		0.552	308		0.345	1,564		0.964
≤138% FPL		12.24 (11.15-13.44)			2.20 (1.86-2.59)			13.37 (12.02-14.85)	
>138% FPL		12.82 (11.38-14.42)			2.50 (2.03-3.08)			13.42 (11.69-15.37)	
PREGNANCY CHARACTERISTICS									
Prepregnancy BMI (kg/m^2)	1,661		<0.001[c]	308		<0.001[c]	1,610		<0.001[c]
<18.5 Underweight		4.31 (2.62-7.01)			0.99 (0.53-2.83)			4.34 (2.64-7.07)	
18.5-24.9 Normal		9.24 (7.90-10.78)			1.43 (1.09-1.88)			9.45 (7.95-11.20)	
25.0-29.9 Overweight		12.97 (11.51-14.59)			2.12 (1.59-2.82)			13.62 (11.74-15.74)	
≥30.0 Obese		16.67 (15.00-18.48)			3.58 (3.01-4.25)			18.72 (16.60-21.03)	
Weight Gain During Pregnancy[e]	1,562		<0.001[c]	287		<0.001[c]	1,502		<0.001[c]
Inadequate		8.48 (7.01-10.23)			1.32 (0.95-1.84)			9.34 (7.64-11.36)	
Appropriate		8.45 (7.15-9.96)			1.30 (0.91-1.75)			10.24 (8.39-12.44)	
Excess		16.32 (14.92-17.83)			3.22 (2.72-3.82)			16.25 (14.66-17.99)	
Parity	1,731		0.002[c]	324		<0.001[c]	1,673		<0.001[c]
First Birth		10.38 (8.92-12.04)			1.51 (1.18-1.93)			9.51 (7.87-11.45)	
Second or Later Birth		13.46 (12.42-14.57)			2.61 (2.25-3.01)			15.28 (13.96-16.71)	
Pregnancy Intention	1,730		0.061	323		0.342	1,673		0.294
Intended		13.62 (12.19-15.19)			2.44 (2.03-2.92)			14.28 (12.63-16.10)	
Unintended		11.85 (10.80-12.98)			2.15 (1.81-2.57)			13.08 (11.71-14.57)	

Table 3: Continued

	Macrosomia								
	Birth weight ≥4,000 grams			Birth weight ≥4,500 grams			Large for Gestational Age (90th percentile)		
	unweighted n	% (95% CI)[a]	p-value[b]	unweighted n	% (95% CI)[a]	p-value[b]	unweighted n	% (95% CI)[a]	p-value[b]
Entry into Prenatal Care	1,679		0.003[c]	317		0.524	1,628		<0.001[c]
1st Trimester		12.82 (11.84-13.86)			2.20 (1.92-2.54)			14.10 (12.87-15.43)	
2nd Trimester		11.99 (9.93-14.41)			2.77 (1.96-3.89)			11.76 (9.72-14.15)	
3rd Trimester or no PNC		6.38 94.15-9.70)			2.12 (1.14-3.91)			6.09 (3.95-9.28)	
Any Reported Diabetes[f]	1,736		<0.001[c]	324		<0.001[c]	1,680		<0.001[c]
Yes		17.93 (15.59-20.53)			4.73 (3.78-5.90)			21.77 (18.67-25.22)	
No		11.64 (10.73-12.62)			1.87 (1.60-2.18)			12.22 (11.10-13.44)	
Hypertension	1,720		0.757	317		0.127	1,661		0.874
Yes		12.07 (9.02-15.98)			3.03 (2.12-4.32)			13.92 (10.46-18.29)	
No		12.64 (11.75-13.58)			2.18 (1.90-2.49)			13.59 (12.47-14.79)	
Smoking During Pregnancy[g]	1,702		<0.001[c]	320		<0.001[c]	1,648		<0.001[c]
Yes		9.00 (7.44-10.85)			1.30 (0.96-1.77)			10.06 (8.12-12.39)	
No		13.54 (12.53-14.61)			2.57 (2.23-2.95)			14.56 (13.31-15.90)	
Reported Nausea	1,718		0.011[c]	322		0.005[c]	1,660		0.277
Yes		10.89 (9.45-12.51)			1.72 (1.32-2.22)			12.67 (10.79-14.82)	
No		13.37 (12.31-14.49)			2.56 (2.22-2.96)			14.01 (12.74-15.39)	
Gestational Age[h]	1,724		<0.001[c]	321		<0.001[c]	1,671		0.504
Preterm		2.39 (1.64-3.48)			0.82 (0.45-1.49)			12.85 (9.79-16.69)	
Term		13.52 (12.58-14.52)			2.41 (2.12-2.75)			13.63 (12.51-14.84)	
Post-term		18.36 (11.27-28046)			1.19 (0.23-5.89)			0	
Infant Gender	1,736		<0.001[c]	324		<0.001[c]	1,679		<0.001[c]
Male		14.98 (13.67-16.39)			3.04 (2.59-3.58)			13.44 (12.05-14.95)	
Female		10.13 (9.06-11.32)			1.51 (1.24-1.84)			13.65 (12.09-15.38)	

Stratified sample sizes may not match total due to missing information

[a] Percent of macrosomia seen within each category (95% CI: Confidence Interval)

[b] χ^2 p-value

[c] Statistically significant, alpha=0.05

[d] Federal Poverty Level determined by maternal self report of income and number of dependents from the year previous to infant's birth

