2017

Association of Gestational Weight Gain during Twin Gestations and Adverse Maternal Outcomes

Kerry Spillane
University of South Carolina

ASSOCIATION OF GESTATIONAL WEIGHT GAIN DURING TWIN GESTATIONS AND ADVERSE MATERNAL OUTCOMES

by

Kerry Spillane

Bachelor of Arts
University of South Carolina, 2014

Submitted in Partial Fulfillment of the Requirements

For the Degree of Master of Science in Public Health in

Epidemiology

Norman J. Arnold School of Public Health

University of South Carolina

2017

Accepted by:

Nansi Boghossian, Director of Thesis

Andrew Ortaglia, Reader

Jihong Liu, Reader

Cheryl L. Addy, Vice Provost and Dean of the Graduate School

ACKNOWLEDGEMENTS

I am indebted to several individuals for their constant encouragement, support, and assistance with this thesis and my Master's degree. I would like to begin by thanking my wonderful fiancé, Mauk, for the most valuable and consistent love, patience, and motivation. I love you. Thank you to my mom and Shannon, who may have not fully understood what I have been working on for the last two years, but nevertheless provided unwavering love, support, and faith in me. I am so lucky to have you all as my family!

I would also like to acknowledge the guidance and support of the individual members of my thesis committee. I am especially grateful to Dr. Nansi Boghossian and Dr. Andrew Ortaglia for their close involvement in this thesis, as well as the entirety of my graduate school career. Thank you both for your continuous guidance and encouragement, and for answering countless questions over the last two years.

And finally, I would like to acknowledge the eight other women in my cohort. I am very lucky to have shared this experience (including all the stress, trials and tribulations) and countless laughs with such intelligent, motivated, and strong women. I am honored to represent women in science with you all!

ABSTRACT

Objective: To examine the association between gestational weight gain (GWG) in twin gestations and the odds of adverse maternal outcomes.

Setting and Participants: Study population included 3,081 women with a twin gestation delivered between 23-42 gestational weeks from 19 hospitals across the United States (2002-2008) participating in the Consortium on Safe Labor (CSL) study.

Main Outcomes: Main outcomes of interest included: gestational hypertension, preeclampsia, gestational diabetes mellitus, and cesarean delivery.

Methods: Quantile regression estimated the 25^{th} and 75^{th} percentiles of total GWG, respective of pre-pregnancy BMI and gestational age at delivery, and was used to create our new total GWG guidelines. Participants' concordance with our GWG guidelines was categorized as below, within, or above respective of total GWG, pre-pregnancy BMI, and gestational age at delivery. Logistic regression was used to estimate adjusted odds ratios and 95% confidence intervals assessing associations between concordance with our GWG guidelines and adverse maternal outcomes of interest. All logistic regression models were adjusted for maternal age, race/ethnicity, pre-pregnancy BMI, marital status, smoking, alcohol, gestational age at delivery, hospital site number, insurance type, and parity. Participants with chronic hypertension and diabetes mellitus were excluded from analyses for gestational hypertension and preeclampsia, and gestational diabetes mellitus, respectively.

Results: We found that after adjusting for confounders, GWG above our guidelines was associated with increased odds of gestational hypertension [OR: 2.04, 95% CI: 1.60, 2.61], and preeclampsia [OR: 1.63, 95% CI: 1.26, 2.10], while GWG below our guidelines was associated with decreased odds of cesarean delivery [OR: 0.79, 95% CI: 0.64, 0.97]. In the adjusted models, a 5 kilogram increase in total GWG was associated with increased odds of gestational hypertension [OR: 1.32, 95% CI: 1.23, 1.42], preeclampsia [OR: 1.16, 95% CI: 1.01, 1.33] (when total GWG was < 19 kilograms), and cesarean delivery [OR: 1.08, 95% CI: 1.01, 1.15]. Adjusted results for gestational diabetes mellitus were not significant.

Conclusions: We found evidence of an increase in the odds of developing gestational hypertension, preeclampsia (when total GWG < 19 kilograms), and having a cesarean delivery for every 5 kilogram increase in total GWG. Weight gain above our guidelines was associated with increased odds of developing gestational hypertension and preeclampsia, while weight gain below our guidelines was associated with decreased odds of having a cesarean delivery. Further research is required to understand the complex association between GWG and adverse maternal outcomes in twin gestations.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS iii

ABSTRACT iv

LIST OF TABLES viii

LIST OF FIGURES x

LIST OF ABBREVIATIONS xi

CHAPTER 1 INTRODUCTION 1

1.1 BACKGROUND 1

1.2 PURPOSE AND SPECIFIC AIMS 3

1.3 ORGANIZATION OF THESIS 4

CHAPTER 2 LITERATURE REVIEW 6

2.1 SEARCH METHODS 6

2.2 FINDINGS 7

2.3 DISCUSSION 10

2.4 MOVING FORWARD 11

CHAPTER 3 METHODS 18

3.1 STUDY POPULATION 18

3.2 EXPOSURE OF INTEREST 19

3.3 OUTCOMES OF INTEREST 19

3.4 POTENTIAL CONFOUNDERS 20

3.5 Analysis 21

Chapter 4 Results 29

4.1 Study Population 29

4.2 Gestational Hypertension 30

4.3 Preeclampsia 31

4.4 Gestational Diabetes Mellitus 32

4.5 Cesarean Delivery 33

Chapter 5 Discussion 39

5.1 Summary of Results 39

5.2 Gestational Hypertension 39

5.3 Preeclampsia 40

5.4 Gestational Diabetes Mellitus 41

5.5 Cesarean Delivery 42

5.6 Differences and Gaps In the Literature 42

5.7 Strengths And Limitations 44

5.8 Future Studies 45

5.9 Conclusions 46

References 47

Appendix A: Full tables from SAS Output Logistic Regression Generalized Linear Models 49

LIST OF TABLES

Table 2.1 Epidemiologic Studies on the Association Between Gestational Weight Gain (GWG) in Twin Gestations and Adverse Maternal Outcomes 14

Table 3.1 Classification of Outcomes of Interest..20

Table 3.2 Demographic Characteristics by Availability of Pre-Pregnancy BMI Status....25

Table 4.1 Demographic Characteristics Based on Concordance with the Quantile Regression Total Gestational Weight Gain (GWG) Guidelines among Twin Gestations in the CSL Study (N=3,081) 34

Table 4.2 Unadjusted Odds Ratios of Adverse Pregnancy Outcomes by Concordance with the Quantile Regression Total Gestational Weight Gain (GWG) Guidelines among Twin Gestations in the CSL Study 36

Table 4.3 Adjusted Odds Ratios of Adverse Pregnancy Outcomes by Concordance with the Quantile Regression Total Gestational Weight Gain (GWG) Guidelines among Twin Gestations in the CSL Study 36

Table 4.4 Unadjusted Odds Ratios of Total Gestational Weight Gain (GWG) and Adverse Pregnancy Outcomes among Twin Gestations in the CSL Study......................................37

Table 4.5 Adjusted Odds Ratios of Total Gestational Weight Gain (GWG) and Adverse Pregnancy Outcomes among Twin Gestations in the CSL Study......................................37

Table 4.6 Quantile Regression Total Gestational Weight Gain (GWG) Guidelines for Twin Gestations, Stratified by Pre-Pregnancy Body Mass Index (BMI) Category (in kilograms) 38

Table A.1 Gestational Hypertension and Concordance with Quantile Regression Gestational Weight Gain (GWG) Guidelines 49

Table A.2 Preeclampsia and Concordance with Quantile Regression Gestational Weight Gain (GWG) Guidelines 51

Table A.3 Gestational Diabetes Mellitus and Concordance with Quantile Regression Gestational Weight Gain (GWG) Guidelines 53

Table A.4 Cesarean Delivery and Concordance with Quantile Regression Gestational Weight Gain (GWG) Guidelines 55

Table A.5 Cesarean Delivery and Total Gestational Weight Gain (GWG).......................57

Table A.6 Cesarean Delivery and Total Gestational Weight Gain (GWG).......................59

Table A.7 Cesarean Delivery and Total Gestational Weight Gain (GWG).......................61

Table A.8 Cesarean Delivery and Total Gestational Weight Gain (GWG).......................62

Table A.9 Association Between Gestational Hypertension and Total GWG and Concordance with GWG Guidelines among Twins in the CSL Study..............................64

Table A.10 Association Between Preeclampsia and Total GWG and Concordance with GWG Guidelines among Twins in the CSL Study 65

Table A.11 Association Between Gestational Diabetes Mellitus and Total GWG and Concordance with GWG Guidelines among Twins in the CSL Study..............................66

Table A.12 Association Between Cesarean Delivery and Total GWG and Concordance with GWG Guidelines among Twins in the CSL Study..67

LIST OF FIGURES

Figure 2.1 Flow Chart of Literature Review Search 13

Figure 3.1 Directed Acyclic Graph (DAG) Minimally Adjusted Model 24

Figure 3.2 Plotted Regressions for Gestational Hypertension 27

Figure 3.3 Plotted Regressions for Preeclampsia 27

Figure 3.4 Plotted Regressions for Gestational Diabetes Mellitus 28

Figure 3.5 Plotted Regressions for Cesarean Delivery 28

LIST OF ABBREVIATIONS

A.OR .... Adjusted Odds Ratio

ART .... Assisted Reproductive Technology

BMI .... Body Mass Index

CI .... Confidence Interval

CSL .... Consortium on Safe Labor

DAG .... Direct Acyclic Graph

GDM .... Gestational Diabetes Mellitus

GWG .... Gestational Weight Gain

ICD-9 .... International Classification of Diseases, Ninth Edition

IOM .... Institute of Medicine

KG .... Kilograms

LBS .... Pounds

MULTI .... Multi-Racial

NICHD .... National Institute of Child Health and Human Development

NHW .... Non-Hispanic White

OR .... Odds Ratio

PI .... Pacific Islander

RR .... Relative Risk

SAS .... Statistical Analysis Software

SGA.. Small-For-Gestational Age

US .... United States

WHO.. World Health Organization

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

Over the last three decades, there has been a substantial increase in twin birth rates in the United States (U.S.)[2]. Twins account for an estimated 3.3% of all live births in the U.S.[7]. The substantial increase in twin gestations has been attributed to the trend in pregnancy delay, with multiples naturally occurring at greater rates among older women, and the increased use of assisted reproductive technology (ART)[2,12,14]. Twin gestations are commonly associated with higher rates of low birthweight, preterm delivery, gestational diabetes mellitus (GDM), preeclampsia, cesarean delivery, and infant mortality[16]. One in six neonatal deaths (defined as death within the first 28 days) is a twin, and approximately 60% of all twin gestations are delivered preterm (defined as < 37 completed weeks of gestation)[3,5].

As the rate of twin gestations continues to increase in the U.S., it is of supreme importance to focus on reducing the risks of associated adverse maternal outcomes. Weight gain during pregnancy has been associated with increased risks of GDM, gestational hypertension, preeclampsia, cesarean delivery, and preterm delivery for both singletons and twins[3,13]. The current epidemiological literature analyzing the association between gestational weight gain (GWG) and maternal outcomes is limited, and has been largely focused on singletons. Twin gestations are considered too different from singleton gestations to be included in the same analyses. The differences in gestational growth patterns and the increased risks for preterm delivery, low birth weight, and small-for-gestational age (SGA), are some of the most commonly noted differences between twin and singleton gestations. Additionally, studies examining the impact of GWG in twin gestations have been primarily focused on neonatal outcomes.

In 2009, the Institute of Medicine (IOM) issued the following provisional total GWG guidelines for term (defined as 37-42 gestational weeks) twin gestations for three pre-pregnancy body mass index (BMI) categories (using the World Health Organization (WHO) definitions): 17-25 kilograms (kg) for normal-weight (18.50-24.9 kg/m^2); 14-23 kg for overweight (25.0-29.9 kg/m^2); 11-19 kg for obese ($\geq$30 kg/m^2)[9]. There were no provisional guidelines issued for women with an underweight pre-pregnancy BMI (<18.50 kg/m^2) due to insufficient evidence[9]. These guidelines reflect the interquartile range (IQR), between the 25th and 75th percentiles, of cumulative GWG for women who delivered twins between 37-42 gestational weeks, with an average twin birthweight of 2,500 grams or greater[9,11]. The IOM deemed these guidelines as provisional since they are entirely based on weight gain percentiles in a specific population of twin gestations, and because the guidelines committee did not conduct the same rigorous, extensive analysis of associated outcomes for multiples as it did for singletons[,11].

The IOM provisional GWG guidelines intend to optimize maternal and neonatal outcomes associated with GWG. However, the guidelines for twin gestations are only intended for term deliveries, and as such only apply to an estimated 40% of all twin gestations[5,9,11]. Furthermore, these provisional guidelines do not properly account for the built-in correlation between gestational duration and total GWG. Women who deliver at earlier gestational ages clearly do not have equal opportunities to gain weight compared to women who deliver at later gestational ages. The most commonly utilized method for adapting the provisional IOM guidelines for preterm deliveries is the average weekly rate of GWG (computed as total GWG divided by gestational age at delivery). However, this average weekly rate calculation assumes a linear increase in GWG throughout pregnancy, and does not properly account for the differences in weight gain patterns by trimester. To best examine the association between GWG and the risk of adverse maternal outcomes in all twin gestations, the GWG guidelines must accurately account for the built-in relationship between GWG and gestational age.

Given the increased prevalence of twins in the U.S., the general higher risk of adverse outcomes in twins compared to singletons, and the different growth trajectories for twins and singletons, it is necessary to: 1) determine optimal GWG guidelines for all twin gestations and 2) focus research on the association between GWG in twin gestations and adverse maternal outcomes.

1.2 PURPOSE AND SPECIFIC AIMS

The purpose of this thesis will be to examine the association between GWG and adverse maternal outcomes (including gestational hypertension, preeclampsia, GDM, and cesarean delivery) in twin gestations. Specifically, we aim to:

I. Examine GWG as a function of gestational age among twin gestations.

   Research Question: Is the relationship between GWG and gestational age approximately linear?

Hypothesis for Aim I: We hypothesize that GWG is not linearly associated with gestational age. A non-parametric function should be used to assess the functional relationship between GWG and gestational age. As such quantile regression should be used to create new GWG guidelines that account for the relationship between GWG and gestational duration in twin gestations.

II. Examine the association between both total GWG and concordance with our quantile regression GWG guidelines and the odds of gestational hypertension, preeclampsia, GDM, and cesarean delivery in twin gestations.

Research Question: Are women with total GWG below or above our developed GWG guidelines at greater risk of developing adverse maternal outcomes of interest compared to women with GWG within our guidelines? Do the odds of adverse maternal outcomes of interest increase as total GWG increases?

Hypothesis for Aim II: Based on previous findings, we hypothesize that the odds of developing gestational hypertension, preeclampsia, GDM, and cesarean delivery are higher for women who gain weight above our GWG guidelines compared to women with weight gain within our guidelines, and that the odds of adverse maternal outcomes increase as total GWG increases.

1.3 ORGANIZATION OF THESIS

Chapter I has provided sufficient background information on both the exposure and population of interest, in addition to outlining the main research aims and objectives of this thesis. Chapter II will consist of a literature review covering previous findings on the association of GWG and adverse maternal outcomes in twin gestations, and demonstrate how this thesis will address the gaps in the current epidemiological literature. Chapter III will explain in detail the methods of research and statistical techniques used to analyze the data. The results of the analyses will be presented in Chapter IV. Chapter V will provide a summary, thorough discussion of findings, and conclusion of the research.

CHAPTER 2

LITERATURE REVIEW

2.1 SEARCH METHODS

Studies evaluating the association between GWG and adverse maternal outcomes in twin gestations were identified through PubMed. Advanced search criteria limited the search results to studies published in the English language, performed on human subjects, and with a full-text edition available. Keywords used to conduct the literature search included: gestational weight gain, twins, multiples. After limiting the search to the above criteria, 43 articles were identified in PubMed.

