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

Kerry Spillane
University of South Carolina

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

by

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Bachelor of Arts
University of South Carolina, 2014

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Norman J. Arnold School of Public Health
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2017

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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 25th and 75th 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.
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>A.OR</td>
<td>Adjusted Odds Ratio</td>
</tr>
<tr>
<td>ART</td>
<td>Assisted Reproductive Technology</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CSL</td>
<td>Consortium on Safe Labor</td>
</tr>
<tr>
<td>DAG</td>
<td>Direct Acyclic Graph</td>
</tr>
<tr>
<td>GDM</td>
<td>Gestational Diabetes Mellitus</td>
</tr>
<tr>
<td>GWG</td>
<td>Gestational Weight Gain</td>
</tr>
<tr>
<td>ICD-9</td>
<td>International Classification of Diseases, Ninth Edition</td>
</tr>
<tr>
<td>IOM</td>
<td>Institute of Medicine</td>
</tr>
<tr>
<td>KG</td>
<td>Kilograms</td>
</tr>
<tr>
<td>LBS</td>
<td>Pounds</td>
</tr>
<tr>
<td>MULTI</td>
<td>Multi-Racial</td>
</tr>
<tr>
<td>NICHD</td>
<td>National Institute of Child Health and Human Development</td>
</tr>
<tr>
<td>NHW</td>
<td>Non-Hispanic White</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PI</td>
<td>Pacific Islander</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
</tbody>
</table>
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.)\textsuperscript{2}. Twins account for an estimated 3.3\% of all live births in the U.S.\textsuperscript{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)\textsuperscript{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\textsuperscript{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)\textsuperscript{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\textsuperscript{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$). There were no provisional guidelines issued for women with an underweight pre-pregnancy BMI (<18.50 kg/m$^2$) due to insufficient evidence. 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. 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.

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. 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. All studies used the 2009 IOM GWG guidelines for twin gestations to categorize and assess GWG. 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. 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. Lucovnik et al evaluated GWG as the total change in gestational BMI; calculated as pre-pregnancy BMI subtracted from BMI at time of delivery. Fox et al 2010, Fox et al 2011, and Gavard & Artal all measured GWG as total GWG. 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.

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). Gavard et al found a significant positive trend between increasing GWG and the development of preeclampsia (p<0.05). 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). 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%). 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). 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).

**Gestational Diabetes**

Five of the studies assessed the association between GWG and the risk of GDM. 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). Fox et al 2011 did not find any significant differences in the risk of GDM across all pre-pregnancy BMI categories (p=0.157). 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). They also found that women with an obese pre-pregnancy BMI were more likely to develop GDM as total GWG increased (p<0.01). 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

<table>
<thead>
<tr>
<th>Author, Time, Place</th>
<th>Study Design, Sample Size</th>
<th>Measure of Gestational Weight Gain</th>
<th>Comparison Groups</th>
<th>Maternal Outcomes of Interest</th>
<th>Control Variables</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fox et al, 2010, US⁵</td>
<td>Retrospective Cohort 297 twin pregnancies</td>
<td>Total GWG</td>
<td>Categories of adequacy of adherence (normal weight gain, low weight gain) to 2009 IOM guidelines across preg- pregnancy BMI categories, dividing all guidelines by 37 to determine IOM recommended weight gain per week</td>
<td>Gestational hypertension, GDM</td>
<td>Pre-pregnancy BMI, gestational age at delivery</td>
<td>“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</td>
</tr>
</tbody>
</table>
| Fox et al, 2011, US⁶ | 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
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample Size</th>
<th>Total GWG</th>
<th>Categories of adequacy of adherence (below, within, above) to 2009 IOM guidelines divided by 37 compared across pre-pregnancy BMI categories</th>
<th>Gestational hypertension, preeclampsia, GDM, pre-pregnancy BMI, maternal age, race, education, parity, chronic hypertension, chronic diabetes, maternal smoking status</th>
<th>Adverse outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gavard &amp; Artal, 2014, US&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Retrospective Cohort</td>
<td>405 twin pregnancies born to women with obese pre-pregnancy BMIs</td>
<td>Total GWG</td>
<td>Three 2009 IOM guidelines categories of GWG (&lt; 25 lbs., 25-42 lbs., &gt;42 lbs.) compared across three BMI classifications of obesity [class I (≥30.0 - &lt; 35.0 kg/m²), class II (≥35.0 - &lt; 40.0 kg/m²), class III (≥40.0 kg/m²)]. Also, looked at outcomes assessed by GWG categories per concordant and discordant birthweight pairs</td>
<td>Preeclampsia, cesarean delivery</td>
<td>Maternal age, race, education, pre-pregnancy BMI, socioeconomic status, smoking status, parity, chronic diabetes, chronic hypertension, gestational age at delivery</td>
<td>“A significant increasing trend with GWG was found for preeclampsia (p &lt;0.05). An increasing trend with gestational weight gain for cesarean delivery was of borderline significant (p=0.06). Women who gained &gt;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 &gt;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&lt;0.05) and cesarean delivery (p&lt;0.05) in concordant twin pairs.”&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
| Lal & Kominiarek, 2015, US<sup>11</sup> | 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, preeclampsia, GDM, pre-pregnancy BMI, maternal age, race, chronic hypertension | Adverse outcomes | “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."  