[e] Weight gain categories determined by 2009 IOM guidelines by each BMI category

[f] Any diabetes includes diagnosis of either prepregnancy diabetes or gestational diabetes

[g] Maternal self-report of any smoking during the last trimester

[h] Preterm: <37 weeks, Term: 37-42 weeks, Post-term: >42 weeks gestation

Figure 3: Distribution of infant birth weight among American Indian/Alaskan Native women

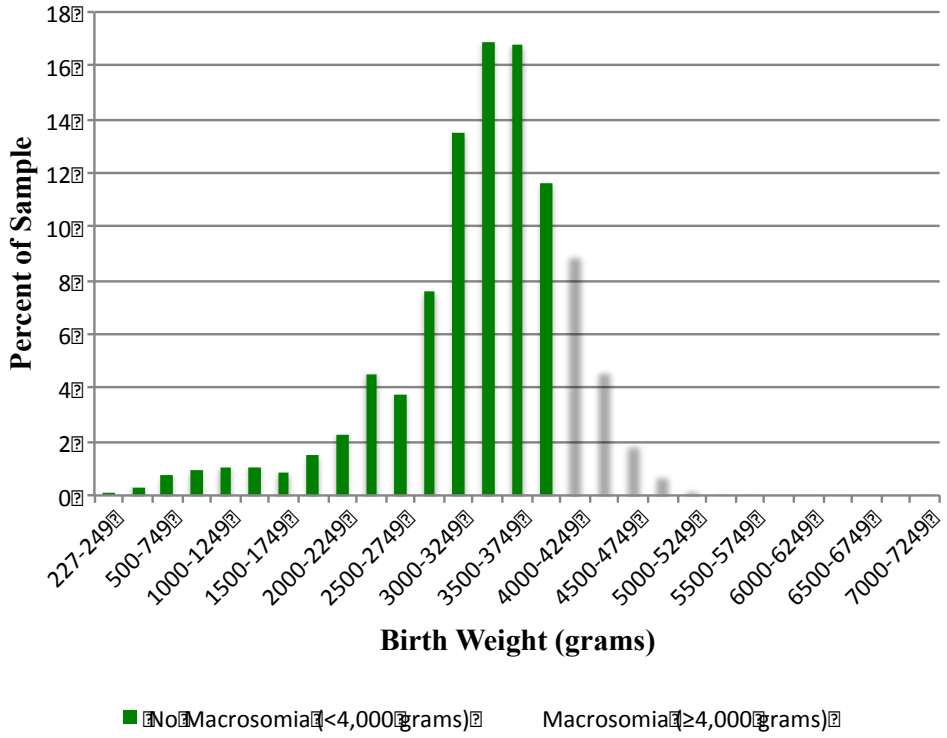

Figure 4: Distribution of body mass index stratified by macrosomia for American Indian/Alaskan Native women

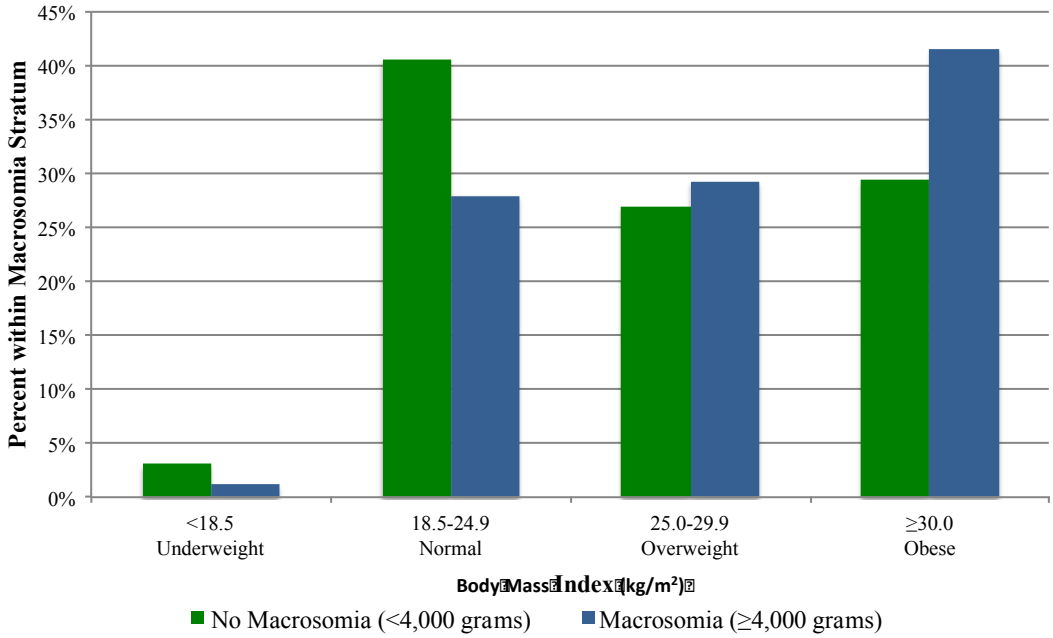

Figure 5: Distribution of gestational weight gain categories stratified by macrosomia for American Indian/Alaskan Native women