We reviewed all 43 articles (titles and abstracts) to identify studies focusing on GWG in twin gestations and maternal outcomes. We screened 13 full articles to confirm they were examining the association between GWG in twin gestations and maternal outcomes. From there, seven studies were assessed for eligibility. To be deemed eligible, studies had to focus on our association of interest using a specified measure of GWG as one of the primary exposures of interest. The bibliographies of each eligible article were then carefully reviewed to identify additional studies that were not present in the original PubMed search results. An additional four articles were identified from the bibliographies and then assessed for eligibility. After applying the above exclusion criteria, a final six studies were included in the literature review. Please refer to Figure 2.1 for a flowchart of the literature review search methods (page 13).

2.2 FINDINGS

All six studies included in the literature review were retrospective cohort studies [5-7, 11, 12, 14]. All studies used the 2009 IOM GWG guidelines for twin gestations to categorize and assess GWG [5-7, 11, 12, 14]. All subsequent references to "guidelines" throughout Chapter 2 refer to the IOM 2009 provisional guidelines. Lal & Kominiarek and Pettit et al measured GWG as the weekly rate of GWG [11, 14]. Weekly rate of weight gain was calculated as total GWG divided by gestational age at delivery (in weeks). They then also divided the 2009 IOM guidelines by 37 to define optimal weekly guidelines, and create the adequacy of adherence to GWG guidelines categories[11, 14]. Lucovnik et al evaluated GWG as the total change in gestational BMI; calculated as pre-pregnancy BMI subtracted from BMI at time of delivery[12]. Fox et al 2010, Fox et al 2011, and Gavard & Artal all measured GWG as total GWG [5-7]. Total GWG was calculated by subtracting the participant's recorded pre-pregnancy weight from the recorded weight at labor and delivery admission. Five studies focused on GWG throughout the entire pregnancy duration, while Pettit et al only focused on GWG between 20-28 gestational weeks[14].

The most commonly controlled for variables included: maternal age, maternal race/ethnicity, gestational age at delivery (weeks), smoking during pregnancy, alcohol consumption during pregnancy, parity, pre-pregnancy BMI, chronic hypertension, and chronic diabetes mellitus. Additional variables less commonly controlled for included: use of ART, socioeconomic status, education level, and cervical length. All variables controlled for in each study are listed in Table 2.1. The main findings for the six studies included in the literature review are summarized by outcome in Table 2.1 which presents study design, sample size, measure of GWG, method of comparison, control variables, and main findings.

Gestational Hypertension

Four studies examined the association between GWG and gestational hypertension in twin gestations[5,6,11,14]. Lal & Kominiarek found a statistically significant positive trend between increasing GWG and gestational hypertension for women with an underweight/normal-weight pre-pregnancy BMI ($p=0.01$), and for women with an obese pre-pregnancy BMI ($p<0.01$)[11]. However, they did not find any significant differences in the rates of gestational hypertension for women with an overweight pre-pregnancy BMI as GWG increased ($p=0.06$)[11]. Fox et al 2010 did not find any significant associations between adequacy of weight gain (comparing weight gain within and above the recommend guidelines to weight gain below the guidelines) and gestational hypertension across all pre-pregnancy BMI categories (normal-weight $p=0.282$; overweight $p=0.410$; obese $p=0.771$)[5]. Fox et al 2011 also did not report any significant differences in the likelihood of developing gestational hypertension as total GWG increased across the three pre-pregnancy BMI groups in any of their analyses ($p=0.943$)[6]. Pettit et al did not find any significant differences in the rates of gestational hypertension when comparing women with adequate GWG (defined as within or below) to those with excessive GWG ($p=0.34$)[14].

Preeclampsia

Four of the studies examined the association between GWG and preeclampsia [6,7,11,14]. Fox et al 2011 did not find any significant differences in the rates of preeclampsia as total GWG increased in any of their analyses ($p=0.864$)[6]. Gavard et al found a significant positive trend between increasing GWG and the development of preeclampsia ($p<0.05$)[7]. Women who gained greater than 42 pounds had 1.72 times the odds of developing preeclampsia compared to women who gained 25-42 pounds, with borderline statistical significance (a.OR 1.72, 95% CI 1.00-2.99, $p=0.052$)[7]. Gavard et al additionally found a significant positive trend between increasing GWG and preeclampsia in a sub-analysis for twin pairs with concordant birth weights (defined as difference in birth weights < 20%)[7]. Lal & Kominiarek found a significant association between increasing total GWG and the likelihood of developing preeclampsia across all pre-pregnancy BMI categories ($p<0.01$)[11]. Pettit et al reported finding a significantly higher rate of preeclampsia among women with adequate GWG at 20-28 gestational weeks compared to women with inadequate GWG at 20-28 gestational weeks ($p=0.01$)[14].

Gestational Diabetes

Five of the studies assessed the association between GWG and the risk of GDM[5,6,11,12,14]. Pettit et al found a borderline statistically significant increase in the rate of GDM for women with inadequate GWG at 20-28 gestational weeks compared to those with adequate GWG ($p=0.06$)[14]. Fox et al 2011 did not find any significant differences in the risk of GDM across all pre-pregnancy BMI categories ($p=0.157$)[6]. Lal & Kominiarek found a positive trend between the development of GDM and increasing GWG for women with an overweight pre-pregnancy BMI ($p=0.04$)[11]. They also found that women with an obese pre-pregnancy BMI were more likely to develop GDM as total GWG increased ($p<0.01$)[11]. However, they did not find any significant differences in the rates of GDM for women with underweight/normal-weight pre-pregnancy BMIs in relation to

GWG adequacy (p=0.2)[11]. Fox et al 2010 did not find any significant differences in the rates of GDM for those with normal weight gain compared to those with low weight gain across all pre-pregnancy BMI categories (normal-weight p=0.499; overweight p=0.739; obese p=0.081)[5]. Lucovnik et al reported that women who developed GDM were more likely to have higher pre-pregnancy BMIs (p<0.001)[12]. Overall, BMI change during pregnancy was significantly less in twin gestations with GDM compared to those without GDM (p<0.001)[12]. This finding is surprising, since it appears that women who gained less weight during pregnancy were more likely to develop GDM. This unexpected change may be explained by dietary counseling intervention after disease diagnosis[12].

Cesarean Delivery

The association between GWG and cesarean delivery was only examined in two studies. Gavard et al and Pettit et al examined the association between GWG and cesarean delivery in twin gestations[7, 14]. Gavard et al found a borderline statistically significant positive trend between increasing total GWG and having a cesarean delivery (p=0.06)[7]. Significant positive trends between increasing GWG and cesarean delivery were also found in a sub-analysis of twin pairs with concordant birthweights (p<0.05)[7]. Pettit et al did not find any significant differences in the rates of cesarean deliveries between women with adequate GWG compared to women with excessive GWG at 20-28 gestational weeks (p=0.34)[14].

2.3 DISCUSSION

The current epidemiological literature analyzing the impact of GWG in twin gestations on adverse maternal outcomes is limited. Further, studies that focus on GWG in twin gestations often exclude preterm deliveries since the IOM provisional GWG guidelines are only intended for term deliveries. Additionally, in most studies, women with an underweight BMI are commonly excluded or combined with the normal-weight category due to the lack of specific 2009 IOM guidelines for women with an underweight pre-pregnancy BMI. It is important to evenly represent and assess the associations of interest for each pre-pregnancy BMI category to make accurate comparisons, and to improve maternal outcomes for all twin gestations.

There are several strengths of the current research evaluating the association between GWG in twin gestations and adverse maternal outcomes. The use of medical records, birth certificates, and strong participation from large hospital networks has made it feasible to identify twin gestations and include them in epidemiological research studies. Large databases have also enabled the current research to obtain relatively diverse sample populations, which greatly improved the generalizability of results.

2.4 MOVING FORWARD

To improve the epidemiological research on the association between GWG and adverse maternal outcomes in twin gestations, researchers should aim to conduct larger, prospective cohort studies. Prospective studies would enable researchers to obtain more accurate measurements of pre-pregnancy BMI, weight gain throughout pregnancy, and gestational age. Larger sample populations may also potentially improve the distribution of participants across pre-pregnancy BMI categories and adequacy of adherence to GWG guidelines categories to improve the accuracy and generalizability of results.

The available current literature calls into question the 2009 IOM recommended provisional GWG guidelines for twin gestations. It is evident from current findings that further investigation is required to develop and define appropriate and optimal GWG guidelines for all twin gestations. Due to the increased rates of preterm birth, low birth weight, and SGA in twin gestations, it is imperative for GWG guidelines to properly account for the pattern of weight gain in twin gestations. As such, additional research should determine optimal GWG in twin gestations to improve maternal outcomes.

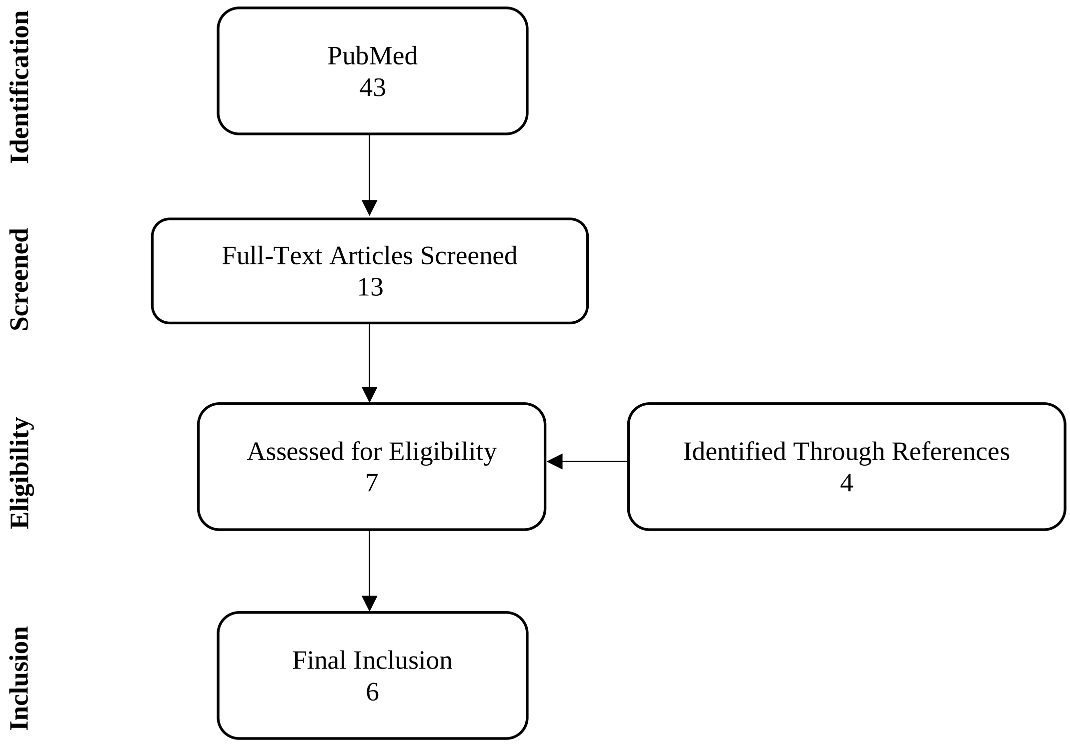

Figure 2.1 Flow Chart of Literature Review Search

Table 2.1 Epidemiologic Studies on the Association Between Gestational Weight Gain (GWG) in Twin Gestations and Adverse Maternal Outcomes

Author, Time, Place	Study Design, Sample Size	Measure of Gestational Weight Gain	Comparison Groups	Maternal Outcomes of Interest	Control Variables	Main Findings
Fox et al, 2010, US[5]	Retrospective Cohort 297 twin pregnancies	Total GWG	Categories of adequacy of adherence (normal weight gain, low weight gain) to 2009 IOM guidelines across pre-pregnancy BMI categories, dividing all guidelines by 37 to determine IOM recommended weight gain per week	Gestational hypertension, GDM	Pre-pregnancy BMI, gestational age at delivery	"There were no significant differences in the likelihood of gestational hypertension or GDM for those with normal weight gain compared to those with low weight gain across all three pre-pregnancy BMI categories (normal-weight: p=0.282, p=0.499; overweight: p=0.410, p=0.739; obese: p=0.771, p=0.081, respectively)."[5]
Fox et al, 2011, US[6]	Retrospective Cohort 170 term twin pregnancies	Total GWG	Categories of adequacy of adherence (below, within, above) to 2009 IOM guidelines compared across pre-pregnancy BMI categories	GDM, gestational hypertension, preeclampsia	Pre-pregnancy BMI, maternal age, IVF pregnancy, multifetal reduction, chorionicity, gestational age at delivery, maternal race	"No significant differences in the likelihood of gestational hypertension, preeclampsia, or GDM across the three pre-pregnancy BMI groups in any of the analyses (p=0.943; p=0.864; p=0.157, respectively). When preterm births were compared to term births, there were no significant differences in mean weight gain per week in all twin pregnancies with GDM compared to all twin pregnancies without GDM (p=0.273), as well as twin pregnancies with gestational

						hypertension or preeclampsia to all twin pregnancies without hypertension or preeclampsia (p=0.315).”[6]
Gavard & Artal, 2014, US[7]	Retrospective Cohort 405 twin pregnancies born to women with obese pre-pregnancy BMIs	Total GWG	Three 2009 IOM guidelines categories of GWG (< 25 lbs., 25-42 lbs., >42 lbs.) compared across three BMI classifications of obesity [class I (≥30.0 - < 35.0 kg/m^2), class II (≥35.0 - <40.0 kg/m^2), class III (≥40.0 kg/m^2)]. Also, looked at outcomes assessed by GWG categories per concordant and discordant birthweight pairs	Preeclampsia, cesarean delivery	Maternal age, race, education, pre-pregnancy BMI, socioeconomic status, smoking status, parity, chronic diabetes, chronic hypertension, gestational age at delivery	“A significant increasing trend with GWG was found for preeclampsia (p <0.05). An increasing trend with gestational weight gain for cesarean delivery was of borderline significant (p=0.06). Women who gained >42 pounds had a borderline significantly higher odds of preeclampsia than women who gained 25-42 pounds (a.OR 1.72, 95% CI 1.00-2.99). Analyses by obesity class showed that women who gained >42 pounds always had an elevated, although nonsignificant, odds of preeclampsia than women who gained 25-42 pounds (data not shown). Significant increasing trends with GWG were found for preeclampsia (p<0.05) and cesarean delivery (p<0.05) in concordant twin pairs.”[7]
Lal & Kominiarek, 2015, US[11]	Retrospective Cohort 2,654 twin pregnancies	Weekly rate of GWG (total GWG divided by gestational age in weeks at delivery)	Categories of adequacy of adherence (below, within, above) to 2009 IOM guidelines divided by 37 compared across pre-pregnancy BMI categories	Gestational hypertension, GDM, preeclampsia	Pre-pregnancy BMI, maternal age, parity, race, chronic hypertension	“For women with underweight/normal-weight pre-pregnancy BMI, the rate of preeclampsia and gestational hypertension increased as GWG increased (p<0.01; p=0.01, respectively). The rates of preeclampsia and GDM in

						women with an overweight pre-pregnancy BMI increased as GWG increased ($p<0.01$; $p=0.04$, respectively). There were no significant differences in the rates of GDM for women with underweight/normal-weight pre-pregnancy BMIs ($p=0.2$), or gestational hypertension for women with an overweight pre-pregnancy BMI ($p=0.6$) in relation to GWG adequacy. Women with an obese pre-pregnancy BMI were statistically significantly more likely to develop preeclampsia, gestational hypertension, and GDM (all $p<0.01$) with increasing GWG." [11]
Lucovnik et al, 2014, Slovenia[12]	Retrospective Cohort 2,046 twin pregnancies delivered at >36 weeks, compared to 6,138 singletons	Total Gestational BMI change (BMI at delivery – pre-gravid BMI)	Twins were compared to singletons (matched by parity and maternal age 3:1), as well as twin pregnancies with diagnosis of GDM compared to those with diagnosis of preeclampsia	Preeclampsia, GDM	Number of fetuses, maternal age, parity, diagnosis of gestational diabetes or preeclampsia	"Mothers with twin pregnancies who developed preeclampsia and GDM had significantly higher pre-pregnancy BMIs than mothers who did not develop preeclampsia or GDM ($p<0.001$). BMI change was significantly less in twin pregnancies with GDM (5.2 ± 2.4kg/m^2 versus 6.1 ± 2.2 kg/m^2, $p<0.001$). Women who gained less weight during pregnancy were more likely to have GDM, which may have been caused by dietary counseling after GDM diagnosis. There was an insignificant trend toward a

						higher incidence of preeclampsia with greater BMI change in twin pregnancies (p=0.07). Higher pre-pregnancy BMI was associated with a higher incidence of preeclampsia and GDM in both twin and singleton pregnancies”[12]
Pettit et al, 2015, US[14]	Retrospective Cohort 489 twin pregnancies	Weekly rate of GWG	Categories of adequacy of adherence (adequate, inadequate) to 2009 IOM guidelines divided by 37 across pre-pregnancy BMI categories	Gestational hypertension, GDM, preeclampsia, cesarean delivery	History of prior preterm birth, short cervical length, chorionicity	“There was a borderline significant positive difference in the rates of GDM for women with inadequate GWG at 20-28 weeks compared to those with adequate GWG at 20-28 weeks (p=0.06). There were no significant differences in the rates of cesarean delivery and gestational hypertension between women with adequate and excessive GWG (p=.0.39; p=0.34, respectively). There was a significantly higher rate of preeclampsia or HEELP syndrome in women with adequate GWG at 20-28 weeks compared to women with inadequate GWG at 20-28 weeks (p=0.01)”[14]