<table>
<thead>
<tr>
<th>Lucovnik et al, 2014, Slovenia</th>
<th>Retrospective Cohort</th>
<th>Total Gestational BMI change (BMI at delivery – pre-gravid BMI)</th>
<th>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</th>
<th>Preeclampsia, GDM</th>
<th>Number of fetuses, maternal age, parity, diagnosis of gestational diabetes or preeclampsia</th>
</tr>
</thead>
</table>
| 2,046 twin pregnancies delivered at >36 weeks, compared to 6,138 singletons | | | | | “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/m² versus 6.1±2.2 kg/m², 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

<table>
<thead>
<tr>
<th>Pettit et al, 2015, US14</th>
<th>Retrospective Cohort</th>
<th>489 twin pregnancies</th>
<th>Weekly rate of GWG</th>
<th>Categories of adequacy of adherence (adequate, inadequate) to 2009 IOM guidelines divided by 37 across pre-pregnancy BMI categories</th>
<th>Gestational hypertension, GDM, preeclampsia, cesarean delivery</th>
<th>History of prior preterm birth, short cervical length, chorionicity</th>
</tr>
</thead>
</table>

“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; ≥ 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\textsuperscript{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, 9\textsuperscript{th} 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), GDM (1-hour glucose challenge test > 140 mg/dl), 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**