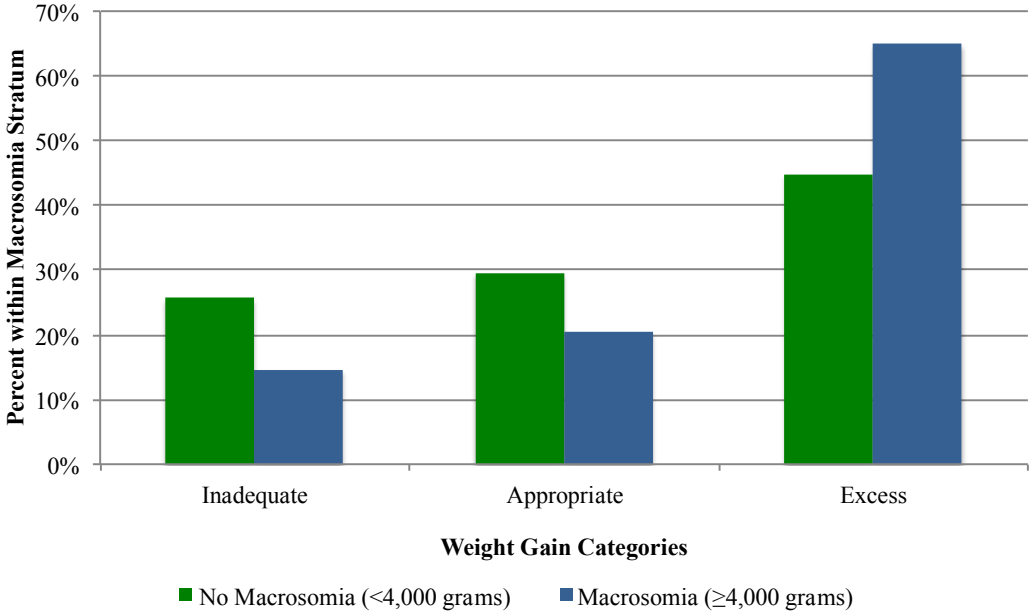

Table 4. Summary statistics for maternal prepregnancy body mass index and gestational weight gain for American Indian/Alaskan Native women stratified by birth weight

	Body Mass Index (kg/m^2)[a]			Gestational Weight Gain (lbs.)[b]		
	Total	No Macrosomia <4,000 grams	Macrosomia ≥4,000 grams	Total	No Macrosomia <4,000 grams	Macrosomia ≥4,000 grams
Unweighted n	9,921	8,230	1,661	9,618	7,961	1,631
Mean	27.49	27.24	29.26	29.40	28.82	33.58
Standard Deviation	0.14	0.15	0.24	0.33	0.37	0.59
Median	25.85	25.75	28.25	27.96	27.34	31.40
25th percentile	22.66	22.46	24.12	19.08	18.92	19.97
75th percentile	30.99	30.67	33.25	38.13	37.27	43.74
Minimum	13.64[c]	13.64	15.18	0	0	0
Maximum	69.97[d]	69.97	62.14	≥97[e]	≥97[e]	≥97[e]
# missing BMI	442	363	75	745	632	105
Mean Comparison[f]						
Statistic		T = -7.07			T = -6.87	
p-value		p<0.001[g]			p<0.001[g]	

[a] 30 observations are excluded from macrosomia strata due to no information on birth weight

[b] 26 observations are excluded from macrosomia strata due to no information on gestational weight gain

[c] Women with BMI less than 13 kg/m^2 were excluded as implausible value

[d] Women with BMI greater than 70 kg/m^2 were excluded as implausible value

[e] Women with 97 lbs. or more were collapsed as gaining 97 lbs.

[f] Pairwise comparison of the mean between macrosomia and no macrosomia

[g] Statistically significant, alpha=0.05

Table 5: Average body mass index stratified by gestational weight gain categories for all American Indian/Alaskan Native women

	Total		Gestational Weight Gain Categories[a]					
			Inadequate		Appropriate		Excess	
	unweighted n	mean (std)[b]	unweighted n	mean (std)[b]	unweighted n	mean (std)[b]	unweighted n	mean (std)[b]
Macrosomia (≥4,000 grams)								
Prepregnancy BMI (kg/m^2)								
<18.5 Underweight	21	17.68 (0.12)	3	16.87 (0.71)	8	17.78 (0.20)	9	17.74 (0.11)
18.5-24.9 Normal	465	22.33 (0.15)	82	22.75 (0.20)	110	22.63 (0.16)	240	22.12 (0.22)
25.0-29.9 Overweight	486	27.31 (0.08)	40	27.54 (0.19)	84	27.62 (0.18)	337	27.17 (0.11)
≥30.0 Obese	689	36.13 (0.26)	104	37.52 (1.08)	117	36.24 (0.44)	428	35.64 (0.28)
No Macrosomia (<4,000 grams)								
Prepregnancy BMI (kg/m^2)								
<18.5 Underweight	254	17.44 (0.13)	105	17.30 (0.19)	74	17.47 (0.31)	63	17.58 (0.21)
18.5-24.9 Normal	3,337	22.19 (0.06)	993	22.31 (0.13)	1,045	22.10 (0.12)	1,103	22.12 (0.10)
25.0-29.9 Overweight	2,223	27.24 (0.06)	367	27.45 (0.15)	565	27.38 (0.14)	1,127	27.10 (0.09)
≥30.0 Obese	2,416	35.79 (0.21)	500	37.35 (0.51)	580	35.80 (0.37)	1,135	35.22 (0.31)
BMI Comparison[c]								
Prepregnancy BMI (kg/m^2)								
<18.5 Underweight	p=0.176		p=0.560		p=0.393		p=0.499	
18.5-24.9 Normal	p=0.375		p=0.063		p=0.008		p=0.985	
25.0-29.9 Overweight	p=0.489		p=0.726		p=0.301		p=0.632	
≥30.0 Obese	p=0.307		p=0.887		p=0.443		p=0.323	