**Abbreviations: p is the abbreviation for P-value; a.OR is the abbreviation for Adjusted Odds Ratio, 95% CI is the abbreviation for 95% Confidence Interval*

1. All pre-pregnancy BMI categories refer to those defined by the WHO (<18.5 kg/m2 = Underweight; 18.5 – 24.99 = Normal; 25.0 – 29.9 = Overweight; $\geq$ 30 = Obese)

CHAPTER 3

METHODS

3.1 STUDY POPULATION

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Consortium on Safe Labor (CSL) retrospective cohort study collected data on 228,438 deliveries from 19 hospitals across the United States from 2002-2008. A more detailed description on the CSL study is provided elsewhere[17, 18]. The CSL contains information on a total of 4,840 twin gestations. Information was obtained from electronic medical records and supplemented with International Classification of Diseases, 9th revision (ICD-9) codes in the patient discharge summary. Medical records provided information on maternal demographics, reproductive history, medical history, prenatal history of current pregnancy, labor admission assessment, labor progression, labor and delivery summary, and maternal postpartum conditions. For this study, only women with a twin gestation delivered between 23-42 gestational weeks with a known pre-pregnancy BMI, pre-pregnancy weight, and weight at labor and delivery admission were included (n=3,081). Observations with a gestational age greater than 42 weeks (n=1), missing pre-pregnancy BMI (n=1,758), pre-pregnancy weight (n=1,544), or weight at labor and delivery admission (n=118) were excluded from the analyses (missing overlap: missing pre-pregnancy BMI and pre-pregnancy weight n=1,544; missing pre-pregnancy BMI and labor admission weight n=658; missing pre-pregnancy weight and labor admission weight n=644).

We compared the demographic characteristics and pregnancy complications for observations with a pre-pregnancy BMI to observations missing pre-pregnancy BMI to evaluate whether they were missing at random. After comparing the demographic characteristics and pregnancy complications between the two groups, we did not detect any differences. Table 3.2 provides the demographic characteristics for observations by availability of pre-pregnancy BMI status.

3.2 EXPOSURE OF INTEREST

The exposure of interest is total GWG and was calculated as maternal pre-pregnancy weight (in kg) subtracted from the recorded maternal weight at labor and delivery admission. Total GWG was examined as both a continuous variable (total kg) and as a categorical variable. For the categorical variable, each observation's total GWG was categorized as below, within, or above our total GWG guidelines that we developed using quantile regression, respective of pre-pregnancy BMI and gestational age at delivery. From this point forward, all references to "guidelines" refer to our developed total GWG guidelines, unless noted otherwise. A detailed description of the methods used to create our guidelines will be discussed later in the chapter. Women with weight gain within our guidelines served as the reference group for comparisons. The quantile regression total GWG guidelines will be presented in Chapter 4.

3.3 OUTCOMES OF INTEREST

The examined maternal outcomes included: gestational hypertension, preeclampsia (systolic BP (SBP) ≥140mm Hg, a diastolic BP (DBP) ≥90mm Hg occurring after 20 weeks' gestation among previously normotensive women without and with proteinuria and urinary excretion ≥0.3g protein in 24-hour urine specimen, respectively)[1], GDM (1-hour glucose challenge test > 140 mg/dl)[8,9], and cesarean delivery. Outcomes of interest were classified using the electronic medical records and the supplemental ICD-9 codes. The ICD-9 codes and definitions of these outcomes are listed in Table 3.1.

Table 3.1 Classification of Outcomes of Interest

Outcome	**ICD-9 Code**	**Source of Data**	**Defined**
Cesarean Delivery	669.7	ICD9 and EMR	Cesarean delivery without mention of indication
Gestational Diabetes Mellitus	648.0	ICD9 and EMR	Diabetes mellitus complicating pregnancy, childbirth, or the puerperia
Gestational Hypertension	642.3	ICD9 and EMR	Transient hypertension of pregnancy
Preeclampsia	642.4 (mild) 642.5 (severe)	ICD9 and EMR	Mild or unspecified preeclampsia Severe preeclampsia

3.4 POTENTIAL CONFOUNDERS

Potential confounders of the association between GWG and the adverse maternal outcomes of interest included: maternal age (continuous variable), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander/Multi-Racial/other/unknown), pre-pregnancy BMI (categorized as underweight (<18.50 kg/m^2), normal-weight (<24.99 kg/m^2), overweight (25.0 – 29.99 kg/m^2), and obese ($\geq$30 kg/m^2), marital status (married, single/widowed/divorced, unknown), smoking (yes vs no), alcohol consumption during pregnancy (yes vs no), gestational age at delivery (continuous variable), hospital site number, insurance type (private, public, self-pay/unknown/other), history of cesarean delivery (yes, no, unknown), and parity (nulliparous vs multiparous). These potential confounders were adjusted for in all analyses using theoretically-based models, based on the literature review and findings from previous epidemiological studies. History of cesarean delivery was only controlled for in the analyses of cesarean delivery. Please refer to the Direct Acyclic Graph (DAG) Minimally Adjusted Model in Figure 3.1.

3.5 ANALYSIS

All analyses were limited to twin gestations delivered between 23-42 gestational weeks with an available maternal pre-pregnancy BMI, pre-pregnancy weight, and weight at admission to labor and delivery (n=3,081). For all analyses, GWG within our guidelines, respective of pre-pregnancy BMI and gestational age at delivery, served as the comparison group. For the analyses of gestational hypertension and preeclampsia, women with chronic hypertension were excluded (n=70). For the analyses of GDM, women with chronic diabetes mellitus were excluded (n=58).

For Study Aim I, we used a non-parametric regression to examine the distribution of GWG as a function of gestational age for each pre-pregnancy BMI category. As hypothesized, our results showed that the relationship between GWG and gestational age is far from linear. After examining the non-parametric regression of the functional relationship between GWG and gestational age, we placed a linear spline knot at 37 gestational weeks to provide the flexibility which allowed the slope coefficients to change after 37 gestational weeks. The placement of the knot was based on the distribution of the raw data, since the relationship between GWG and gestational age evidently changed after 37 gestational weeks. Using the spline knot enabled us to more accurately represent the relationship between gestational age and total GWG.

We then used quantile regression, keeping a linear spline knot placed at 37 gestational weeks, to create new GWG guidelines for twin gestations that more accurately reflect the functional relationship between GWG and gestational age. Quantile regression was used to estimate the 25^{th} and 75^{th} percentiles of total GWG as a function of gestational age for each pre-pregnancy BMI category. We created our total GWG guidelines using the interquartile range (IQR), between the 25^{th} and 75^{th} percentiles, of total GWG as the recommended range of total GWG for each gestational age at delivery, respective of pre-pregnancy BMI. We then categorized each observation's concordance with our total GWG guidelines. Concordance was categorized as either below, within, or above if total GWG was less than the 25^{th} percentile, between the 25^{th} and 75^{th} percentiles, or greater than the 75^{th} percentile, respectively, respective of each observation's pre-pregnancy BMI and gestational age at delivery.

For Study Aim II, logistic regression was used to estimate the odds of adverse maternal outcomes in association with increasing total GWG or concordance with our total GWG guidelines. Estimates of the exposure-outcome relationships were obtained after adjusting for all potential confounders using theoretically-based models, and are presented as odds ratios (ORs) with their 95% confidence intervals (95% CIs). For the analyses using continuous total GWG as the exposure of interest, we first ran non-parametric regression models to examine the relationships between increasing total GWG and the log odds of each maternal outcome and to assess the appropriateness of using logistic regression. The non-parametric regression results suggested that it is appropriate to model the relationships between total GWG and the log odds of gestational hypertension, GDM, and cesarean delivery using logistic regression. However, the relationship between total GWG and the log odds of preeclampsia was far from linear, and a linear spline knot was needed to match the logistic regression to the non-parametric regression. Based on the non-parametric regression results for preeclampsia, a linear spline knot was placed at 19 kilograms to force the logistic regression model to better reflect the non-parametric relationship. Please refer to Figure 3.2, Figure 3.3, Figure 3.4, and Figure 3.5 for SAS generated graphs that simultaneously plot the non-parametric regression, logistic regression, and modified logistic regression with linear spline knots (when applicable) for each outcome of interest (pages 28-29). Results from SAS outputs of logistic regression models using generalized linear models can be found in Appendix A. Statistical significance was set at the 5% level. Statistical analyses were carried out using Statistical Analysis Software (SAS) 9.4.

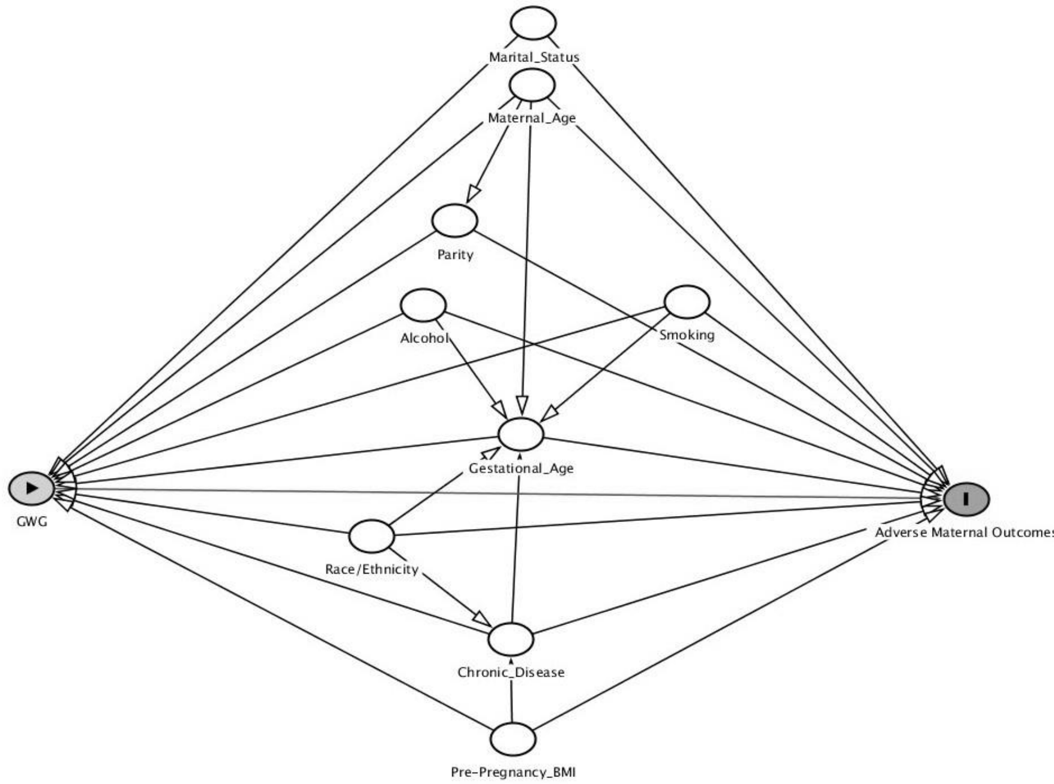

Figure 3.1 Directed Acyclic Graph (DAG) Minimally Adjusted Model [12]

Table 3.2 Demographic Characteristics by Availability of Pre-Pregnancy BMI Status

Characteristic	Pre-Pregnancy BMI (n=3,082)	Missing Pre-Pregnancy BMI (n=1,758)	*P*-Value
Total GWG, mean, SD (kg)[a]	16.97, 7.81	17.45, 7.87	<.0001
Gestational Age, mean, SD (weeks)	34.92, 3.37	34.37, 3.69	<.0001
Maternal Age, mean, SD (years)[b]	29.74, 6.49	29.65, 6.59	<.0001
Pre-Pregnancy Weight, mean, SD (kg)[c]	70.46, 19.08	71.24, 17.68	<.0001
Admission Weight, mean, SD (kg)[d]	87.21, 19.16	89.18, 20.81	<.0001
Race/Ethnicity n (%)[e]			
Non-Hispanic White	1,723 (57.51)	942 (54.96)	<.0001
Non-Hispanic Black	646 (21.56)	466 (27.19)	
Hispanic	471 (15.72)	174 (10.15)	
Asian/PI/Multi/Other/Unknown	156 (5.21)	132 (7.70)	
Marital Status n (%)			
Married	2,094 (67.94)	1,009 (57.39)	<.0001
Divorced/Widowed/Single	924 (29.98)	583 (33.16)	
Unknown	64 (2.08)	166 (9.44)	
Smoking Status n (%)			
Yes	2,896 (93.96)	1,633 (92.89)	0.14
No	186 (6.04)	125 (7.11)	
Alcohol Status n (%)			
Yes	3,023 (98.09)	1,730 (98.41)	0.42
No	59 (1.91)	28 (1.59)	
Chronic Hypertension n (%)			
Yes	70 (2.27)	40 (2.28)	0.99
No	3,012 (97.73)	1,718 (97.72)	
Chronic Diabetes Mellitus n (%)			
Yes	58 (1.88)	37 (2.10)	0.59
No	3,024 (98.12)	1,721 (97.90)	

Parity n (%)[f]			
Nulliparous	1,340 (43.48)	788 (44.85)	0.36
Multiparous	1,742 (56.52)	969 (55.15)	
History of Cesarean Delivery n (%)			
Yes	420 (13.63)	245 (13.94)	
No	2,564 (83.19)	1,382 (78.61)	<.0001
Unknown	98 (3.18)	131 (7.45)	
Insurance Type n (%)			
Private	1,735 (56.29)	1,236 (70.31)	
Public	980 (31.80)	466 (26.51)	<.0001
Self-Pay/Other/Unknown	367 (11.91)	56 (3.19)	
Gestational Hypertension n (%)[g]			
Yes	138 (4.58)	65 (3.78)	0.19
No	2,874 (95.42)	1,653 (96.22)	
Preeclampsia n (%)[g]			
Yes	171 (5.55)	111 (6.31)	0.27
No	2,911 (94.45)	1,647 (93.69)	
Gestational Diabetes Mellitus n (%)[h]			
Yes	207 (6.85)	150 (8.72)	0.02
No	2,817 (93.15)	1,571 (91.28)	
Cesarean Delivery n (%)			
Yes	2,063 (66.94)	1,178 (67.01)	0.96
No	1,019 (33.06)	580 (32.99)	

All p-values obtained using chi square test.

[a] Pre-Pregnancy BMI category frequency missing n=104; Missing Pre-Pregnancy BMI category frequency missing n=1,558

[b] Missing Pre-Pregnancy BMI category frequency missing n=12

[c] Missing Pre-Pregnancy BMI category frequency missing n=1,544

[d] Pre-Pregnancy BMI category frequency missing n=104; Missing Pre-Pregnancy BMI category frequency missing n=658

[e] Pre-Pregnancy BMI category frequency missing n=86; Missing Pre-Pregnancy BMI category frequency missing n=44

[f] Missing Pre-Pregnancy BMI category frequency missing n=1

[g] Women with chronic hypertension (n=70) were excluded from the analyses of gestational hypertension and preeclampsia.