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

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/m²), normal-weight (<24.99 kg/m²), overweight (25.0 – 29.99 kg/m²), and obese (≥30 kg/m²), 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 25th and 75th 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 25th and 75th 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 25th percentile, between the 25th and 75th percentiles, or greater than the 75th 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
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-Pregnancy BMI (n=3,082)</th>
<th>Missing Pre-Pregnancy BMI (n=1,758)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total GWG, mean, SD (kg)</td>
<td>16.97, 7.81</td>
<td>17.45, 7.87</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Gestational Age, mean, SD (weeks)</td>
<td>34.92, 3.37</td>
<td>34.37, 3.69</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Maternal Age, mean, SD (years)</td>
<td>29.74, 6.49</td>
<td>29.65, 6.59</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Pre-Pregnancy Weight, mean, SD (kg)</td>
<td>70.46, 19.08</td>
<td>71.24, 17.68</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Admission Weight, mean, SD (kg)</td>
<td>87.21, 19.16</td>
<td>89.18, 20.81</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Race/Ethnicity n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>1,723 (57.51)</td>
<td>942 (54.96)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>646 (21.56)</td>
<td>466 (27.19)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>471 (15.72)</td>
<td>174 (10.15)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Asian/PI/Multi/Other/Unknown</td>
<td>156 (5.21)</td>
<td>132 (7.70)</td>
<td></td>
</tr>
<tr>
<td>Marital Status n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>2,094 (67.94)</td>
<td>1,009 (57.39)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Divorced/Widowed/Single</td>
<td>924 (29.98)</td>
<td>583 (33.16)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>64 (2.08)</td>
<td>166 (9.44)</td>
<td></td>
</tr>
<tr>
<td>Smoking Status n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2,896 (93.96)</td>
<td>1,633 (92.89)</td>
<td>0.14</td>
</tr>
<tr>
<td>No</td>
<td>186 (6.04)</td>
<td>125 (7.11)</td>
<td></td>
</tr>
<tr>
<td>Alcohol Status n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3,023 (98.09)</td>
<td>1,730 (98.41)</td>
<td>0.42</td>
</tr>
<tr>
<td>No</td>
<td>59 (1.91)</td>
<td>28 (1.59)</td>
<td></td>
</tr>
<tr>
<td>Chronic Hypertension n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>70 (2.27)</td>
<td>40 (2.28)</td>
<td>0.99</td>
</tr>
<tr>
<td>No</td>
<td>3,012 (97.73)</td>
<td>1,718 (97.72)</td>
<td></td>
</tr>
<tr>
<td>Chronic Diabetes Mellitus n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58 (1.88)</td>
<td>37 (2.10)</td>
<td>0.59</td>
</tr>
<tr>
<td>No</td>
<td>3,024 (98.12)</td>
<td>1,721 (97.90)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Private</td>
<td>Public</td>
<td>Self-Pay/Other/Unknown</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------</td>
<td>--------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>Parity</strong> n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>1,340 (43.48)</td>
<td>788 (44.85)</td>
<td></td>
</tr>
<tr>
<td>Multiparous</td>
<td>1,742 (56.52)</td>
<td>969 (55.15)</td>
<td></td>
</tr>
<tr>
<td><strong>History of Cesarean Delivery</strong> n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>420 (13.63)</td>
<td>245 (13.94)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2,564 (83.19)</td>
<td>1,382 (78.61)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>98 (3.18)</td>
<td>131 (7.45)</td>
<td></td>
</tr>
<tr>
<td><strong>Insurance Type</strong> n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>1,735 (56.29)</td>
<td>1,236 (70.31)</td>
<td></td>
</tr>
<tr>
<td>Public</td>
<td>980 (31.80)</td>
<td>466 (26.51)</td>
<td></td>
</tr>
<tr>
<td>Self-Pay/Other/Unknown</td>
<td>367 (11.91)</td>
<td>56 (3.19)</td>
<td></td>
</tr>
<tr>
<td><strong>Gestational Hypertension</strong> n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>138 (4.58)</td>
<td>65 (3.78)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2,874 (95.42)</td>
<td>1,653 (96.22)</td>
<td></td>
</tr>
<tr>
<td><strong>Preeclampsia</strong> n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>171 (5.55)</td>
<td>111 (6.31)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2,911 (94.45)</td>
<td>1,647 (93.69)</td>
<td></td>
</tr>
<tr>
<td><strong>Gestational Diabetes Mellitus</strong> n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>207 (6.85)</td>
<td>150 (8.72)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2,817 (93.15)</td>
<td>1,571 (91.28)</td>
<td></td>
</tr>
<tr>
<td><strong>Cesarean Delivery</strong> n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2,063 (66.94)</td>
<td>1,178 (67.01)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1,019 (33.06)</td>
<td>580 (32.99)</td>
<td></td>
</tr>
</tbody>
</table>

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* Pre-Pregnancy BMI category frequency missing n=12