[a] Weight gain categories determined by 2009 IOM guidelines by each BMI category

[b] Standard deviation of the mean

[c] Pairwise comparisons of prepregnancy body mass index by weight gain category between macrosomic and non-macrosomic births, Bonferonii adjusted statistically significant, alpha=0.004

Table 6A: Average weight gained by prepregnancy body mass index category among American Indian/ Alaskan Native women who gained an inadequate amount of

	Macrosomia (≥4,000 grams)		No Macrosomia (<4,000 grams)		
	mean[b]	(std)[c]	mean[b]	(std)[c]	p-value[d]
Prepregnancy BMI (kg/m^2)					
Total	-7.27	(0.51)	-8.02	(0.33)	0.221
<18.5 Underweight	-7.14	(3.59)	-11.03	(2.34)	0.363
18.5-24.9 Normal	-9.24	(0.71)	-8.68	(0.47)	0.506
25.0-29.9 Overweight	-6.93	(0.70)	-7.45	(0.50)	0.545
≥30.0 Obese	-6.02	(0.74)	-6.17	(0.40)	0.852

Table 6B: Average weight gained by prepregnancy body mass index category among American Indian/ Alaskan Native women who gained an excess amount of weight[a]

	Macrosomia (≥4,000 grams)		No Macrosomia (<4,000 grams)		
	mean[b]	(std)[c]	mean[b]	(std)[c]	p-value[d]
Prepregnancy BMI (kg/m^2)					
Total	17.25	(0.55)	13.45	(0.43)	<0.001[e]
<18.5 Underweight	9.60	(1.56)	15.94	(6.13)	0.316
18.5-24.9 Normal	14.85	(0.99)	11.19	(0.56)	0.001[e]
25.0-29.9 Overweight	18.84	(0.99)	14.69	(0.93)	0.002[e]
≥30.0 Obese	17.62	(0.83)	14.24	(0.59)	0.001[e]

[a] Categorization of gestational weight gain according to the IOM 2009 guidelines

[b] Mean (lbs.), continuous variable representing the number of pounds gained from the appropriate range of weight gain recommended for each BMI category recommended by the IOM 2009 guidelines

[c] Standard deviation of mean

[d] Chi-square p-values for mean pairwise comparisons of average number of pounds gained outside of the recommended amount stratified by BMI between macrosomic and non-macrosomic infants

[e] Bonferonii adjusted statistically significant, alpha = 0.006

Table 7: Crude associations between demographic and pregnancy characteristics and macrosomia among American Indian/Alaskan Native women

	Macrosomia (≥4,000 grams)	
	crude OR (95%CI)[a]	p-value[b]
DEMOGRAPHIC FACTORS		
AI/AN		<0.001[c]
American Indian	0.83 (0.60-1.14)	
Alaskan Native	1.57 (1.14-2.16)	
Mixed- AI/AN with other	1.00	
Maternal Age (years)		0.035[c]
20-24	1.00	
25-29	1.02 (0.85-1.24)	
30-34	1.31 (1.03-1.66)	
≥35	1.31 (1.02-1.69)	
Education (years)		0.221
>12	0.83 (0.67-1.03)	
12	1.00	
<12	0.96 (0.80-1.15)	
Marital Status		0.284
Married	1.00	
Not Married	0.91 (0.78-1.08)	
Federal Poverty Level[d]		0.552
≤138% FPL	1.00	
>138% FPL	1.05 (0.89-1.25)	
PREGNANCY CHARACTERISTICS		
Prepregnancy BMI (kg/m^2)		<0.001[c]
<18.5 Underweight	0.44 (0.26-0.76)	
18.5-24.9 Normal	1.00	
25.0-29.9 Overweight	1.46 (1.18-1.82)	
≥30.0 Obese	1.96 (1.59-2.43)	
Weight Gain (lbs.)[e]		<0.001[c]
Continuous Weight Gain	1.03 (1.02-1.04)	
Parity		0.003[c]
First Birth	1.00	
Second Birth	1.34 (1.11-1.63)	
Pregnancy Intention		0.059
Intended	1.00	
Unintended	0.85(0.72-1.01)	
Entry into Prenatal Care		0.005[c]
1st Trimester	1.00	
2nd Trimester	0.93 (0.74-1.17)	
3rd Trimester or no PNC	0.46 (0.29-0.74)	
Any Reported Diabetes[f]		
Yes	1.66 (1.37-2.01)	<0.001[c]
No	1.00	

Table 7: Continued

	Macrosomia (≥4,000 grams)	
	crude OR (95%CI)[a]	p-value[b]
Hypertension		0.760
Yes	0.95 (0.68-1.33)	
No	1.00	
Smoking During Pregnancy[g]		<0.001[c]
Yes	1.00	
No	1.58 (1.26-1.99)	
Reported Nausea		0.013[c]
Yes	0.79 (0.66-0.95)	
No	1.00	
Gestational Age[h]		<0.001[c]
Preterm	0.16 (0.11-0.23)	
Term	1.00	
Post-term	1.44 (0.81-2.56)	
Infant Gender		<0.001[c]
Male	1.56 (1.33-1.84)	
Female	1.00	