[h] Women with chronic diabetes mellitus (n=58) were excluded from the analyses of GDM.

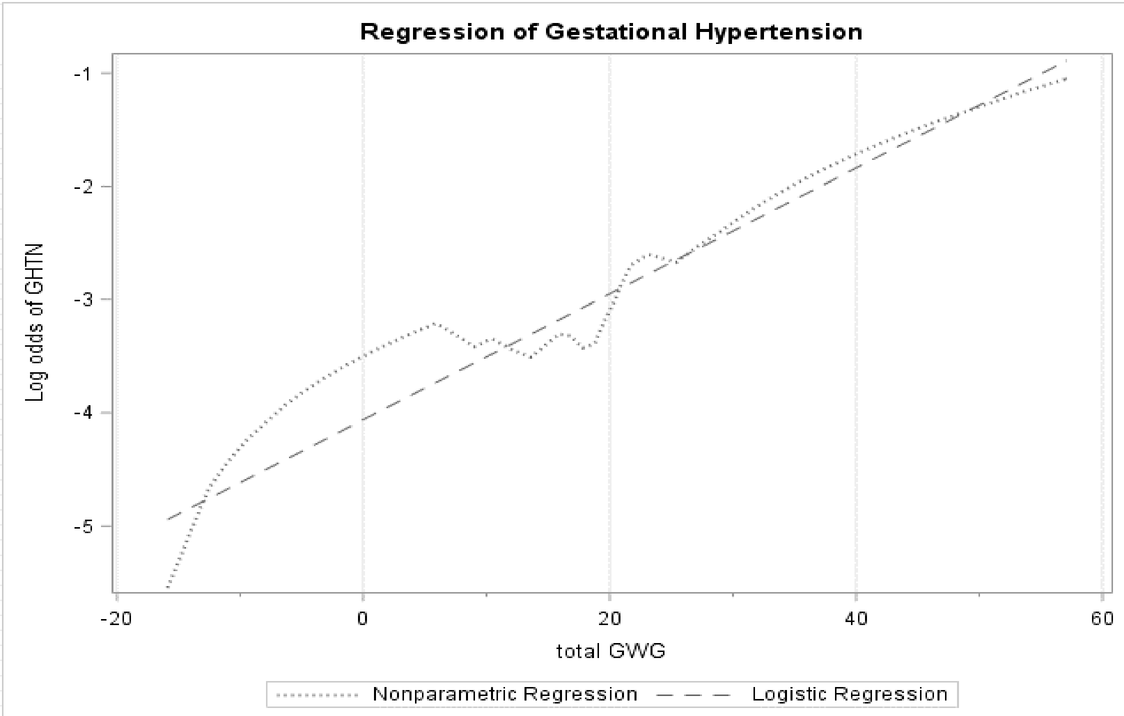

Figure 3.2 Plotted Regressions for Gestational Hypertension

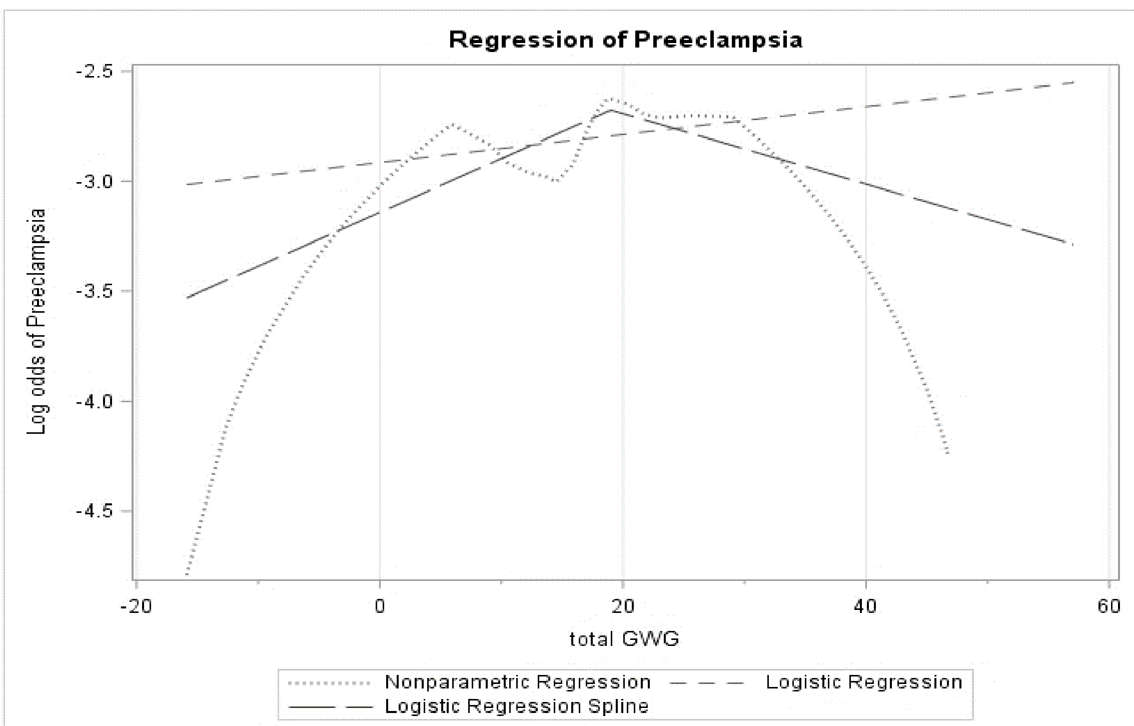

Figure 3.3 Plotted Regressions for Preeclampsia

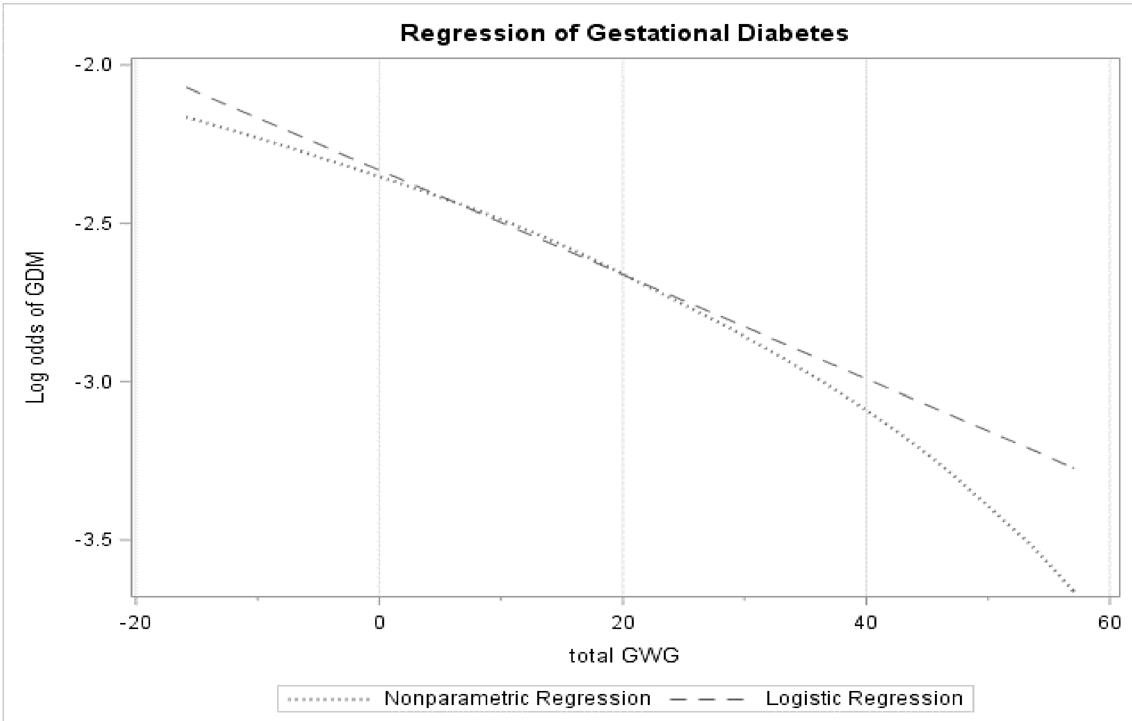

Figure 3.4 Plotted Regressions for Gestational Diabetes Mellitus

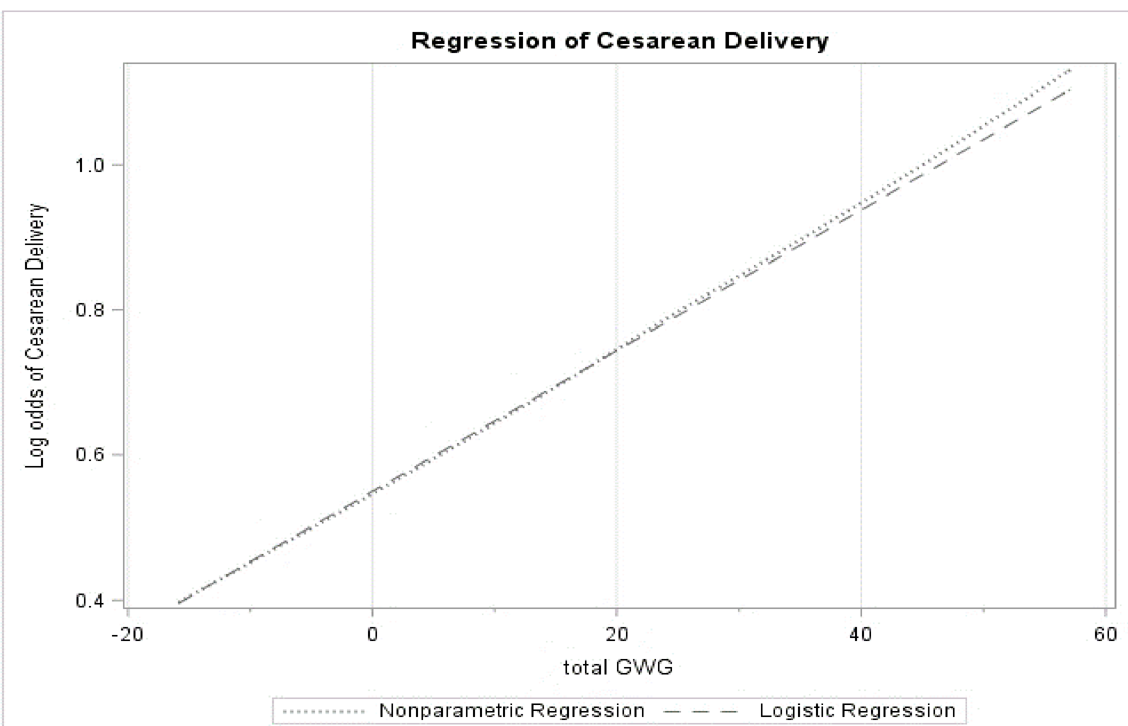

Figure 3.5 Plotted Regressions for Cesarean Delivery

CHAPTER 4

RESULTS

4.1 STUDY POPULATION

The average total GWG for the study population was 16.97 kg, with a minimum and maximum value of -15.88 and 57.08 kg, respectively. Of the 3,081 women included in our study, 52.52% (n=1,618) were within, 26.94% (n=830) were below, and 20.55% (n=633) were above our GWG guidelines, respective of pre-pregnancy BMI and gestational age at delivery. We did not observe any large differences in the percentages of pre-pregnancy BMI categories between our concordance categories. Outcomes of interest included gestational hypertension (n=138), preeclampsia (n=171), GDM (n=207), and cesarean delivery (n=2,063). Table 4.1 provides demographic information for the study population categorized by concordance with our GWG guidelines.

Compared to women with GWG within our guidelines, women with GWG below our guidelines were significantly more likely to have an obese pre-pregnancy BMI (22.77 vs 18.97%, $p<.0001$), be non-Hispanic black (24.58 vs 17.0%, $p<.0001$), Hispanic (19.16 vs 15.08%, $p<.0001$), not married (35.18 vs 25.28%, $p<.0001$), smokers (7.83 vs 5.25%, $p=0.01$), multiparous (63.37 vs 55.13%, $p<.0001$), and have public health insurance (37.71 vs 27.50%, $p<.0001$).

Women with GWG above our guidelines were significantly less likely to be Hispanic (10.74 vs 17.0%, p<.0001), but were significantly more likely to have an obese pre-pregnancy BMI (25.75 vs 18.97%, p<.0001), be non-Hispanic black (26.38 vs 17.0%, p<.0001), not married (35.23 vs 25.28%, p<.0001), nulliparous (48.82 vs 44.87%, p<.0001), have chronic diabetes mellitus (2.84 vs 1.48%, p=0.03), and have public health insurance (35.07 vs 27.50%), p=0.001) compared to women with GWG within our guidelines.

Quantile regression was used to create GWG guidelines with the IQR serving as the recommended range of total GWG, respective of pre-pregnancy BMI and gestational age at delivery. Concordance between total GWG and our guidelines was categorized as below, within, or above if total GWG was less than the 25th percentile, between the 25th and 75th percentiles, or greater than the 75th percentile, respectively. The quantile regression total GWG guidelines are presented in Table 4.6.

4.2 GESTATIONAL HYPERTENSION

The unadjusted and adjusted results for the association between concordance with our guidelines and total GWG and the odds of gestational hypertension are presented in Tables 4.2, 4.3, 4.4., and 4.5, respectively. In the crude model, weight gain below our GWG guidelines was not significantly associated with gestational hypertension [OR: 0.76, 95% CI: 0.47, 1.23] (Table 4.2). Weight gain above our GWG guidelines was found to be significantly associated with increased odds of gestational hypertension in the crude model [OR: 2.20, 95% CI: 1.50, 3.24] (Table 4.2). After adjusting for maternal age, pre-pregnancy BMI, race/ethnicity, marital status, smoking, alcohol, parity, insurance, and hospital site number, weight gain above our GWG guidelines was significantly associated with increased odds of gestational hypertension [OR: 2.04, 95% CI: 1.60, 2.61] (Table 4.3). In the adjusted model, GWG below our guidelines was not found to be significantly associated with gestational hypertension [OR: 0.82, 95% CI: 0.61, 1.11] (Table 4.3).

In the crude model for total GWG, a 5 kilogram increase in total GWG was found to be significantly associated with the odds of gestational hypertension [OR: 1.32, 95% CI 1.23, 1.42] (Table 4.4) In the adjusted model, a 5 kilogram increase in total GWG was again found to be significantly associated with gestational hypertension [OR: 1.31, 95% CI 1.23, 1.40] (Table 4.5). The odds of developing gestational hypertension increased by 31% for each 5 kg increase in total GWG, after controlling for all covariates in the model.

4.3 PREECLAMPSIA

The unadjusted and adjusted results for the association between concordance with our guidelines and total GWG and the odds of preeclampsia are presented in Tables 4.2, 4.3, 4.4., and 4.5, respectively. In the crude model, GWG below our guidelines was not significantly associated with preeclampsia [OR: 0.90, 95% CI: 0.60, 1.34] (Table 4.2). GWG above our guidelines was significantly associated with increased odds of developing preeclampsia in the crude model [OR: 1.59, 95% CI: 1.10, 2.30] (Table 4.2). After adjusting for potential confounders, weight gain above our GWG guidelines was significantly associated with increased odds of preeclampsia [OR: 1.63, 95% CI: 1.26, 2.10] (Table 4.3). GWG below our guidelines remained statistically insignificant after adjusting for potential confounders [OR: 0.95, 95% CI: 0.72, 1.25] (Table 4.4).