*c* 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* 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>
<thead>
<tr>
<th>Characteristics</th>
<th>Below (n=830)</th>
<th>Within (n=1,618)</th>
<th>Above (n=633)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total GWG, mean, SD (kg)</strong></td>
<td>8.46, 5.06**</td>
<td>17.06, 4.35</td>
<td>26.50, 5.93**</td>
</tr>
<tr>
<td><strong>Gestational Age, mean, SD (weeks)</strong></td>
<td>34.82, 3.39**</td>
<td>34.96, 3.44</td>
<td>34.94, 3.10**</td>
</tr>
<tr>
<td><strong>Maternal Age, mean, SD (years)</strong></td>
<td>29.38, 6.44**</td>
<td>30.13, 6.53</td>
<td>29.21, 6.39**</td>
</tr>
<tr>
<td><strong>Pre-Pregnancy BMI n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>39 (4.70)*</td>
<td>72 (4.54)</td>
<td>33 (5.21)**</td>
</tr>
<tr>
<td>Normal</td>
<td>408 (49.16)</td>
<td>902 (55.75)</td>
<td>261 (41.23)</td>
</tr>
<tr>
<td>Overweight</td>
<td>194 (23.37)</td>
<td>337 (20.83)</td>
<td>176 (27.80)</td>
</tr>
<tr>
<td>Obese</td>
<td>189 (22.77)</td>
<td>307 (18.97)</td>
<td>163 (25.75)</td>
</tr>
<tr>
<td><strong>Race/Ethnicity n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>402 (48.43)**</td>
<td>978 (60.44)</td>
<td>342 (54.03)**</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>204 (24.58)</td>
<td>275 (17.0)</td>
<td>167 (26.38)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>159 (19.16)</td>
<td>244 (15.08)</td>
<td>68 (10.74)</td>
</tr>
<tr>
<td>Asian/PI/Multi/Other/Unknown</td>
<td>42 (5.06)</td>
<td>72 (4.45)</td>
<td>42 (6.64)</td>
</tr>
<tr>
<td>Missing</td>
<td>23 (2.77)</td>
<td>49 (3.03)</td>
<td>14 (2.21)</td>
</tr>
<tr>
<td><strong>Marital Status n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>516 (62.17)**</td>
<td>1,180 (72.93)</td>
<td>397 (62.72)**</td>
</tr>
<tr>
<td>Divorced/Widowed/Single</td>
<td>292 (35.18)</td>
<td>409 (25.28)</td>
<td>223 (35.23)</td>
</tr>
<tr>
<td>Unknown</td>
<td>22 (2.65)</td>
<td>29 (1.79)</td>
<td>13 (2.05)</td>
</tr>
<tr>
<td><strong>Smoking Status n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>765 (92.17)*</td>
<td>1,533 (94.75)</td>
<td>597 (94.31)</td>
</tr>
<tr>
<td>Yes</td>
<td>65 (7.83)</td>
<td>85 (5.25)</td>
<td>36 (5.69)</td>
</tr>
<tr>
<td><strong>Alcohol Status n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>813 (97.95)</td>
<td>1,586 (98.02)</td>
<td>623 (98.42)</td>
</tr>
<tr>
<td>Yes</td>
<td>17 (2.05)</td>
<td>32 (1.98)</td>
<td>10 (1.58)</td>
</tr>
<tr>
<td><strong>Chronic Hypertension n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>809 (97.47)</td>
<td>1,588 (98.15)</td>
<td>614 (97.00)</td>
</tr>
<tr>
<td>Yes</td>
<td>21 (2.53)</td>
<td>30 (1.85)</td>
<td>19 (3.00)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>Chronic Diabetes</strong> n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>814 (98.07)</td>
<td>1,594 (98.52)</td>
<td>615 (97.16)*</td>
</tr>
<tr>
<td>Yes</td>
<td>16 (1.93)</td>
<td>24 (1.48)</td>
<td>18 (2.84)</td>
</tr>
<tr>
<td><strong>Parity</strong> n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>304 (36.63)**</td>
<td>726 (44.87)</td>
<td>309 (48.82)</td>
</tr>
<tr>
<td>Multiparous</td>
<td>526 (63.37)</td>
<td>892 (55.13)</td>
<td>324 (51.18)</td>
</tr>
<tr>
<td><strong>History of Cesarean Delivery</strong> n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>674 (81.20)*</td>
<td>1,363 (84.24)</td>
<td>526 (83.10)</td>
</tr>
<tr>
<td>Yes</td>
<td>115 (13.86)</td>
<td>212 (13.10)</td>
<td>93 (14.69)</td>
</tr>
<tr>
<td>Unknown</td>
<td>41 (4.94)</td>
<td>43 (2.66)</td>
<td>14 (2.21)</td>
</tr>
<tr>
<td><strong>Insurance Type</strong> n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>411 (49.52)**</td>
<td>974 (60.20)</td>
<td>349 (55.13)**</td>
</tr>
<tr>
<td>Public</td>
<td>313 (37.71)</td>
<td>445 (27.50)</td>
<td>222 (35.07)</td>
</tr>
<tr>
<td>Self-Pay/Other/Unknown</td>
<td>106 (12.77)</td>
<td>199 (12.30)</td>
<td>62 (9.79)</td>
</tr>
</tbody>
</table>