[a] Crude Odds Ratios (95% CI: Confidence Intervals) between selected characteristic and macrosomia using logistic regression

[b] Wald F-test p-value for coefficient of categorical variable in crude logistic regression model

[c] Statistically significant, alpha = 0.05

[d] Federal Poverty Level determined by maternal self report of income and number of dependents from the year previous to infant's birth

[e] Continuous variable representing the number of pounds gained from the appropriate range of weight gain recommended for each BMI category according to the IOM 2009 guidelines

[f] Any diabetes includes diagnosis of either prepregnancy diabetes or gestational diabetes

[g] Maternal self-report of any smoking during the last trimester

[h] Preterm: <37 weeks, Term: 37-42 weeks, Post-term: >42 weeks gestation

Table 8. Crude associations between demographic and pregnancy characteristics and body mass index among American Indian/Alaskan Native women

	Prepregnancy Body Mass Index (kg/m^2)			
	<18.5 Underweight vs. 18.5-24.9 Normal	25.0-29.9 Overweight vs. 18.5-24.9 Normal	≥30.0 Obese vs. 18.5-24.9 Normal	
	crude OR (95%CI)[a]	crude OR (95%CI)[a]	crude OR (95%CI)[a]	p-value[b]
DEMOGRAPHIC FACTORS				
AI/AN				<0.001[c]
American Indian	0.84 (0.40-1.76)	1.46 (1.06-2.00)	1.41 (1.03-1.92)	
Alaskan Native	0.43 (0.21-0.89)	1.48 (1.09-2.00)	1.25 (0.93-1.69)	
Mixed- AI/AN with other	1.00	1.00	1.00	
Maternal Age (years)				<0.001[c]
20-24	1.00	1.00	1.00	
	0.52 (0.28-0.98)	1.23 (0.97-1.56)	1.61 (1.28-2.04)	
30-34	0.52 (0.25-1.09)	1.40 (1.06-1.86)	2.45 (1.86-3.24)	
≥35	0.69 (0.23-2.13)	1.32 (0.92-1.89)	2.38 (1.68-3.36)	
PREGNANCY CHARACTERISTICS				
Weight Gain (lbs.)[d]				<0.001[c]
Continuous Weight Gain	0.98 (0.92-1.03)	1.04 (1.03-1.05)	1.04 (1.03-1.05)	
Parity				<0.001[c]
First Birth	1.00	1.00	1.00	
Second Birth	0.63 (0.36-1.10)	1.16 (0.93-1.45)	1.49 (1.20-1.86)	
Entry into Prenatal Care				0.099
1st Trimester	1.00	1.00	1.00	
2nd Trimester	0.90 (0.42-1.92)	0.85 (0.64-1.13)	0.82 (0.62-1.08)	
3rd Trimester or no PNC	0.28 (0.11-0.69)	0.99 (0.56-1.75)	0.76 (0.41-1.41)	
Any Reported Diabetes[e]				<0.001[c]
Yes	1.11 (0.56-2.22)	1.90 (1.36-2.66)	4.45 (3.29-6.01)	
No	1.00	1.00	1.00	
Smoking During Pregnancy[f]				0.008[c]
Yes	1.00	1.00	1.00	
No	0.51 (0.29-0.91)	0.98 (0.77-1.26)	1.26 (1.00-1.60)	

Table 8. Continued

	Prepregnancy Body Mass Index (kg/m^2)			
	<18.5 Underweight vs. 18.5-24.9 Normal	25.0-29.9 Overweight vs. 18.5-24.9 Normal	≥30.0 Obese vs. 18.5-24.9 Normal	
	crude OR (95%CI)[a]	crude OR (95%CI)[a]	crude OR (95%CI)[a]	p-value[b]
Reported Nausea				0.101
Yes	0.85 (0.49-1.48)	0.91 (0.73-1.13)	1.19 (0.96-1.47)	
No	1.00	1.00	1.00	
Gestational Age[g]				<0.001[c]
Preterm	1.73 (0.85-3.53)	1.12 (0.83-1.52)	1.08 (0.82-1.40)	
Term	1.00	1.00	1.00	
Post-term	0.00	0.94 (0.51-1.72)	1.00 (0.58-1.75)	
Infant Gender				0.858
Male	1.00 (0.59-1.72)	0.95 (0.77-1.16)	0.92 (0.76-1.12)	
Female	1.00	1.00	1.00	

[a] Crude Odds Ratios (95% CI: Confidence Intervals) between selected characteristic and body mass index using polytamous logistic regression

[b] Wald F-test p-value for coefficient of categorical variable in crude polytamous logistic regression model

[c] Statistically significant, alpha = 0.05

[d] Continuous variable representing the number of pounds gained from the appropriate range of weight gain recommended for each BMI category according to the IOM 2009 guidelines

[e] Any diabetes includes diagnosis of either prepregnancy diabetes or gestational diabetes

[f] Maternal self-report of any smoking during the last trimester

[g] Preterm: <37 weeks, Term: 37-42 weeks, Post-term: >42 weeks gestation

Table 9. Crude associations between demographic and pregnancy characteristics and gestational weight gain among American Indian/Alaskan Native women