In the crude model for total GWG, a 5 kilogram increase in total GWG was not significantly associated with increased odds of preeclampsia [OR: 1.04, 95% CI: 0.97, 1.12] (Table 4.4). As previously mentioned, a linear spline knot was placed at 19 kg in the adjusted model for total GWG and preeclampsia to better match the logistic regression to the non-parametric regression. The association between total GWG and preeclampsia was significantly different when total GWG was less than 19 kilograms compared to when total GWG was greater than 19 kilograms (p=0.0002). When total GWG was less than 19 kilograms, a 5 kilogram increase in total GWG was found to be borderline significantly associated with the odds of developing preeclampsia [OR: 1.16, 95% CI: 1.01, 1.33] (Table 4.5). When total GWG was greater than 19 kilograms, a 5 kilogram increase in total GWG was not significantly associated with preeclampsia [OR: 0.80, 95% CI: 0.62, 1.02] (Table 4.5).

4.4 GESTATIONAL DIABETES MELLITUS

The unadjusted and adjusted results for the association between concordance with our guidelines and total GWG and the odds of GDM are presented in Tables 4.2, 4.3, 4.4., and 4.5, respectively. In the crude model, GWG below [OR: 1.10, 95% CI: 0.78, 1.54] or GWG above [OR: 0.92, 95% CI: 0.62, 1.36] our guidelines were not significantly associated with GDM (Table 4.2). After adjustment, weight gain below [OR: 1.15, 95% CI: 0.90, 1.47] or above [OR: 0.92, 95% CI: 0.69, 1.23] our GWG guidelines remained insignificantly associated with the odds of GDM (Table 4.3).

In the crude model for total GWG, a 5 kilogram increase in total GWG was significantly associated with decreased odds of GDM [OR: 0.91, 95% CI: 0.84, 0.98] (Table 4.4). However, after adjustment, increasing total GWG was not significantly associated with GDM [OR: 0.96, 95% CI: 0.89, 1.03] (Table 4.5).

4.5 CESAREAN DELIVERY

The unadjusted and adjusted results for the association between concordance with our guidelines and total GWG and the odds of cesarean delivery are presented in Tables 4.2, 4.3, 4.4., and 4.5, respectively. In the crude model, GWG below our guidelines was significantly associated with decreased odds of cesarean delivery [OR: 0.74, 95% CI: 0.62, 0.88] (Table 4.2). Weight gain above our guidelines was not significantly associated with cesarean delivery in the crude model [OR: 1.19, 95% CI: 0.97, 1.45] (Table 4.2). After adjustment, weight gain below our GWG guidelines was significantly associated with decreased odds of cesarean delivery [OR: 0.79, 95% CI: 0.64, 0.97] (Table 4.3). GWG above our guidelines remained insignificantly associated with the odds of cesarean delivery in the adjusted model [OR: 1.16, 95% CI: 0.91, 1.46] (Table 4.3).

In the crude model for total GWG, increasing total GWG was not significantly associated with cesarean delivery [OR: 1.06, 95% CI: 1.00, 1.12] (Table 4.4). After adjustment, a 5 kilogram increase in total GWG was borderline significantly associated with increased odds of cesarean delivery in the adjusted model [OR: 1.08, 95% CI: 1.01, 1.15] (Table 4.5). For each 5 kilogram increase in total GWG, the odds of having a cesarean delivery increased by 8%, after controlling for all covariates in the model.

Table 4.1 Demographic Characteristics Based on Concordance with the Quantile Regression Total Gestational Weight Gain (GWG) Guidelines among Twin Gestations in the CSL Study (N=3,081)

Characteristics	**Below (n=830)**	**Within (n=1,618)**	**Above (n=633)**
Total GWG, mean, SD (kg)	8.46, 5.06**	17.06, 4.35	26.50, 5.93**
Gestational Age, mean, SD (weeks)	34.82, 3.39**	34.96, 3.44	34.94, 3.10**
Maternal Age, mean, SD (years)	29.38, 6.44**	30.13, 6.53	29.21, 6.39**
Pre-Pregnancy BMI n (%)[a]			
Underweight	39 (4.70)*	72 (4.54)	33 (5.21)**
Normal	408 (49.16)	902 (55.75)	261 (41.23)
Overweight	194 (23.37)	337 (20.83)	176 (27.80)
Obese	189 (22.77)	307 (18.97)	163 (25.75)
Race/Ethnicity n (%)			
Non-Hispanic White	402 (48.43)**	978 (60.44)	342 (54.03)**
Non-Hispanic Black	204 (24.58)	275 (17.0)	167 (26.38)
Hispanic	159 (19.16)	244 (15.08)	68 (10.74)
Asian/PI/Multi/Other/Unknown	42 (5.06)	72 (4.45)	42 (6.64)
Missing	23 (2.77)	49 (3.03)	14 (2.21)
Marital Status n (%)			
Married	516 (62.17)**	1,180 (72.93)	397 (62.72)**
Divorced/Widowed/Single	292 (35.18)	409 (25.28)	223 (35.23)
Unknown	22 (2.65)	29 (1.79)	13 (2.05)
Smoking Status n (%)			
No	765 (92.17)*	1,533 (94.75)	597 (94.31)
Yes	65 (7.83)	85 (5.25)	36 (5.69)
Alcohol Status n (%)			
No	813 (97.95)	1,586 (98.02)	623 (98.42)
Yes	17 (2.05)	32 (1.98)	10 (1.58)
Chronic Hypertension n (%)			
No	809 (97.47)	1,588 (98.15)	614 (97.00)
Yes	21 (2.53)	30 (1.85)	19 (3.00)

Chronic Diabetes n (%)			
No	814 (98.07)	1,594 (98.52)	615 (97.16)*
Yes	16 (1.93)	24 (1.48)	18 (2.84)
Parity n (%)			
Nulliparous	304 (36.63)**	726 (44.87)	309 (48.82)
Multiparous	526 (63.37)	892 (55.13)	324 (51.18)
History of Cesarean Delivery n (%)			
No	674 (81.20)*	1,363 (84.24)	526 (83.10)
Yes	115 (13.86)	212 (13.10)	93 (14.69)
Unknown	41 (4.94)	43 (2.66)	14 (2.21)
Insurance Type n (%)			
Private	411 (49.52)**	974 (60.20)	349 (55.13)**
Public	313 (37.71)	445 (27.50)	222 (35.07)
Self-Pay/Other/Unknown	106 (12.77)	199 (12.30)	62 (9.79)

P-values were obtained using chi-square tests. Concordance categorized as "within" our recommended guidelines (n=1618) served as the reference group.

* Indicates *P* <.05

** Indicates *P* <.0001

[a] *Maternal pre-pregnancy BMI is categorized as underweight if BMI is <18.5 kg/m^2, normal-weight if BMI is 18.5 to 24.9 kg/m^2, overweight if BMI is 25.0 to 29.9 kg/m^2, obese if BMI is $\geq$ 30.0*

Table 4.2 Unadjusted Odds Ratios of Adverse Pregnancy Outcomes by Concordance with the Quantile Regression Total Gestational Weight Gain (GWG) Guidelines among Twin Gestations in the CSL Study

Outcome	Below (n=830)	Within (n=1,618)	Above (n=633)
Gestational Hypertension [a]	0.76 (0.47, 1.23)	1.00 (ref.)	2.20 (1.50, 3.24)*
Preeclampsia [a]	0.90 (0.60, 1.34)	1.00 (ref.)	1.59 (1.10, 2.30)*
Gestational Diabetes Mellitus [b]	1.10 (0.78, 1.54)	1.00 (ref.)	0.92 (0.62, 1.36)
Cesarean Delivery	0.74 (0.62, 0.88)*	1.00 (ref.)	1.19 (0.97, 1.45)

All numbers are ORs with 95% CIs. ORs are obtained from logistic regression using generalized linear models. Concordance categorized as "within" our quantile regression GWG guidelines (n=1,618) served as the reference group.
**Indicates significant results.*
[a] *Women with chronic hypertension (n=70) were excluded from the analyses of gestational hypertension and preeclampsia.*
[b] *Women with chronic diabetes mellitus (n=58) were excluded from the analyses of GDM.*

Table 4.3 Adjusted Odds Ratios of Adverse Pregnancy Outcomes by Concordance with the Quantile Regression Total Gestational Weight Gain (GWG) Guidelines among Twin Gestations in the CSL Study

Outcome	Below (n=830)	Within (n=1,618)	Above (n=633)
Gestational Hypertension [a]	0.82 (0.61, 1.11)	1.00 (ref.)	2.04 (1.60, 2.61)*
Preeclampsia [a]	0.95 (0.72, 1.25)	1.00 (ref.)	1.63 (1.26, 2.10)*
Gestational Diabetes Mellitus [b]	1.15 (0.90, 1.47)	1.00 (ref.)	0.92 (0.69, 1.23)
Cesarean Delivery	0.79 (0.64, 0.97)*	1.00 (ref.)	1.16 (0.91, 1.46)

All numbers are ORs with 95% CIs. ORs are obtained from logistic regression using generalized linear models. All results are adjusted for maternal age, race/ethnicity, gestational age, pre-pregnancy BMI, smoking status, alcohol status, parity, insurance type, marital status, and hospital site number. Concordance categorized as 'within" our quantile regression GWG guidelines (n=1,618) served as the reference group.
*Indicates significant results.
[a] *Women with chronic hypertension (n=70) were excluded from the analyses of gestational hypertension and preeclampsia.*
[b] *Women with chronic diabetes mellitus (n=58) were excluded from the analyses of GDM.*

Table 4.4 Unadjusted Odds Ratios for a 5 Kilogram Increase in Total Gestational Weight Gain (GWG) and Adverse Pregnancy Outcomes among Twin Gestations in the CSL Study

Outcome	**Odds Ratio, (95% CI)**
Gestational Hypertension [a]	1.32 (1.23, 1.42)*
Preeclampsia [a]	1.04 (0.97, 1.12)
Gestational Diabetes Mellitus [b]	0.91 (0.84, 0.98)*
Cesarean Delivery	1.06 (1.00, 1.12)

All numbers are ORs with 95% CIs. ORs are obtained from logistic regression using generalized linear models
**Indicates significant results.*
[a] Women with chronic hypertension (n=70) were excluded from the analyses of gestational hypertension and preeclampsia.
[b] Women with chronic diabetes mellitus (n=58) were excluded from the analyses of GDM.

Table 4.5 Unadjusted Odds Ratios for a 5 Kilogram Increase in Total Gestational Weight Gain (GWG) and Adverse Pregnancy Outcomes among Twin Gestations in the CSL Study

Outcome	**Odds Ratio (95% CI)**
Gestational Hypertension [a]	1.31 (1.23, 1.40)*
Preeclampsia [a]	
Total GWG < 19 kg	1.16 (1.01, 1.33)*
Total GWG > 19 kg	0.80 (0.62, 1.02)
Gestational Diabetes Mellitus [b]	0.96 (0.89, 1.03)
Cesarean Delivery	1.08 (1.01, 1.15)*

All numbers are ORs with 95% CIs. ORs are obtained from logistic regression using generalized linear models. All results are adjusted for maternal age, race/ethnicity, gestational age, pre-pregnancy BMI, smoking status, alcohol status, parity, insurance type, marital status, and hospital site number.
*Indicates significant results.
[a] Women with chronic hypertension (n=70) were excluded from the analyses of gestational hypertension and preeclampsia.
[b] Women with chronic diabetes mellitus (n=58) were excluded from the analyses of GDM.

Table 4.6 Quantile Regression Total Gestational Weight Gain (GWG) Guidelines for Twin Gestations, Stratified by Pre-Pregnancy Body Mass Index (BMI) Category (in kilograms)

Gestational Age (weeks)	Underweight BMI	Normal Weight BMI	Overweight BMI	Obese BMI
23	6.93 – 15.76	5.34 – 12.10	4.65 – 9.78	3.60 – 8.79
24	7.58 – 16.22	6.09 – 17.93	5.27 – 10.77	4.00 – 9.63
25	8.23 – 16.69	6.84 – 18.39	5.90 – 11.76	4.39 – 10.48
26	8.88 – 17.15	7.60 – 18.86	6.52 – 12.76	4.79 – 11.33
27	9.53 – 17.62	8.35 – 19.32	7.14 – 13.75	5.18 – 12.18
28	10.17 – 18.08	9.10 – 19.79	7.77 – 14.74	5.58 – 13.03
29	10.82 – 18.55	9.85 – 20.25	8.39 – 15.73	5.97 – 13.88
30	11.47 – 19.02	10.60 – 20.72	9.02 – 16.72	6.37 – 14.72
31	12.12 – 19.48	11.35 – 21.18	9.64 – 17.71	6.76 – 15.57
32	12.77 – 19.95	12.10 – 21.65	10.26 – 18.71	7.16 – 16.42
33	13.41 – 20.41	12.85 – 22.11	10.89 – 19.70	7.56 – 17.27
34	14.06 – 20.88	13.61 – 22.58	11.51 – 20.69	7.95 – 18.12
35	14.71 – 21.34	14.36 – 23.05	12.13 – 21.68	8.35 – 18.97
36	15.36 – 21.81	15.11 – 23.51	12.76 – 22.67	8.74 – 19.81
37	16.01 – 22.27	15.86 – 23.98	13.38 – 23.66	9.14 – 20.66
38	16.33 – 32.60	15.87 – 37.34	13.61– 23.28	9.38 – 20.90
39	16.65 – 33.20	15.89 – 37.60	13.84– 22.89	9.62 – 21.14
40	16.98 – 33.80	15.90 – 37.86	14.06 – 22.50	9.87 – 21.37
41	17.30 – 34.39	15.92 – 38.12	14.29 – 22.11	10.11 – 21.61
42	17.63 – 34.99	15.93 – 38.37	14.52 – 21.73	10.35 - 21.84

CHAPTER 5

DISCUSSION

5.1 SUMMARY OF RESULTS

In summary, we found that GWG below our guidelines was significantly associated with decreased odds of having a cesarean delivery compared to GWG within our guidelines. GWG above our guidelines was associated with increased odds of developing gestational hypertension and preeclampsia compared to GWG within our guidelines. We found a significant positive trend between increasing total GWG and the odds of developing gestational hypertension, preeclampsia (when total GWG < 19 kilograms), and cesarean delivery. When total GWG was greater than 19 kilograms, increasing GWG was insignificantly negatively associated with the odds of preeclampsia. There were no significant associations with GDM.

5.2 GESTATIONAL HYPERTENSION

In the adjusted model, GWG above our GWG guidelines was found to be significantly associated with an increase in the odds of developing gestational hypertension. In the adjusted model for total GWG, increasing total GWG was also found to be significantly associated with increased odds of gestational hypertension. While we found significant associations for gestational hypertension for both GWG above our guidelines and total GWG, most other studies have not found this to be true [5,6,11,14]. Lal & Kominiarek found a positive trend with increasing total GWG and development of gestational hypertension which supports our findings[11]. Fox et al 2010 and Fox et al 2011 did not find any significant differences between adequacy of adherence to IOM GWG guidelines and the odds of gestational hypertension [5,6]. Gavard & Artal also did not find any significant differences in the odds of gestational hypertension as total GWG increased[7]. However, Gavard & Artal only assessed the association between GWG and gestational hypertension in women with an obese pre-pregnancy BMI [7]. The differences between our findings and the findings from previous studies can be attributed to the substantial variation in the study populations, sample sizes, GWG guidelines used, measure of GWG, and differences in inclusion criteria. Fox et al 2010, Fox et al 2011, and Gavard & Artal all used the 2009 IOM provisional guidelines[5-7]. Further, Fox et al 2010 used the common weekly rate of GWG, which unlike our guidelines does not account for the built-in relationship between gestational duration and total GWG[5].

5.3 PREECLAMPSIA

In the adjusted model, GWG above our guidelines and an increase in total GWG (when total GWG was less than 19 kg) were both found to be significantly associated with an increase in the odds of developing preeclampsia. When total GWG was greater than 19 kilograms, the odds of preeclampsia insignificantly decreased as total GWG increased. Studies within the literature support our findings of a positive trend between increasing GWG and preeclampsia[7,11]. Gavard & Artal found a significant positive trend between increasing GWG and the likelihood of developing preeclampsia[7]. Lal & Kominiarek also found a significant increase in the rates of preeclampsia for women with an underweight//normal-weight pre-pregnancy BMI whose GWG was above the IOM guidelines[11]. They additionally found a significant decrease in the likelihood of developing preeclampsia for women with an obese pre-pregnancy BMI with weight gain below the IOM guidelines[7]. Lucovnik et al and Fox et al 2011 did not report any significant associations between preeclampsia and GWG [6, 12].