*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/m², normal-weight if BMI is 18.5 to 24.9 kg/m², overweight if BMI is 25.0 to 29.9 kg/m², obese if BMI is ≥ 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)**            |
| Gestational Hypertension        | 0.76 (0.47, 1.23)               | 1.00 (ref.)                     |
|                                 |                                 | 2.20 (1.50, 3.24)*              |
| Preeclampsia                    | 0.90 (0.60, 1.34)               | 1.00 (ref.)                     |
|                                 |                                 | 1.59 (1.10, 2.30)*              |
| Gestational Diabetes Mellitus   | 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)               |
| **Outcome**                     | **Below (n=830)**               | **Within (n=1,618)**            | **Above (n=633)** |
| Gestational Hypertension        | 0.82 (0.61, 1.11)               | 1.00 (ref.)                     | 2.04 (1.60, 2.61)* |
| Preeclampsia                    | 0.95 (0.72, 1.25)               | 1.00 (ref.)                     | 1.63 (1.26, 2.10)* |
| Gestational Diabetes Mellitus   | 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. 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

<table>
<thead>
<tr>
<th><strong>Outcome</strong></th>
<th><strong>Below (n=830)</strong></th>
<th><strong>Within (n=1,618)</strong></th>
<th><strong>Above (n=633)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Hypertension</td>
<td>0.82 (0.61, 1.11)</td>
<td>1.00 (ref.)</td>
<td>2.04 (1.60, 2.61)*</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>0.95 (0.72, 1.25)</td>
<td>1.00 (ref.)</td>
<td>1.63 (1.26, 2.10)*</td>
</tr>
<tr>
<td>Gestational Diabetes Mellitus</td>
<td>1.15 (0.90, 1.47)</td>
<td>1.00 (ref.)</td>
<td>0.92 (0.69, 1.23)</td>
</tr>
<tr>
<td>Cesarean Delivery</td>
<td>0.79 (0.64, 0.97)*</td>
<td>1.00 (ref.)</td>
<td>1.16 (0.91, 1.46)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio, (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Hypertension (^a)</td>
<td>1.32 (1.23, 1.42)*</td>
</tr>
<tr>
<td>Preeclampsia (^a)</td>
<td>1.04 (0.97, 1.12)</td>
</tr>
<tr>
<td>Gestational Diabetes Mellitus (^b)</td>
<td>0.91 (0.84, 0.98)*</td>
</tr>
<tr>
<td>Cesarean Delivery</td>
<td>1.06 (1.00, 1.12)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Hypertension (^a)</td>
<td>1.31 (1.23, 1.40)*</td>
</tr>
<tr>
<td>Preeclampsia (^a)</td>
<td></td>
</tr>
<tr>
<td>Total GWG &lt; 19 kg</td>
<td>1.16 (1.01, 1.33)*</td>
</tr>
<tr>
<td>Total GWG &gt; 19 kg</td>
<td>0.80 (0.62, 1.02)</td>
</tr>
<tr>
<td>Gestational Diabetes Mellitus (^b)</td>
<td>0.96 (0.89, 1.03)</td>
</tr>
<tr>
<td>Cesarean Delivery</td>
<td>1.08 (1.01, 1.15)*</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Gestational Age (weeks)</th>
<th>Underweight BMI</th>
<th>Normal Weight BMI</th>
<th>Overweight BMI</th>
<th>Obese BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>6.93 – 15.76</td>
<td>5.34 – 12.10</td>
<td>4.65 – 9.78</td>
<td>3.60 – 8.79</td>
</tr>
<tr>
<td>24</td>
<td>7.58 – 16.22</td>
<td>6.09 – 17.93</td>
<td>5.27 – 10.77</td>
<td>4.00 – 9.63</td>
</tr>
<tr>
<td>26</td>
<td>8.88 – 17.15</td>
<td>7.60 – 18.86</td>
<td>6.52 – 12.76</td>
<td>4.79 – 11.33</td>
</tr>
<tr>
<td>27</td>
<td>9.53 – 17.62</td>
<td>8.35 – 19.32</td>
<td>7.14 – 13.75</td>
<td>5.18 – 12.18</td>
</tr>
<tr>
<td>32</td>
<td>12.77 – 19.95</td>
<td>12.10 – 21.65</td>
<td>10.26 – 18.71</td>
<td>7.16 – 16.42</td>
</tr>
<tr>
<td>36</td>
<td>15.36 – 21.81</td>
<td>15.11 – 23.51</td>
<td>12.76 – 22.67</td>
<td>8.74 – 19.81</td>
</tr>
<tr>
<td>40</td>
<td>16.98 – 33.80</td>
<td>15.90 – 37.86</td>
<td>14.06 – 22.50</td>
<td>9.87 – 21.37</td>
</tr>
<tr>
<td>42</td>
<td>17.63 – 34.99</td>
<td>15.93 – 38.37</td>
<td>14.52 – 21.73</td>
<td>10.35 – 21.84</td>
</tr>
</tbody>
</table>
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\textsuperscript{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\textsuperscript{5,6}. Gavard & Artal also did not find any significant differences in the odds of gestational hypertension as total GWG increased\textsuperscript{7}. However, Gavard & Artal only assessed the association between GWG and gestational hypertension in women with an obese pre-pregnancy BMI\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{7,11}. Gavard & Artal found a significant positive trend between increasing GWG and the likelihood of developing preeclampsia\textsuperscript{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\textsuperscript{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. Lucovnik et al and Fox et al 2011 did not report any significant associations between preeclampsia and GWG.