	Gestational Weight Gain (lbs.)[a]	
	mean (95%CI)[b]	p-value[c]
DEMOGRAPHIC FACTORS		
AI/AN		0.078
American Indian	5.12 (4.44-5.80)	
Alaskan Native	4.28 (3.83-4.73)	
Mixed- AI/AN with other	5.36 (3.80-6.91)	
Maternal Age (years)		0.202
20-24	5.45 (4.55-6.35)	
25-29	5.13 (4.13-6.13)	
30-34	4.46 (3.55-5.36)	
≥35	3.80 (2.31-5.29)	
PREGNANCY CHARACTERISTICS		
Prepregnancy BMI (kg/m^2)		<0.001[d]
<18.5 Underweight	-0.52 (-5.98-4.95)	
18.5-24.9 Normal	1.90 (1.20-2.61)	
25.0-29.9 Overweight	8.09 (6.93-9.26)	
≥30.0 Obese	7.00 (6.18-7.82)	
Parity		<0.001[d]
First Birth	7.60 (6.37-8.83)	
Second Birth	3.90 (3.36-4.44)	
Entry into Prenatal Care		0.901
1st Trimester	5.03 (4.46-5.59)	
2nd Trimester	5.39 (3.56-7.22)	
3rd Trimester or no PNC	4.76 (2.27-7.25)	
Any Reported Diabetes[e]		0.337
Yes	5.82 (4.05-7.60)	
No	4.91 (4.36-5.47)	
Smoking During Pregnancy[f]		0.230
Yes	4.28 (2.98-5.59)	
No	5.16 (4.58-5.73)	
Reported Nausea		<0.001[d]
Yes	3.66 (2.77-4.54)	
No	5.71 (5.05-6.38)	
Gestational Age[g]		<0.001[d]
Preterm	1.67 (0.65-2.70)	
Term	5.35 (4.76-5.93)	
Post-term	6.55 (4.06-9.05)	
Infant Gender		0.135
Male	5.46 (4.62-6.29)	
Female	4.64 (3.95-5.32)	

[a] Number of pounds gained from the appropriate range of weight gain recommended for each BMI category recommended by the IOM 2009 guidelines

[b] Conditional least square means (95% CI: Confidence Interval), number of pounds gained from the appropriate range recommended

[c] Adjusted Wald F-test p-value for parameter coefficient

[d] Statistically significant, alpha = 0.05

[e] Any diabetes includes diagnosis of either prepregnancy diabetes or gestational diabetes

[f] Maternal self-report of any smoking during the last trimester

[g] Preterm: <37 weeks, Term: 37-42 weeks, Post-term: >42 weeks

Figure 6: Directed Acyclic Graphs depicting possible causal pathways for two main exposures, body mass index and gestational weight gain, and macrosomia

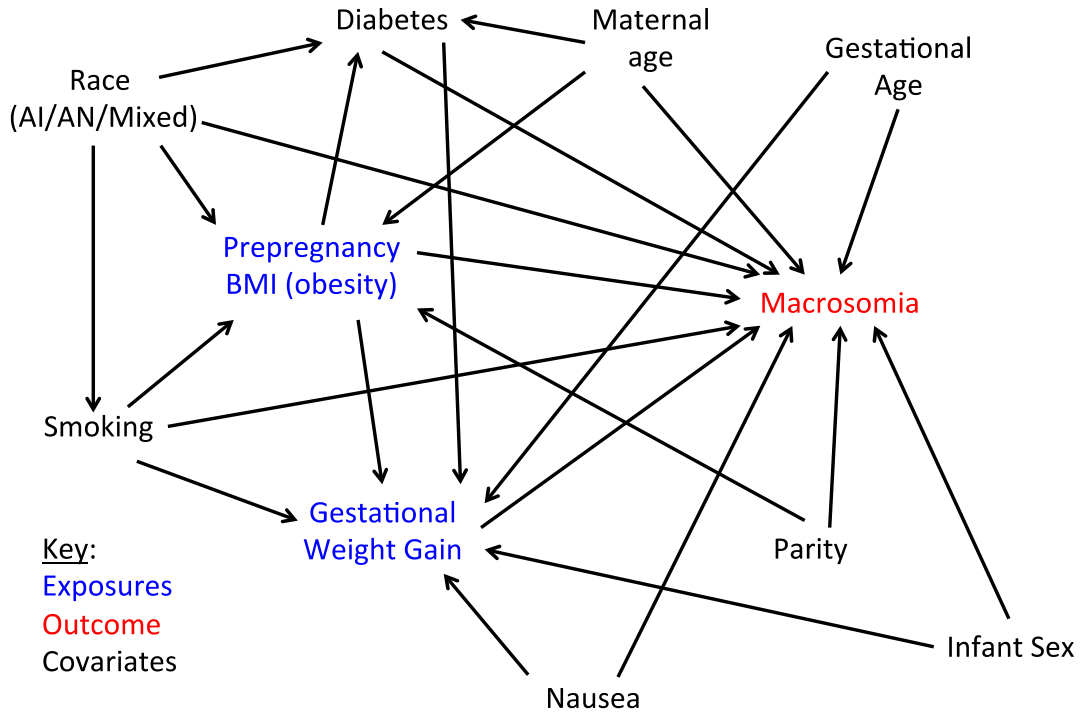

Table 10: Adjusted odds ratios of prepregnancy body mass index and gestational weight gain for macrosomia among American Indian/Alaskan Native women