Although the existing literature supports our findings of a positive association between increasing total GWG and preeclampsia, the insignificant negative trend we observed after total GWG reaches 19 kilograms has not been reported in previous studies. Considering the substantial number of preeclampsia cases and the adequate diversity of our large sample population, we hypothesize that the unexpected change in the association between total GWG and preeclampsia resulted from random variation in the study. Given that previous research has repeatedly found an increased risk of preeclampsia in twin gestations compared to singletons, our findings require corroboration from larger future studies to further explain the shift we observed in the association between increasing GWG and preeclampsia. Additional potential explanations for our findings for preeclampsia will be discussed later in the chapter.

5.4 GESTATIONAL DIABETES MELLITUS

Both GWG below and above our guidelines were not found to be significantly associated with the odds of GDM in our study. These null findings are consistent with the existing literature[5,6,11,12]. Fox et all 2010 and Fox et al 2011 also examined the association between increasing total GWG and GDM and reported null findings[5,6]. Fox et al 2010 did not find any significant differences between adequacy of adherence to the IOM guidelines and the likelihood of GDM for women with an underweight/normal-weight pre-pregnancy BMI[11]. Additionally, Lucovnik et al a reported that change in BMI during pregnancy was not significantly associated with the likelihood of developing GDM[12]. Possible explanations for these null results will be discussed later in the chapter.

5.5 CESAREAN DELIVERY

In both the crude and adjusted models, GWG below our guidelines was found to be significantly associated with decreased odds of cesarean delivery. The association between GWG above our guidelines and having a cesarean delivery were insignificant. In the adjusted model, the association between total GWG was found to be borderline significantly associated with increased odds of cesarean delivery. Supporting our findings, Gavard et al also found a borderline statistically significant positive trend between increasing GWG and cesarean delivery[7]. However, most of the literature analyzing GWG and adverse maternal outcomes in twin gestations did not specifically investigate the odds of cesarean delivery. The risk for cesarean delivery is consistently greater in twin gestations than in singleton gestations, highlighting the importance of exploring the potential association between GWG and cesarean delivery in twin gestations[2].

5.6 DIFFERENCES AND GAPS IN THE LITERATURE

The majority of findings in the current literature regarding the associations between GWG and gestational hypertension, preeclampsia, and GDM in twin gestations are either insignificant or contradictory between studies[2,5,6,7,11,12]. Previous studies have postulated that both the inconsistency and the lack of significant findings for these associations may be related to the impact of disease diagnosis on GWG[2]. Most studies used pre-pregnancy weight and weight at labor and delivery admission to calculate total GWG, which does not account for disease diagnosis temporality. Being diagnosed with gestational hypertension, preeclampsia, or GDM is highly likely to influence the trajectory and total amount of GWG throughout one's pregnancy[2,9]. Previous research supports the hypothesis that medical interventions, counseling, and other external influential factors may modify the associations between GWG and gestational hypertension, preeclampsia, and GDM[2]. Considering the increased risk of developing these maternal outcomes during twin gestations, the inconsistencies between existing findings, and the results reported from our study, it is extremely important to explore the influence of disease diagnosis on GWG and adherence to either the IOM or other GWG guidelines in twin gestations[2,9].

Additionally, there are several differences in the literature regarding the associations between GWG and the odds of preeclampsia and cesarean delivery in twin gestations. The odds of developing preeclampsia and having a cesarean delivery, as well as other adverse maternal outcomes, have been hypothesized to differ by twin chorionicity (referring to placental chorionicity)[2,7]. However, it is currently unknown whether chorionicity influences GWG in twin gestations[2]. Research shows that approximately 20% of all twin gestations are monochorionic, and that monochorionic twin gestations experience greater risks for adverse perinatal outcomes than dichorionic gestations[2]. Unfortunately, chorionicity is not evaluated in most existing twin studies due to a lack of information and missing data. Despite the lack of available data on chorionicity and the potential influence it may have on the associations between GWG and adverse maternal outcomes in twin gestations, it is essential that future studies evaluate it as a potential confounder.

5.7 STRENGTHS AND LIMITATIONS

There are several strengths of this study. The quantile regression GWG guidelines we created are more inclusive and detailed than the 2009 IOM provisional guidelines for twin gestations. An advantage of our guidelines is that they are applicable to all twin gestations delivered between 23-42 gestational weeks, unlike the IOM guidelines which are only intended for term twin gestations[9]. Our guidelines are additionally more inclusive since they are applicable to women with an underweight pre-pregnancy BMI. Unlike previous studies, we created separate guidelines for the underweight women rather than combining them with the normal-weight women, and risking compromising the accuracy of the guidelines and results. Furthermore, our quantile regression guidelines were based off the built-in functional relationship between gestational age and total GWG. Accounting for the correlation between gestational duration and total GWG allowed the guidelines to more accurately reflect the true rate and pattern of weight gain in twin gestations at each gestational week.

Another strength of our study was our large sample size. The average sample size for twin studies are typically substantially smaller than singleton studies. The large twin population in the CSL allowed us to examine a wide range of outcomes and potential confounders, and examine exposure-outcome associations for all four pre-pregnancy BMI categories. Additionally, the CSL collected data from 19 different hospitals throughout the U.S. which greatly increased the study population diversity, and thus the generalizability of our results.

Despite the strengths of our study, there are a few key limitations to be noted. Given the smaller sample size for the underweight pre-pregnancy BMI category (n=144), the generalizability of the underweight guidelines may be more limited than the generalizability for the other BMI categories. Additionally, a substantial number of observations were excluded using complete case analysis for missing values for key maternal weight variables and pre-pregnancy BMI (n=1,780; n=1,758, respectively). To improve our research and handling of missing data in future analyses, we intend to perform a sensitivity analysis using multiple imputations. Lastly, it is important to again note that information on chorionicity was not available in the CSL study. We were unable to explore whether chorionicity impacted the associations between GWG and the outcomes of interest. Given that data on chorionicity wasn't adjusted for in the model, there is potential for residual confounding.

5.8 FUTURE STUDIES

The current epidemiological research analyzing the associations between GWG and adverse maternal outcomes in twin gestations is quite limited. Previous studies have commonly had smaller sample populations with a lack of diversity in comparison groups, and have employed extensive exclusion criteria. The common exclusion criteria have led to smaller sample sizes, and thus a consequential reduction of the statistical power of previous studies[2]. Excluding preterm deliveries and participants with underweight pre-pregnancy BMIs due to the lack of IOM guidelines is a serious limitation of the current research. It is imperative to include preterm deliveries and all pre-pregnancy BMI categories in future studies to accurately assess the influence of GWG and the role GWG guidelines play in improving maternal health in twin gestations. As previously mentioned, the assessment of diagnosis temporality and chorionicity are needed to improve the epidemiological research on the topic. Further research is needed to optimize twin GWG guidelines and maternal health during twin gestations.

5.9 CONCLUSIONS

The results of this study suggest that women with GWG below our GWG guidelines are significantly less likely to have a cesarean delivery than women with GWG within our guidelines. Women with GWG above our guidelines were found to be significantly more likely to develop gestational hypertension and preeclampsia than women within the guidelines. Increasing total GWG was found to be significantly associated with increased odds of gestational hypertension, preeclampsia (for total GWG less than 19 kilograms), and cesarean delivery. These results support the majority of previous findings, but additional research involving larger, prospective cohorts with available data on time of disease diagnosis and chorionicity are needed to further understand the complex association between GWG and adverse maternal outcomes in twin gestations.

REFERENCES

1. American College of Obstetricians and Gynecologists. Hypertension in Pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. The American College of Obstetrics and Gynecology. 2013;122:1122-1131.

2. Bodnar LM, Siega-Riz AM, Simhan HN, et al. Severe obesity, gestational weight gain, and adverse birth outcomes. The American Journal of Clinical Nutrition. 2010;91(6):1642–1648.

3. Chu SY, D'Angelo DV. Gestational weight gain among US women who deliver twins, 2001–2006. American Journal of Obstetrics & Gynecology. 2009;200(4):390, e1–6.

4. DiGiuseppe DL, Aron DC, Ranbom L, et al. Reliability of birth certificate data: A multi-hospital comparison to medical records information. Maternal and Child Health Journal. 2002;6(3), 169-179.

5. Fox NS, Rebarber A, Roman AS, et al. Weight gain in twin pregnancies and adverse outcomes: Examining the 2009 Institute of Medicine guidelines. The American College of Obstetrics & Gynecology. 2010;116(1):100–106.

6. Fox NS, Saltzman DH, Kurtz H, et al. Excessive weight gain in term twin pregnancies: Examining the 2009 Institute of Medicine definitions. The American College of Obstetricians and Gynecologists. 2011;118(5), 1000-1004.

7. Gavard JA, Artal R. Gestational weight gain and maternal and neonatal outcomes in term twin pregnancies in obese women. Twin Research and Human Genetics. 2014;17(2), 127–133.

8. Homko C, Sivan E, Chen X, Reece EA, Boden G. Insulin secretion during and after pregnancy in patients with gestational diabetes mellitus. The Journal of Clinical Endocrinology and Metabolism. 2001;86;568-573.

9. IOM. Weight Gain During Pregnancy: Reexamining the Guidelines. National Academies Press: Washington, DC, USA 2009

10. Kautzky-Willer A, Prager R, Waldhausl W, et al. Pronounced insulin resistance and inadequate beta-cell secretion characterize lean gestational diabetes during and after pregnancy. Diabetes Care. 1997;20;1717-1723.

11. Lal AK, Kominiarek MA. Weight gain in twin gestations: Are the Institute of Medicine guidelines optimal for neonatal outcomes? Journal of Perinatology. 2015;35(6), 405–410.

12. Lucovnik M, Blickstein I, Verdenik I, et al. Impact of pre-gravid body mass index and body mass index change on preeclampsia and gestational diabetes in singleton and twin pregnancies. Journal of Maternal-Fetal & Neonatal Medicine. 2014;27(18), 1901-1904.

13. Luke B, Min SJ, Gillespie B, et al. The importance of early weight gain in the intrauterine growth and birth weight of twins. American Journal of Obstetrics & Gynecology. 1998;179(5):1155–1161.

14. Pettit KE, Lacoursiere DY, Schrimmer DB, et al. The association of inadequate mid-pregnancy weight gain and preterm birth in twin pregnancies. Journal of Perinatology. 2015;35(2), 85-89.

15. Textor J, Hardt J, Knüppel S. Daggity: A graphical tool for analyzing causal diagrams. Epidemiology. 2011;22(5), 745.

16. Yeh J, Shelton JA. Association of pre-pregnancy maternal body mass and maternal weight gain to newborn outcomes in twin pregnancies. Acta Obstetricia et Gynecologica Scandinavica. 2007;86(9), 1051-1057.

17. Zhang J, Landy HJ, Branch DW, et al. Contemporary patterns of spontaneous labor with normal neonatal outcomes. Obstetrics & Gynecology. 2010;116, 1281-1287.

18. Zhang J, Troendle J, Reddy UM, et al. Contemporary cesarean delivery practices in the United States. American Journal of Obstetrics & Gynecology. 2010;203, e1-326 e10.

APPENDIX A – FULL TABLES FROM SAS OUTPUT LOGISTIC REGRESSION USING GENERALIZED LINEAR MODELS

Table A.1 Gestational Hypertension and Concordance with Quantile Regression Gestational Weight Gain (GWG) Guidelines

Analysis Of Maximum Likelihood Parameter Estimates							
Parameter		**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > Chi Sq**
Intercept		-5.1659	1541.14	-3025.75	3015.413	0	0.9973
MomAge		0.0044	0.0106	-0.0165	0.0253	0.17	0.68
Concordance	Below	-0.1949	0.1511	-0.4909	0.1012	1.66	0.1971
Concordance	Above	0.7139	0.1242	0.4704	0.9574	33.02	<.0001
BMIcat	Under	-0.3381	0.3219	-0.969	0.2929	1.1	0.2936
BMIcat	Overweight	0.2106	0.1467	-0.077	0.4981	2.06	0.1512
BMIcat	Obese	0.9499	0.1328	0.6896	1.2101	51.18	<.0001
Racecat	Black	0.1563	0.182	-0.2003	0.513	0.74	0.3902
Racecat	Hispanic	-0.2249	0.2077	-0.6321	0.1822	1.17	0.2789
Racecat	A/PI/Mixed/Other/Unknown	-0.5975	0.324	-1.2325	0.0375	3.4	0.0652
Smokecat		-0.8661	0.3312	-1.5153	-0.2169	6.84	0.0089
Alcoholcat		0.1897	0.3841	-0.5631	0.9426	0.24	0.6214
Paritycat2		-0.7557	0.117	-0.985	-0.5264	41.71	<.0001
Insurancecat	Public	0.1649	0.153	-0.1351	0.4648	1.16	0.2814
Insurancecat	Self-Pay/Other	-0.4683	0.3232	-1.1018	0.1653	2.1	0.1474
Maritalstat	Divorced/Single/Widowed	-0.1014	0.1695	-0.4336	0.2307	0.36	0.5494

Maritalstat	Unknown	-0.5633	0.6365	-1.8109	0.6843	0.78	0.3762
Sitenum	41	2.4292	1541.14	-3018.15	3023.008	0	0.9987
Sitenum	42	-20.3035	16952.54	-33246.7	33206.07	0	0.999
Sitenum	43	0.5287	1541.14	-3020.05	3021.108	0	0.9997
Sitenum	44	2.4801	1541.14	-3018.1	3023.059	0	0.9987
Sitenum	45	1.3455	1541.14	-3019.23	3021.925	0	0.9993
Sitenum	46	2.2568	1541.14	-3018.32	3022.836	0	0.9988
Sitenum	47	2.0037	1541.14	-3018.58	3022.583	0	0.999
Sitenum	48	1.7838	1541.14	-3018.8	3022.363	0	0.9991
Sitenum	49	1.6686	1541.14	-3018.91	3022.248	0	0.9991
Sitenum	50	1.3303	1541.14	-3019.25	3021.91	0	0.9993
Sitenum	51	1.4865	1541.14	-3019.09	3022.066	0	0.9992
Scale		0.6007	0	0.6007	0.6007		

Table A.2 Preeclampsia and Concordance with Quantile Regression Gestational Weight Gain (GWG) Guidelines

Analysis Of Maximum Likelihood Parameter Estimates							
Parameter		**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > Chi Sq**
Intercept		-3.7482	0.3526	-4.4393	-3.0571	112.99	<.0001
MomAge		0.0302	0.01	0.0106	0.0498	9.14	0.0025
Concordance	Below	-0.0547	0.141	-0.331	0.2216	0.15	0.698
Concordance	Above	0.4857	0.1313	0.2284	0.7431	13.68	0.0002
BMIcat	Under	-0.2945	0.2936	-0.87	0.281	1.01	0.3158
BMIcat	Overweight	-0.088	0.1415	-0.3654	0.1893	0.39	0.5338
BMIcat	Obese	0.0782	0.1494	-0.2146	0.3709	0.27	0.6008
Racecat	Black	-0.2858	0.1902	-0.6586	0.0871	2.26	0.1331
Racecat	Hispanic	0.2118	0.1802	-0.1415	0.5651	1.38	0.2399
Racecat	A/PI/Mixed/Other/Unknown	0.3942	0.2278	-0.0523	0.8407	2.99	0.0836
Smokecat		-0.0427	0.2593	-0.5508	0.4655	0.03	0.8693
Alcoholcat		0.5652	0.3416	-0.1044	1.2347	2.74	0.0981
Paritycat2		-0.5654	0.1164	-0.7935	-0.3374	23.61	<.0001
Insurancecat	Public	0.114	0.1581	-0.196	0.4239	0.52	0.4712
Insurancecat	Self-Pay/Other	0.342	0.222	-0.0931	0.7771	2.37	0.1234
Maritalstat	Divorced/Single/Windowed	0.1972	0.1567	-0.11	0.5044	1.58	0.2084
Maritalstat	Unknown	-1.3649	0.7065	-2.7497	0.0199	3.73	0.0534
Sitenum	41	0.1133	0.1458	-0.1725	0.3992	0.6	0.4371
Sitenum	42	0.8993	0.2349	0.4388	1.3597	14.65	0.0001
Sitenum	43	-0.9832	0.3323	-1.6345	-0.3318	8.75	0.0031
Sitenum	44	0.3615	0.1879	-0.0068	0.7297	3.7	0.0544
Sitenum	45	0.5184	0.2152	0.0965	0.9402	5.8	0.016
Sitenum	46	-0.0233	0.3005	-0.6123	0.5657	0.01	0.9382
Sitenum	47	0.3695	0.2619	-0.1438	0.8829	1.99	0.1583
Sitenum	48	0.0215	0.1894	-0.3497	0.3926	0.01	0.9098