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. Fox et al 2010 and Fox et al 2011 also examined the association between increasing total GWG and GDM and reported null findings. 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. Additionally, Lucovnik et al reported that change in BMI during
pregnancy was not significantly associated with the likelihood of developing GDM\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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. 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. 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.

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). However, it is currently unknown whether chorionicity influences GWG in twin gestations. 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. 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. 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


### 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**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>Wald 95% Confidence Limits</th>
<th>Wald Chi-Square</th>
<th>Pr &gt; Chi Sq</th>
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Table A.2 Preeclampsia and Concordance with Quantile Regression Gestational Weight Gain (GWG) Guidelines

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

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<th>Wald Chi-Square</th>
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Table A.4 Cesarean Delivery and Concordance with Quantile Regression Gestational Weight Gain (GWG) Guidelines

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

Analysis of Maximum Likelihood Parameter Estimates

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

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<th>Wald Chi-Square</th>
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<td>Intercept</td>
<td>-4.63</td>
<td>0.6433</td>
<td>-5.8908 -3.3692</td>
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<tr>
<td>MomAge</td>
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<td>-0.0081</td>
<td>0.0072</td>
<td>-0.0223 0.006</td>
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<td>0.2602</td>
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<tr>
<td>BESTGA</td>
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<td>0.0165</td>
<td>-0.0425 0.0222</td>
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<td>0.54</td>
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<td>BMIcat Under</td>
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<td>0.3561</td>
<td>-0.9945 0.4012</td>
<td>0.69</td>
<td>0.4048</td>
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<tr>
<td>BMIcat Overweight</td>
<td>0.5802</td>
<td>0.1346</td>
<td>0.3164 0.8441</td>
<td>18.58</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMIcat Obese</td>
<td>1.1088</td>
<td>0.1368</td>
<td>0.8406 1.3769</td>
<td>65.68</td>
<td>&lt;0.0001</td>
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<td>Racecat Black</td>
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<td>Racecat Hispanic</td>
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<tr>
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<td>-0.0294 0.6432</td>
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<td>Insurancecat Public</td>
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<td>Maritalstat Divorced/Single/Windowed</td>
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<td>0.162</td>
<td>-0.4998 0.1352</td>
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<td>Maritalstat Unknown</td>
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<td>-0.5223 0.0026</td>
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<td>Sitenum 43</td>
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<td>Sitenum 46</td>
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<td>Sitenum 47</td>
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<td>-1.3234 -0.027</td>
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<td>-0.4822 0.2133</td>
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<td>-0.3554 0.9979</td>
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<td>Sitenum 51</td>
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<td>-0.2131 0.4682</td>
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### Table A.8 Cesarean Delivery and Total Gestational Weight Gain (GWG)