	Gestational Weight Gain		
	Every 5 lbs. Under Appropriate[a]	Appropriate	Every 5 lbs. Over Appropriate[a]
	aOR (95% CI)[b]	aOR (95% CI)[b]	aOR (95% CI)[b]
Prepregnancy BMI (kg/m^2)			
<18.5 Underweight	0.49 (0.24-0.99)[c]	0.57 (0.28-1.15)	0.66 (0.33-1.34)
18.5-24.9 Normal	0.86 (0.83-0.89)[c]	1.00	1.16 (1.12-1.20)[c]
25.0-29.9 Overweight	1.08 (0.89-1.32)	1.26 (1.00-1.58)	1.46 (1.20-1.78)[c]
≥30.0 Obese	1.40 (1.17-1.69)[c]	1.63 (1.29-2.07)[c]	1.90 (1.58-2.28)[c]

8,871 women were included in analysis due to missing information on covariates

[a] Gestational weight gain above and below the recommended appropriate range by 5 lb. intervals

[b] Adjusted Odds Ratios (95% CI: Confidence Intervals) determined by multivariable logistic regression, controlled for: AI/AN race, maternal age, parity, any diabetes, smoking during pregnancy, reported nausea, gestational age of infant,

[c] Statistically significant aOR, alpha=0.05

Table 11. Geographic distribution of outcome and exposures by state among American Indian/Alaskan Native women by state of residence

	Alaska	Minnesota	Nebraska	New Mexico
	unweighted n =2,819 % (95% CI)[a]	unweighted n = 1,018 % (95% CI)[a]	unweighted n = 1,079 % (95% CI)[a]	unweighted n = 394 % (95% CI)[a]
Percent of Sample[b]	15.59 (14.98-16.22)	7.47 (6.74-8.27)	3.58 (3.39-3.79)	7.12 (6.55-7.73)
Macrosomia (≥4,000 grams)				
Yes	18.83 (17.43-20.31)	13.88 (10.72-17.78)	13.66 (11.35-16.35)	9.92 (7.38-13.20)
No	81.17 (79.69-82.57)	86.12 (82.22-89.28)	86.34 (83.65-88.65)	90.08 (86.80-92.62)
Body Mass Index (kg/m^2)				
<18.5 Underweight	1.57 (1.18-2.07)	1.94 (1.30-2.88)	3.17 (2.40-4.17)	2.39 (1.17-4.82)
18.5-24.9 Normal	40.28 (38.45-42.15)	33.37 (28.32-38.84)	40.12 (37.14-43.17)	36.81 (32.08-41.80)
25.0-29.9 Overweight	29.89 (28.18-31.65)	31.69 (26.42-37.47)	25.07 (22.28-28.08)	31.45 (27.02-36.24)
≥30.0 Obese	28.26 (26.60-29.98)	33.00 (28.10-38.30)	31.65 (28.89-34.54)	29.35 (24.98-34.15)
Gestational Weight Gain[c]				
Inadequate	25.32 (23.68-27.04)	24.79 (19.33-31.20)	24.49 (21.87-27.32)	26.58 (22.13-31.57)
Appropriate	29.66 (27.90-31.48)	28.74 (23.92-34.10)	22.58 (20.10-25.27)	32.78 (27.95-38.01)
Excess	45.02 (43.08-46.97)	46.47 (40.69-52.34)	52.93 (49.68-56.16)	40.64 (35.55-45.93)
Diabetes				
Yes	10.04 (9.01-11.16)	16.42 (13.32-20.07)	15.89 (13.75-18.29)	14.76 (11.59-18.62)
No	89.96 (88.84-90.99)	83.58 (79.93-86.68)	84.11 (81.71-86.25)	85.24 (81.38-88.41)

Table 11: Continued

	Oklahoma	Oregon	Utah	Washington
	unweighted n = 1,448 % (95% CI)[a]	unweighted n = 1,997 % (95% CI)[a]	unweighted n = 139 % (95% CI)[a]	unweighted n = 1,469 % (95% CI)[a]
Percent of Sample[b]	38.85 (36.79-40.95)	7.22 (6.88-7.57)	3.86 (3.20-4.65)	16.31 (14.99-17.72)
Macrosomia (≥4,000 grams)				
Yes	9.27 (8.29-10.35)	13.38 (11.95-14.96)	8.00 (4.44-14.01)	15.13 (11.98-18.94)
No	90.73 (89.65-91.71)	86.62 (85.04-88.05)	92.00 (85.99-95.56)	84.87 (81.06-88.02)
Body Mass Index (kg/m^2)				
<18.5 Underweight	4.12 (2.74-6.15)	2.45 (1.93-3.12)	3.27 (1.14-8.99)	2.41 (1.05-5.41)
18.5-24.9 Normal	39.37 (35.21-43.69)	39.49 (37.37-41.65)	47.49 (37.60-57.59)	43.20 (38.23-48.32)
25.0-29.9 Overweight	27.03 (23.35-31.06)	25.05 (23.17-27.03)	21.95 (15.15-30.69)	25.94 (22.32-29.91)
≥30.0 Obese	29.48 (25.75-33.51)	33.01 (30.97-35.11)	27.29 (19.41-36.89)	28.46 (24.57-32.69)
Gestational Weight Gain[c]				
Inadequate	20.27 (16.98-24.00)	17.84 (16.29-19.51)	14.92 (8.54-24.78)	24.24 (19.75-29.38)
Appropriate	30.93 (26.99-35.16)	27.21 (25.34-29.17)	35.87 (26.59-46.35)	25.75 (21.46-30.56)
Excess	48.80 (44.45-53.18)	54.95 (52.75-57.12)	49.21 (38.93-59.56)	50.01 (44.72-55.30)
Diabetes				
Yes	15.22 (12.67-18.67)	13.01 (11.42-14.77)	15.00 (9.75-22.38)	11.48 (9.15-14.29)
No	84.56 (81.33-87.33)	86.99 (85.23-88.58)	85.00 (77.62-90.25)	88.52 (85.71-90.85)