Sitenum	49	0.3815	0.1915	0.0062	0.7567	3.97	0.0463
Sitenum	50	-0.1135	0.4607	-1.0164	0.7895	0.06	0.8055
Sitenum	51	-0.2072	0.2087	-0.6164	0.2019	0.99	0.3209
Scale		0.6722	0	0.6722	0.6722		

Table A.3 Gestational Diabetes Mellitus and Concordance with Quantile Regression Gestational Weight Gain (GWG) Guidelines

Analysis Of Maximum Likelihood Parameter Estimates							
Parameter		**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > Chi Sq**
Intercept		-5.109	0.3574	-5.8094	-4.4086	204.39	<.0001
MomAge		0.0724	0.0098	0.0531	0.0917	54.11	<.0001
Concordance	Below	0.1395	0.1268	-0.1091	0.388	1.21	0.2714
Concordance	Above	-0.0792	0.1466	-0.3666	0.2082	0.29	0.5893
BMIcat	Under	-0.1051	0.3373	-0.7662	0.5559	0.1	0.7553
BMIcat	Overweight	0.625	0.139	0.3526	0.8974	20.22	<.0001
BMIcat	Obese	1.1435	0.1378	0.8734	1.4135	68.88	<.0001
Racecat	Black	-0.289	0.1857	-0.6529	0.0749	2.42	0.1196
Racecat	Hispanic	0.3697	0.1721	0.0324	0.7069	4.61	0.0317
Racecat	A/PI/Mixed/Other/Unknown	0.1651	0.2498	-0.3245	0.6546	0.44	0.5087
Smokecat		-0.6183	0.3172	-1.2401	0.0034	3.8	0.0513
Alcoholcat		0.3581	0.3884	-0.4031	1.1193	0.85	0.3564
Paritycat2		-0.1348	0.1163	-0.3627	0.0932	1.34	0.2465
Insurancecat	Public	-0.0909	0.1613	-0.4071	0.2252	0.32	0.5729
Insurancecat	Self-Pay/Other	-0.2576	0.2126	-0.6744	0.1592	1.47	0.2257
Maritalstat	Divorced/Single/Windowed	-0.3178	0.1683	-0.6477	0.0122	3.56	0.0591
Maritalstat	Unknown	-0.2549	0.4067	-1.0519	0.5422	0.39	0.5308
Sitenum	41	-0.2893	0.1364	-0.5566	-0.022	4.5	0.0339
Sitenum	42	-0.0931	0.3144	-0.7092	0.523	0.09	0.7671
Sitenum	43	0.155	0.2016	-0.2402	0.5502	0.59	0.442
Sitenum	44	0.3459	0.1767	-0.0005	0.6923	3.83	0.0503
Sitenum	45	-0.1853	0.2234	-0.6232	0.2525	0.69	0.4068
Sitenum	46	0.1193	0.2717	-0.4132	0.6518	0.19	0.6605
Sitenum	47	-0.4851	0.3128	-1.0983	0.128	2.4	0.121
Sitenum	48	-0.1499	0.1829	-0.5084	0.2086	0.67	0.4124
Sitenum	49	-0.1912	0.212	-0.6066	0.2242	0.81	0.3671
Sitenum	50	0.3665	0.3255	-0.2714	1.0045	1.27	0.2601

Sitenum	51	0.0849	0.1785	-0.265	0.4349	0.23	0.6343
Scale		0.7062	0	0.7062	0.7062		

Table A.4 Cesarean Delivery and Concordance with Quantile Regression Gestational Weight Gain (GWG) Guidelines

Analysis Of Maximum Likelihood Parameter Estimates							
Parameter		**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > Chi Sq**
Intercept		-0.7127	0.2922	-1.2854	-0.14	5.95	0.0147
MomAge		0.0505	0.0087	0.0333	0.0676	33.35	<.0001
Concordance	Below	-0.2395	0.1055	-0.4462	-0.0328	5.16	0.0232
Concordance	Above	0.1456	0.1198	-0.0892	0.3804	1.48	0.2243
BMIcat	Under	-0.3871	0.2047	-0.7883	0.0141	3.58	0.0586
BMIcat	Overweight	0.1182	0.1143	-0.1058	0.3423	1.07	0.3009
BMIcat	Obese	0.3071	0.1233	0.0655	0.5488	6.21	0.0127
Racecat	Black	0.3537	0.1531	0.0537	0.6537	5.34	0.0208
Racecat	Hispanic	0.2166	0.1553	-0.0878	0.5209	1.94	0.1632
Racecat	A/PI/Mixed/Other/Unknown	0.1392	0.2209	-0.2937	0.5722	0.4	0.5285
Smokecat		0.1271	0.1951	-0.2554	0.5095	0.42	0.5149
Alcoholcat		0.0582	0.3232	-0.5752	0.6916	0.03	0.857
Paritycat2		-0.6686	0.0995	-0.8637	-0.4735	45.11	<.0001
Insurancecat	Public	0.1633	0.1274	-0.0864	0.413	1.64	0.1998
Insurancecat	Self-Pay/Other	-0.751	0.2049	-1.1526	-0.3494	13.43	0.0002
Maritalstat	Divorced/Single/Windowed	-0.1612	0.1335	-0.4229	0.1005	1.46	0.2273
Maritalstat	Unknown	-0.2242	0.3245	-0.8602	0.4118	0.48	0.4896
Sitenum	41	0.0669	0.1124	-0.1533	0.2872	0.35	0.5513
Sitenum	42	0.0548	0.2431	-0.4215	0.5312	0.05	0.8215
Sitenum	43	-1.1823	0.1645	-1.5047	-0.8598	51.64	<.0001
Sitenum	44	0.2055	0.1559	-0.1	0.511	1.74	0.1874
Sitenum	45	-0.3282	0.1869	-0.6946	0.0381	3.08	0.079
Sitenum	46	-0.1506	0.2128	-0.5677	0.2665	0.5	0.4792
Sitenum	47	-0.1306	0.2579	-0.6362	0.3749	0.26	0.6126
Sitenum	48	0.6294	0.1634	0.3091	0.9497	14.83	0.0001
Sitenum	49	-0.0939	0.1674	-0.4219	0.2341	0.31	0.5747
Sitenum	50	-0.3172	0.311	-0.9268	0.2924	1.04	0.3078
Sitenum	51	0.7577	0.1861	0.3929	1.1225	16.58	<.0001

Cesareanhist	Yes	2.162	0.2069	1.7565	2.5676	109.19	<.0001
Cesareanhist	Unknown	-1.0074	0.3071	-1.6094	-0.4054	10.76	0.001
Scale		1.0575	0	1.0575	1.0575		

Table A.5 Gestational Hypertension and Total Gestational Weight Gain (GWG)

Analysis Of Maximum Likelihood Parameter Estimates							
Parameter		**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > Chi Sq**
Intercept		-8.562	1739.906	-3418.72	3401.592	0	0.9961
MomAge		0.0022	0.0105	-0.0184	0.0228	0.05	0.8318
totalGWG		0.0538	0.0067	0.0407	0.0668	65.2	<.0001
BESTGA		0.0693	0.0204	0.0294	0.1093	11.59	0.0007
BMIcat	Under	-0.1659	0.3106	-0.7746	0.4428	0.29	0.5932
BMIcat	Overweight	0.2786	0.1456	-0.0067	0.564	3.66	0.0557
BMIcat	Obese	1.2512	0.1319	0.9927	1.5098	89.96	<.0001
Racecat	Black	0.2177	0.1797	-0.1345	0.5698	1.47	0.2257
Racecat	Hispanic	-0.1781	0.2032	-0.5764	0.2202	0.77	0.3808
Racecat	A/PI/Mixed/Other/Unknown	-0.5569	0.3132	-1.1708	0.057	3.16	0.0754
Smokecat		-0.737	0.3264	-1.3768	-0.0972	5.1	0.024
Alcoholcat		0.118	0.3806	-0.6279	0.864	0.1	0.7564
Paritycat2		-0.8072	0.1155	-1.0335	-0.5809	48.87	<.0001
Insurancecat	Public	0.097	0.1533	-0.2034	0.3975	0.4	0.5268
Insurancecat	Self-Pay/Other	-0.3945	0.3094	-1.001	0.212	1.63	0.2024
Maritalstat	Divorced/Single/Windowed	0.0016	0.1678	-0.3273	0.3304	0	0.9924
Maritalstat	Unknown	-0.4393	0.6174	-1.6493	0.7707	0.51	0.4767
Sitenum	41	2.5303	1739.906	-3407.62	3412.684	0	0.9988
Sitenum	42	-20.3658	19138.97	-37532.1	37491.32	0	0.9992
Sitenum	43	0.1237	1739.906	-3410.03	3410.277	0	0.9999
Sitenum	44	2.6477	1739.906	-3407.51	3412.801	0	0.9988
Sitenum	45	1.4785	1739.906	-3408.67	3411.632	0	0.9993
Sitenum	46	2.1521	1739.906	-3408	3412.305	0	0.999
Sitenum	47	2.0819	1739.906	-3408.07	3412.235	0	0.999
Sitenum	48	1.8589	1739.906	-3408.29	3412.012	0	0.9991
Sitenum	49	1.6905	1739.906	-3408.46	3411.844	0	0.9992

Sitenum	50	1.4598	1739.906	-3408.69	3411.613	0	0.9993
Sitenum	51	1.4734	1739.906	-3408.68	3411.627	0	0.9993
Scale		0.5792	0	0.5792	0.5792		

Table A.6 Preeclampsia and Total Gestational Weight Gain (GWG)

Analysis Of Maximum Likelihood Parameter Estimates							
Parameter		**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > Chi Sq**
Intercept		-1.5782	2159.900	-4234.90	4231.748	0.00	0.9994
MomAge		0.0303	0.0098	0.0111	0.0495	9.59	0.0020
totalGWG		0.0749	0.0150	0.0454	0.1044	24.80	<.0001
gwg19		-0.0891	0.0248	-0.1376	-0.0405	12.93	0.0003
BESTGA		-0.1455	0.0151	-0.1751	-0.1160	93.25	<.0001
BMIcat	Under	-0.2880	0.2823	-0.8414	0.2653	1.04	0.3076
BMIcat	Overweight	0.0013	0.1388	-0.2708	0.2734	0.00	0.9926
BMIcat	Obese	0.3431	0.1488	0.0515	0.6346	5.32	0.0211
Racecat	Black	-0.3353	0.1892	-0.7061	0.0356	3.14	0.0764
Racecat	Hispanic	0.2504	0.1740	-0.0905	0.5914	2.07	0.1500
Racecat	A/PI/Mixed/Other/Unknown	0.4179	0.2196	-0.0126	0.8484	3.62	0.0571
Smokecat		-0.2671	0.2616	-0.7799	0.2457	1.04	0.3072
Alcoholcat		0.6300	0.3270	-0.0108	1.2709	3.71	0.0540
Paritycat2		-0.5401	0.1142	-0.7640	-0.3163	22.37	<.0001
Insurancecat	Public	0.2345	0.1531	-0.0656	0.5345	2.35	0.1256
Insurancecat	Self-Pay/Other	0.3411	0.2183	-0.0868	0.7690	2.44	0.1182
Maritalstat	Divorced/Single/Windowed	0.1952	0.1528	-0.1042	0.4946	1.63	0.2014
Maritalstat	Unknown	-1.1710	0.6764	-2.4966	0.1547	3.00	0.0834
Sitenum	41	1.8479	2159.9	-4231.48	4235.174	0	0.9993
Sitenum	42	2.8049	2159.9	-4230.52	4236.131	0	0.999
Sitenum	43	0.8033	2159.9	-4232.52	4234.13	0	0.9997
Sitenum	44	1.8763	2159.9	-4231.45	4235.203	0	0.9993
Sitenum	45	2.191	2159.9	-4231.14	4235.517	0	0.9992
Sitenum	46	1.8343	2159.9	-4231.49	4235.161	0	0.9993
Sitenum	47	2.1608	2159.9	-4231.17	4235.487	0	0.9992

Sitenum	48	1.5468	2159.9	-4231.78	4234.873	0	0.9994
Sitenum	49	2.0471	2159.9	-4231.28	4235.373	0	0.9992
Sitenum	50	1.9493	2159.9	-4231.38	4235.276	0	0.9993
Sitenum	51	1.6062	2159.9	-4231.72	4234.933	0	0.9994
Scale		0.6399	0.0000	0.6399	0.6399		

Table A7 Gestational Diabetes Mellitus and Total Gestational Weight Gain (GWG)

Analysis Of Maximum Likelihood Parameter Estimates							
Parameter		**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > Chi Sq**
Intercept		-4.63	0.6433	-5.8908	-3.3692	51.8	<.0001
MomAge		0.0723	0.0095	0.0536	0.091	57.45	<.0001
totalGWG		-0.0081	0.0072	-0.0223	0.006	1.27	0.2602
BESTGA		-0.0101	0.0165	-0.0425	0.0222	0.38	0.54
BMIcat	Under	-0.2966	0.3561	-0.9945	0.4012	0.69	0.4048
BMIcat	Overweight	0.5802	0.1346	0.3164	0.8441	18.58	<.0001
BMIcat	Obese	1.1088	0.1368	0.8406	1.3769	65.68	<.0001
Racecat	Black	-0.3096	0.1819	-0.6661	0.0469	2.9	0.0888
Racecat	Hispanic	0.4056	0.1655	0.0813	0.7299	6.01	0.0142
Racecat	A/PI/Mixed/Other/Unknown	0.1742	0.2393	-0.2948	0.6432	0.53	0.4666
Smokecat		-0.5587	0.3047	-1.1559	0.0386	3.36	0.0667
Alcoholcat		0.3424	0.3717	-0.3861	1.071	0.85	0.3569
Paritycat2		-0.068	0.1138	-0.291	0.1551	0.36	0.5505
Insurancecat	Public	-0.2128	0.1573	-0.5212	0.0956	1.83	0.1763
Insurancecat	Self-Pay/Other	-0.2792	0.2041	-0.6793	0.1208	1.87	0.1713
Maritalstat	Divorced/Single/Windowed	-0.1823	0.162	-0.4998	0.1352	1.27	0.2604
Maritalstat	Unknown	-0.0235	0.3907	-0.7892	0.7421	0	0.952
Sitenum	41	-0.2598	0.1339	-0.5223	0.0026	3.76	0.0524
Sitenum	42	0.0299	0.3345	-0.6258	0.6856	0.01	0.9288
Sitenum	43	0.2091	0.1956	-0.1743	0.5925	1.14	0.2851
Sitenum	44	0.3592	0.1723	0.0214	0.6969	4.34	0.0371
Sitenum	45	-0.2144	0.2262	-0.6577	0.2289	0.9	0.3432
Sitenum	46	0.0061	0.2786	-0.54	0.5522	0	0.9825
Sitenum	47	-0.6752	0.3307	-1.3234	-0.027	4.17	0.0412
Sitenum	48	-0.1345	0.1774	-0.4822	0.2133	0.57	0.4486
Sitenum	49	-0.1791	0.2044	-0.5797	0.2216	0.77	0.3811
Sitenum	50	0.3212	0.3453	-0.3554	0.9979	0.87	0.3521
Sitenum	51	0.1276	0.1738	-0.2131	0.4682	0.54	0.463
Scale		0.6755	0	0.6755	0.6755		

Table A.8 Cesarean Delivery and Total Gestational Weight Gain (GWG)