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<tr>
<th>Parameter</th>
<th>Estimate</th>
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<th>Wald Chi-Square</th>
<th>Pr &gt; Chi Sq</th>
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<tbody>
<tr>
<td>Intercept</td>
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<td>0.5975</td>
<td>0.2965, 2.6387</td>
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<td>BMIcat: Overweight</td>
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<td>BMIcat: Obese</td>
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<td>Racecat: Hispanic</td>
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<td>Smokecat</td>
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<td>0.8759</td>
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Table A.9 Association between Gestational Hypertension and Total GWG and Concordance with GWG Guidelines among Twins in the CSL Study

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<th>Total GWG Model b</th>
<th>95% CI</th>
<th>Concordance Model c</th>
<th>95% CI</th>
</tr>
</thead>
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<td>1.31</td>
<td>1.23, 1.40*</td>
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<tr>
<td><strong>Gestational Age (1 week)</strong></td>
<td>1.07</td>
<td>1.03, 1.12*</td>
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<tr>
<td><strong>Concordance</strong></td>
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<tr>
<td>Below vs Within</td>
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<td>0.98, 1.02</td>
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<tr>
<td>Above vs Within</td>
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</tr>
<tr>
<td><strong>Maternal Age</strong></td>
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<tr>
<td><strong>Pre-Pregnancy BMI c</strong></td>
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<tr>
<td>Underweight vs Normal</td>
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<td>0.46, 1.56</td>
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<tr>
<td>Overweight vs Normal</td>
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<td>0.99, 1.76</td>
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<tr>
<td>Obese vs Normal</td>
<td>3.50</td>
<td>2.70, 4.53*</td>
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<td><strong>Race/Ethnicity</strong></td>
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<tr>
<td>Divorced/Widowed/Single vs Married</td>
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<td>0.72, 1.39</td>
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<td>Unknown vs Married</td>
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<td><strong>Smoking Status</strong></td>
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<td><strong>Alcohol Status</strong></td>
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<td>Public vs Private</td>
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<tr>
<td>Self-Pay/Other/Unknown vs Private</td>
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<td>0.37, 1.24</td>
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</table>

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.

Women with chronic hypertension were excluded from the analyses of gestational hypertension and preeclampsia.

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.

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.

Maternal pre-pregnancy BMI is categorized as underweight if BMI is <18.5 kg/m², normal-weight if BMI is 18.5 to 24.9 kg/m², overweight if BMI is 25.0 to 29.9 kg/m², obese if BMI is ≥ 30.0.
Table A.10 Association between Preeclampsia and Total GWG and Concordance with GWG Guidelines among Twins in the CSL Study

<table>
<thead>
<tr>
<th></th>
<th>Total GWG Model b</th>
<th>Concordance Model c</th>
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<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
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<tr>
<td><strong>Total GWG (5 kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before 19 kg</td>
<td>1.16</td>
<td>1.01, 1.33*</td>
</tr>
<tr>
<td>After 19 kg</td>
<td>0.80</td>
<td>0.62, 1.02</td>
</tr>
<tr>
<td><strong>Gestational Age (1 week)</strong></td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Below vs Within</td>
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<td>0.63, 1.43</td>
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<tr>
<td>Above vs Within</td>
<td>1.63</td>
<td>1.11, 2.38*</td>
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<tr>
<td><strong>Maternal Age</strong></td>
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<tr>
<td>Pre-Pregnancy BMI c</td>
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<tr>
<td>Underweight vs Normal</td>
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<td>0.43, 1.30</td>
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<tr>
<td>Overweight vs Normal</td>
<td>1.00</td>
<td>0.76, 1.31</td>
</tr>
<tr>
<td>Obese vs Normal</td>
<td>1.41</td>
<td>1.05, 1.89*</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
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<td></td>
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<tr>
<td>Non-Hispanic Black vs NHW</td>
<td>0.72</td>
<td>0.49, 1.04</td>
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<tr>
<td>Hispanic vs NHW</td>
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<td>0.91, 1.81</td>
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<tr>
<td>Asian/PI/Multi/Other/Unknown vs NHW</td>
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<td>0.99, 2.34</td>
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<td><strong>Marital Status</strong></td>
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<td>1.22</td>
<td>0.90, 1.64</td>
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<td>Unknown vs Married</td>
<td>0.31</td>
<td>0.08, 1.17</td>
</tr>
<tr>
<td><strong>Smoking Status</strong></td>
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<td></td>
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<tr>
<td>Yes vs No</td>
<td>0.77</td>
<td>0.46, 1.28</td>
</tr>
<tr>
<td><strong>Alcohol Status</strong></td>
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<tr>
<td>Yes vs No</td>
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<td>0.99, 3.56</td>
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<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
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<tr>
<td>Multiparous vs Nulliparous</td>
<td>0.58</td>
<td>0.47, 0.73*</td>
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<tr>
<td><strong>Insurance</strong></td>
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<td></td>
</tr>
<tr>
<td>Public vs Private</td>
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<td>0.94, 1.71</td>
</tr>
<tr>
<td>Self-Pay/Other/Unknown vs Private</td>
<td>1.41</td>
<td>0.92, 2.16</td>
</tr>
</tbody>
</table>