[a] Prevalence (95% CI: Confidence Interval)

[b] Weighted proportion of sample that resides in each state

[c] Weight gain categories determined by 2009 IOM guidelines by each BMI category

Table 12: Adjusted odds ratios for independent effects of prepregnancy body mass index and gestational weight gain on macrosomia among American Indian/Alaskan Native women by state of residence

	Alaska	Minnesota	Nebraska	New Mexico
	unweighted n=2,301	unweighted n=856	unweighted n=943	unweighted n=325
	aOR (95%CI)[a]	aOR (95%CI)[a]	aOR (95%CI)[a]	aOR (95%CI)[a]
Cases of Macrosomia	392	124	112	36
Prepregnancy BMI (kg/m^2)				
<18.5 Underweight vs. 18.5-24.9 Normal	0.59 (0.16-2.21)	0.98 (0.22-4.41)	0.49 (0.15-1.60)	-[b]
25.0-29.9 Overweight vs. 18.5-24.9 Normal	1.45 (1.09-1.92)[c]	1.31 (0.67-2.56)	1.25 (0.66-2.37)	1.55 (0.60-4.02)
≥30.0 Obese vs. 18.5-24.9 Normal	1.92 (1.44-2.55)[c]	1.63 (0.63-4.24)	1.63 (0.99-2.68)	1.82 (0.63-5.25)
Gestational Weight Gain[d]				
Every 5 lbs. under appropriate	0.86 (0.82-0.90)[c]	0.86 (0.79-0.94)[c]	0.86 (0.79-0.94)[c]	0.86 (0.74-1.00)
Every 5 lbs. gained over appropriate	1.16 (1.11-1.22)[c]	1.16 (1.06-1.27)[c]	1.16 (1.07-1.26)[c]	1.16 (1.00-1.35)

	Oklahoma	Oregon	Utah	Washington
	unweighted n=1,331	unweighted n=1,770	unweighted n=116	unweighted n=1,229
	aOR (95%CI)[a]	aOR (95%CI)[a]	aOR (95%CI)[a]	aOR (95%CI)[a]
Cases of Macrosomia	429	243	10	168
Prepregnancy BMI (kg/m^2)				
<18.5 Underweight vs. 18.5-24.9 Normal	0.92 (0.38-2.25)	1.08 (0.45-2.60)	-[b]	0.24 (0.03-2.21)
25.0-29.9 Overweight vs. 18.5-24.9 Normal	1.07 (0.72-1.60)	1.35 (0.92-1.99)	8.08 (0.48-134.88)	1.08 (0.57-2.05)
≥30.0 Obese vs. 18.5-24.9 Normal	1.60 (1.09-2.35)[c]	1.95 (1.39-2.74)[c]	4.81 (0.65-35.58)	1.22 (0.68-2.20)
Gestational Weight Gain[d]				
Every 5 lbs. under appropriate	0.82 (0.77-0.88)[c]	0.90 (0.86-0.95)[c]	0.86 (0.71-1.05)	0.90 (0.84-0.97)[c]
Every 5 lbs. gained over appropriate	1.22 (1.14-1.41)[c]	1.11 (1.06-1.16)[c]	1.16 (0.96-1.41)	1.11 (1.03-1.19)[c]

[a] Adjusted Odds Ratios (95% CI: Confidence Intervals) determined by multivariable logistic regression, controlled for: AI/AN race, maternal age, parity, any diabetes, smoking during pregnancy, reported nausea, gestational age of infant, and infant sex

[b] No cases of macrosomia within stratum

[c] Statistically significant aOR, alpha=0.05

[d] Gestational weight gain above and below appropriate weight gain recommended by 5 lb. intervals

Table 13: Adjusted odds ratios of prepregnancy body mass index and gestational weight gain on macrosomia among non-diabetic American Indian/Alaskan Native women

	Gestational Weight Gain		
	Every 5 lbs. Under Appropriate[a]	Appropriate	Every 5 lbs. Over Appropriate[a]
	aOR (95% CI)[b]	aOR (95% CI)[b]	aOR (95% CI)[b]
Prepregnancy BMI (kg/m^2)			
<18.5 Underweight	0.49 (0.22-1.09)	0.57 (0.25-1.26)	0.66 (0.29-1.47)
18.5-24.9 Normal	0.86 (0.83-0.89)[c]	1.00	1.16 (1.12-1.20)[c]
25.0-29.9 Overweight	1.12 (0.91-1.37)	1.30 (1.01-1.66)[c]	1.51 (1.23-1.85)[c]
≥30.0 Obese	1.43 (1.17-1.75)[c]	1.67 (1.28-2.17)[c]	1.93 (1.58-2.37)[c]

7,662 women were included in analysis due to missing information on covariates

[a] Gestational weight gain above and below the recommended appropriate range by 5 lb. intervals

[b] Adjusted Odds Ratios (95% CI: Confidence Intervals) determined by multivariable logistic regression, controlled for: AI/AN race, maternal age, parity, smoking during pregnancy, reported nausea, gestational age of infant, and infant sex

[c] Statistically significant aOR, alpha=0.05