Analysis Of Maximum Likelihood Parameter Estimates							
Parameter		**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > Chi Sq**
Intercept		1.4676	0.5975	0.2965	2.6387	6.03	0.014
MomAge		0.0503	0.0089	0.0328	0.0678	31.72	<.0001
totalGWG		0.0152	0.0064	0.0027	0.0278	5.63	0.0176
BESTGA		-0.4653	0.2086	-0.8742	-0.0564	4.98	0.0257
BMIcat	Under	0.1289	0.1166	-0.0996	0.3574	1.22	0.2688
BMIcat	Overweight	0.3532	0.1296	0.0992	0.6073	7.43	0.0064
BMIcat	Obese	-0.0709	0.0155	-0.1012	-0.0405	20.93	<.0001
Racecat	Black	0.3357	0.1572	0.0275	0.6439	4.56	0.0328
Racecat	Hispanic	0.2417	0.1583	-0.0685	0.5519	2.33	0.1267
Racecat	A/PI/Mixed/Other/Unknown	0.1235	0.2238	-0.3152	0.5622	0.3	0.5812
Smokecat		0.0318	0.2037	-0.3674	0.4311	0.02	0.8759
Alcoholcat		0.0468	0.3305	-0.6009	0.6945	0.02	0.8874
Paritycat2		-0.6603	0.1016	-0.8596	-0.4611	42.21	<.0001
Insurancecat	Public	0.1702	0.131	-0.0866	0.427	1.69	0.194
Insurancecat	Self-Pay/Other	-0.8223	0.2091	-1.2322	-0.4125	15.46	<.0001
Maritalstat	Divorced/Single/Windowed	-0.2072	0.137	-0.4757	0.0613	2.29	0.1305
Maritalstat	Unknown	-0.2346	0.3395	-0.9	0.4309	0.48	0.4897
Sitenum	41	0.0918	0.1158	-0.1353	0.3188	0.63	0.4282
Sitenum	42	-0.0219	0.2859	-0.5822	0.5383	0.01	0.9389
Sitenum	43	-1.1831	0.1716	-1.5195	-0.8467	47.52	<.0001
Sitenum	44	0.1664	0.1595	-0.1462	0.479	1.09	0.2969
Sitenum	45	-0.379	0.1965	-0.7641	0.006	3.72	0.0537
Sitenum	46	-0.0472	0.2174	-0.4732	0.3788	0.05	0.828
Sitenum	47	-0.1999	0.2683	-0.7258	0.326	0.55	0.4563
Sitenum	48	0.6189	0.167	0.2916	0.9462	13.73	0.0002
Sitenum	49	-0.0936	0.1701	-0.427	0.2398	0.3	0.5821
Sitenum	50	-0.2395	0.338	-0.9019	0.423	0.5	0.4786
Sitenum	51	0.8607	0.1907	0.4869	1.2344	20.37	<.0001
Cesareanhist	Yes	2.2417	0.2141	1.822	2.6614	109.58	<.0001

Cesareanhist	Unknown	-0.881	0.3303	-1.5284	-0.2336	7.11	0.0076
Scale		1.0576	0	1.0576	1.0576		

Table A.9 Association between Gestational Hypertension and Total GWG and Concordance with GWG Guidelines among Twins in the CSL Study [a]

	Total GWG Model [b]		Concordance Model [c]	
	OR	95% CI	OR	95% CI
Total GWG (5 kg)	1.31	1.23, 1.40*		
Gestational Age (1 week)	1.07	1.03, 1.12*		
Concordance				
Below vs Within			0.82	0.61, 1.07
Above vs Within			0.40	0.30, 0.55*
Maternal Age	1.00	0.98, 1.02		
Pre-Pregnancy BMI [c]				
Underweight vs Normal	0.85	0.46, 1.56	0.71	0.38, 1.34
Overweight vs Normal	1.32	0.99, 1.76	1.23	0.93, 1.65
Obese vs Normal	3.50	2.70, 4.53*	2.59	1.99, 3.35*
Race/Ethnicity				
Non-Hispanic Black vs NHW	1.24	0.87, 1.77	1.17	0.82, 1.57
Hispanic vs NHW	0.84	0.56, 1.25	0.80	0.53, 1.20
Asian/PI/Multi/Other/Unknown vs NHW	0.57	0.31, 1.06	0.55	0.29, 1.04
Marital Status				
Divorced/Widowed/Single vs Married	1.00	0.72, 1.39	0.90	0.65, 1.26
Unknown vs Married	0.64	0.19, 2.16	0.57	0.16, 1.98
Smoking Status				
Yes vs No	0.48	0.25, 0.91*	0.42	0.22, 0.81*
Alcohol Status				
Yes vs No	1.13	0.53, 2.37	1.21	0.57, 2.57
Parity				
Multiparous vs Nulliparous	0.45	0.36, 0.56*	0.47	0.37, 0.59*
Insurance				
Public vs Private	1.10	0.82, 1.49	1.18	0.87, 1.59
Self-Pay/Other/Unknown vs Private	0.67	0.37, 1.24	0.63	0.33, 1.18

All numbers are ORs with 95% CIs. ORs are obtained from binary logistic regression using generalized linear models. The following groups served as the reference groups in both models: concordance=within, pre-pregnancy BMI=normal-weight, race/ethnicity=non-Hispanic white (NHW), marital status=married, smoking status=no, alcohol status=no, parity=nulliparous, and insurance=private.
**Indicates significant results.*
[a] Women with chronic hypertension were excluded from the analyses of gestational hypertension and preeclampsia.
[b] Total GWG Model uses the continuous, total GWG as the exposure of interest variable. All results are adjusted for maternal age, race/ethnicity, gestational age at delivery, pre-pregnancy BMI category, smoking status, alcohol status, parity, insurance type, marital status, and hospital site number.
[c] Concordance Model used concordance within the quantile regression total GWG guidelines variable for exposure of interest variable. All results are adjusted for maternal age, race/ethnicity, pre-pregnancy BMI category, smoking status, alcohol status, parity, insurance type, marital status, and hospital site number.
[d] Maternal pre-pregnancy BMI is categorized as underweight if BMI is <18.5 kg/m^2, normal-weight if BMI is 18.5 to 24.9 kg/m^2, overweight if BMI is 25.0 to 29.9 kg/m^2, obese if BMI is $\geq$ 30.0.

Table A.10 Association between Preeclampsia and Total GWG and Concordance with GWG Guidelines among Twins in the CSL Study [a]

	Total GWG Model [b]		Concordance Model [c]	
	OR	95% CI	OR	95% CI
Total GWG (5 kg)				
Before 19 kg	1.16	1.01, 1.33*		
After 19 kg	0.80	0.62, 1.02		
Gestational Age (1 week)	0.86	0.84, 0.89*		
Concordance				
Below vs Within			0.95	0.63, 1.43
Above vs Within			1.63	1.11, 2.38*
Maternal Age	1.03	1.01, 1.05*	1.03	1.00, 1.06
Pre-Pregnancy BMI [c]				
Underweight vs Normal	0.75	0.43, 1.30	0.74	0.32, 1.75
Overweight vs Normal	1.00	0.76, 1.31	0.92	0.61, 1.38
Obese vs Normal	1.41	1.05, 1.89*	1.08	0.70, 1.67
Race/Ethnicity				
Non-Hispanic Black vs NHW	0.72	0.49, 1.04	0.75	0.43, 1.31
Hispanic vs NHW	1.28	0.91, 1.81	1.24	0.73, 2.09
Asian/PI/Multi/Other/Unknown vs NHW	1.52	0.99, 2.34	1.48	0.76, 2.88
Marital Status				
Divorced/Widowed/Single vs Married	1.22	0.90, 1.64	1.22	0.77, 1.92
Unknown vs Married	0.31	0.08, 1.17	0.26	0.03, 2.00
Smoking Status				
Yes vs No	0.77	0.46, 1.28	0.96	0.45, 2.04
Alcohol Status				
Yes vs No	1.88	0.99, 3.56	1.76	0.65, 4.76
Parity				
Multiparous vs Nulliparous	0.58	0.47, 0.73*	0.57	0.40, 0.80*
Insurance				
Public vs Private	1.26	0.94, 1.71	1.12	0.71, 1.78
Self-Pay/Other/Unknown vs Private	1.41	0.92, 2.16	1.41	0.74, 2.69

All numbers are ORs with 95% CIs. ORs are obtained from binary logistic regression using generalized linear models. The following groups served as the reference groups in both models: concordance=within, pre-pregnancy BMI=normal-weight, race/ethnicity=non-Hispanic white, marital status=married, smoking status=no, alcohol status=no, parity=nulliparous, and insurance=private.
**Indicates significant results.*
[a] Women with chronic hypertension were excluded from the analyses of gestational hypertension and preeclampsia.
[b] Total GWG Model uses the continuous, total GWG as the exposure of interest variable. All results are adjusted for maternal age, race/ethnicity, gestational age at delivery, pre-pregnancy BMI category, smoking status, alcohol status, parity, insurance type, marital status, and hospital site number. Variables for spline knots were included in the model.
[c] Concordance Model used concordance with the quantile regression total GWG guidelines variable for exposure of interest variable. All results are adjusted for maternal age, race/ethnicity, pre-pregnancy BMI category, smoking status, alcohol status, parity, insurance type, marital status, and hospital site number.
[d] Maternal pre-pregnancy BMI is categorized as underweight if BMI is <18.5 kg/m^2, normal-weight if BMI is 18.5 to 24.9 kg/m^2, overweight if BMI is 25.0 to 29.9 kg/m^2, obese if BMI is $\geq$ 30.0.

Table A.11 Association Between Gestational Diabetes Mellitus and Total GWG and Concordance with GWG Guidelines among Twins in the CSL Study [a]

	Total GWG Model [b]		**Concordance Model [c]**	
		95% CI	OR	95% CI
Total GWG (5 kg)	0.96	0.89, 1.03		
Gestational Age (1 week)	0.99	0.96, 1.02		
Concordance				
Below vs Within			1.15	0.81, 1.63
Above vs Within			0.92	0.62, 1.39
Maternal Age	1.08	1.06, 1.10*	1.08	1.05, 1.10*
Pre-Pregnancy BMI [c]				
Underweight vs Normal	0.74	0.37, 1.49	0.90	0.35, 2.30
Overweight vs Normal	1.79	1.37, 2.33*	1.87	1.27, 2.75*
Obese vs Normal	3.03	2.32, 3.96*	3.14	2.14, 4.60*
Race/Ethnicity				
Non-Hispanic Black vs NHW	0.73	0.51, 1.05	0.75	0.45, 1.25
Hispanic vs NHW	1.50	1.08, 2.07*	1.45	0.90, 2.33
Asian/PI/Multi/Other/Unknown vs NHW	1.19	0.74, 1.90	1.18	0.59, 2.36
Marital Status				
Divorced/Widowed/Single vs Married	0.83	0.61, 1.14	0.73	0.46, 1.16
Unknown vs Married	0.98	0.45, 2.10	0.78	0.25, 2.40
Smoking Status				
Yes vs No	0.57	0.31, 1.04	0.54	0.22, 1.30
Alcohol Status				
Yes vs No	1.41	0.68, 2.92	1.43	0.49, 4.20
Parity				
Multiparous vs Nulliparous	0.93	0.75, 1.17	0.87	0.63, 1.21
Insurance				
Public vs Private	0.81	0.59, 1.10	0.91	0.58, 1.43
Self-Pay/Other/Unknown vs Private	0.76	0.51, 1.13	0.77	0.43, 1.39

All numbers are ORs with 95% CIs. ORs are obtained from binary logistic regression with generalized linear models. The following groups served as the reference groups in both models: concordance=within, pre-pregnancy BMI=normal-weight, race/ethnicity=non-Hispanic white (NHW), marital status=married, smoking status=no, alcohol status=no, parity=nulliparous, and insurance=private.
Indicates significant results.
[a] *Women with chronic diabetes mellitus were excluded from the analyses of GDM.*
[b] *Total GWG Model uses the continuous, total GWG as the exposure of interest variable. All results are adjusted for maternal age, race/ethnicity, gestational age at delivery, pre-pregnancy BMI category, smoking status, alcohol status, parity, insurance type, marital status, and hospital site number. Variables for spline knots were included in the model.*
[c] *Concordance Model used concordance with the quantile regression total GWG guidelines variable for exposure of interest variable. All results are adjusted for maternal age, race/ethnicity, pre-pregnancy BMI category, smoking status, alcohol status, parity, insurance type, marital status, and hospital site number.*
[d] *Maternal pre-pregnancy BMI is categorized as underweight if BMI is <18.5 kg/m^2, normal-weight if BMI is 18.5 to 24.9 kg/m^2, overweight if BMI is 25.0 to 29.9 kg/m^2, obese if BMI is $\geq$ 30.0.*

Table A.12 Association Between Cesarean Delivery and Total GWG and Concordance with GWG Guidelines among Twins in the CSL Study

	Total GWG Model [a]		**Concordance Model** [b]	
	OR	95% CI	OR	95% CI
Total GWG (5 kg)	1.08	1.01, 1.15*		
Gestational Age	0.93	0.90, 0.96*		
Concordance				
Below vs Within			0.79	0.65, 0.96*
Above vs Within			1.16	0.93, 1.44
Maternal Age	1.05	1.03, 1.07*	1.05	1.03, 1.07*
Pre-Pregnancy BMI [c]				
Underweight vs Normal	0.63	0.41, 0.95*	0.68	0.46, 0.99*
Overweight vs Normal	1.14	0.91, 1.43	1.13	0.91, 1.39
Obese vs Normal	1.42	1.10, 1.84*	1.36	1.08, 1.71*
Race/Ethnicity				
Non-Hispanic Black vs NHW	1.39	1.03, 1.90*	1.42	1.07, 1.89*
Hispanic vs NHW	1.27	0.93, 1.74	1.24	0.93, 1.66
Asian/PI/Multi/Other/Unknown vs NHW	1.13	0.73, 1.75	1.15	0.76, 1.73
Marital Status				
Divorced/Widowed/Single vs Married	0.81	0.62, 1.06	0.85	0.66, 1.09
Unknown vs Married	0.79	0.41, 1.54	0.80	0.44, 1.46
Smoking Status				
Yes vs No	1.03	0.69, 1.54	1.14	0.79, 1.63
Alcohol Status				
Yes vs No	1.05	0.55, 2.00	1.06	0.58, 1.93
Parity				
Multiparous vs Nulliparous	0.52	0.42, 0.63*	0.51	0.43, 0.62*
Insurance				
Public vs Private	1.19	0.92, 1.53	1.18	0.93, 1.49
Self-Pay/Other/Unknown vs Private	0.44	0.29, 0.66	0.47	0.32, 0.69
History of Cesarean Delivery				
Yes vs No	9.41	6.18, 14.32*	8.69	5.92, 12.75
Unknown vs No	0.41	0.22, 0.79*	0.37	0.21, 0.65*

All numbers are ORs with 95% CIs. ORs are obtained from binary logistic regression using generalized linear models. The following groups served as the reference groups in both models: concordance=within, pre-pregnancy BMI=normal-weight, race/ethnicity=non-Hispanic white (NHW), marital status=married, smoking status=no, alcohol status=no, parity=nulliparous, insurance=private, history of cesarean delivery=no.

*Indicates significant results.

[a] *Total GWG Model uses the continuous, total GWG as the exposure of interest variable. All results are adjusted for maternal age, race/ethnicity, gestational age at delivery, pre-pregnancy BMI category, smoking status, alcohol status, parity, insurance type, marital status, and hospital site number. Variables for spline knots were included in the model.*

[b] *Concordance Model used concordance with the quantile regression total GWG guidelines variable for exposure of interest variable. All results are adjusted for maternal age, race/ethnicity, pre-pregnancy BMI category, smoking status, alcohol status, parity, insurance type, marital status, and hospital site number.*

[c] *Maternal pre-pregnancy BMI is categorized as underweight if BMI is <18.5 kg/m^2, normal-weight if BMI is 18.5 to 24.9 kg/m^2, overweight if BMI is 25.0 to 29.9 kg/m^2, obese if BMI is $\geq$ 30.0.*