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.

Women with chronic hypertension were excluded from the analyses of gestational hypertension and preeclampsia.

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.

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.

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 ≥30.0.
Table A.11 Association Between Gestational Diabetes Mellitus and Total GWG and Concordance with GWG Guidelines among Twins in the CSL Study $^a$

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

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 $<18.5 \text{ kg/m}^2$, 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 $\geq 30.0$. 

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

<table>
<thead>
<tr>
<th></th>
<th>Total GWG Model</th>
<th>Concordance Model</th>
<th>Total GWG Model</th>
<th>Concordance Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Total GWG (5 kg)</strong></td>
<td>1.08</td>
<td>1.01, 1.15*</td>
<td>0.79</td>
<td>0.65, 0.96*</td>
</tr>
<tr>
<td><strong>Gestational Age</strong></td>
<td>0.93</td>
<td>0.90, 0.96*</td>
<td>1.16</td>
<td>0.93, 1.44</td>
</tr>
<tr>
<td><strong>Concordance</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below vs Within</td>
<td>1.05</td>
<td>1.03, 1.07*</td>
<td>1.05</td>
<td>1.03, 1.07*</td>
</tr>
<tr>
<td>Above vs Within</td>
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<tr>
<td><strong>Maternal Age</strong></td>
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<tr>
<td><strong>Pre-Pregnancy BMI</strong></td>
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<tr>
<td>Underweight vs Normal</td>
<td>0.63</td>
<td>0.41, 0.95*</td>
<td>0.68</td>
<td>0.46, 0.99*</td>
</tr>
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<td>Overweight vs Normal</td>
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<td>0.91, 1.43</td>
<td>1.13</td>
<td>0.91, 1.39</td>
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<td>Obese vs Normal</td>
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<td>1.10, 1.84*</td>
<td>1.36</td>
<td>1.08, 1.71*</td>
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<td><strong>Race/Ethnicity</strong></td>
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<tr>
<td>Non-Hispanic Black vs NHW</td>
<td>1.39</td>
<td>1.03, 1.90*</td>
<td>1.42</td>
<td>1.07, 1.89*</td>
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<tr>
<td>Hispanic vs NHW</td>
<td>1.27</td>
<td>0.93, 1.74</td>
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<td>0.93, 1.66</td>
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<tr>
<td>Asian/PI/Multi/Other/Unknown vs NHW</td>
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<td>0.73, 1.75</td>
<td>1.15</td>
<td>0.76, 1.73</td>
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<td>Divorced/Widowed/Single vs Married</td>
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<td><strong>Smoking Status</strong></td>
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<tr>
<td>Yes vs No</td>
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<td>0.69, 1.54</td>
<td>1.14</td>
<td>0.79, 1.63</td>
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<td><strong>Alcohol Status</strong></td>
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<td><strong>Parity</strong></td>
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<td>Multiparous vs Nulliparous</td>
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<td>0.42, 0.63*</td>
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<td>0.43, 0.62*</td>
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<td>Public vs Private</td>
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<td>1.18</td>
<td>0.93, 1.49</td>
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<td>Self-Pay/Other/Unknown vs Private</td>
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<td>6.18, 14.32*</td>
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<td>0.22, 0.79*</td>
<td>0.37</td>
<td>0.21, 0.65*</td>
</tr>
</tbody>
</table>

*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 < 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 ≥ 30.0.