2015

Interpregnancy Weight Change and Adverse Maternal Outcomes

Chelsea Lynes
University of South Carolina

INTERPREGNANCY WEIGHT CHANGE AND ADVERSE MATERNAL OUTCOMES

by

Chelsea Lynes

Bachelor of Science
University of Massachusetts - Boston, 2012

Submitted in Partial Fulfillment of the Requirements

For the Degree of Master of Science in Public Health in

Epidemiology

The Norman J. Arnold School of Public Health

University of South Carolina

2015

Accepted by:

Nansi Boghossian, Director of Thesis

Alex McLain, Reader

Jihong Liu, Reader

Lacy Ford, Senior Vice Provost and Dean of Graduate Studies

DEDICATION

This document is dedicated to my family and to old and new friends that have become family. Additionally, this is dedicated to the faculty of the Department of Epidemiology and Biostatistics that have served as mentors and friends throughout my time at Carolina. I cannot thank all of you enough.

ACKNOWLEDGEMENTS

I would like to thank my thesis chair, Dr. Nansi Boghossian, for her vital insight, hard work, and patience. Similarly, I would like to thank my committee members, Drs. Alex McLain and Jihong Liu for their guidance and diligence. I am thankful for the staff at the NICHD that collaborated with us and helped us get this project off the ground (Drs. Paul Albert, Katherine Laughon-Grantz, Stefanie Hinkle, and Edwina Yeung). Finally, I would like to thank Drs. Linda Hazlett, Kellee White, and Lyndie Forthofer for their words of encouragement throughout this process.

ABSTRACT

Obesity during pregnancy is associated with a high risk of adverse maternal outcomes. Little is known about how weight change between consecutive pregnancies impacts subsequent pregnancy complications and newborn outcomes. This study aimed to explore the association between interpregnancy BMI change and adverse maternal outcomes, specifically, gestational diabetes mellitus (GDM), gestational hypertension, pre-eclampsia, non-repeat cesarean delivery (C-section), and vaginal birth after cesarean delivery (VBAC). The study sample was derived from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Consecutive Pregnancy Study, which collected data from 20 hospitals in Utah utilizing electronic medical records and International Classification of Diseases ninth revision codes. The study collected extensive information on maternal demographic, reproductive and medical history, pregnancy complications, and labor and delivery information. Women with at least two pregnancies during the study period who delivered between 2002-2010 were included (n=51,086 women yielding 114,679 pregnancies). After data exclusions, the study sample included 46,521 women and the outcomes of their first two pregnancies. Between their first two consecutive pregnancies, these women gained an average of 0.81 BMI units (interquartile range (IQR) -0.34 to 1.77) over an average interpregnancy interval of 634 days (IQR 373 to 814). Poisson regression with robust variance estimators was utilized to estimate the relative risks of the outcomes. After adjusting for potential confounders, every one unit increase in BMI between consecutive pregnancies increased the risk of

GDM (relative risk (RR): 1.09 (95% confidence interval (CI): 1.07 – 1.11)), pre-eclampsia (RR: 1.06 (95% CI: 1.04 – 1.09)), and gestational hypertension in the second pregnancy increased (RR: 1.08 (95% CI: 1.06 – 1.10). For every one unit increase in BMI, the risk of having a successful VBAC decreased (RR: 0.95 (95% CI: 0.93 – 0.98)). There was no significant association seen between interpregnancy BMI change and a non-repeat C-section. Women with a BMI ≥ 3 units increase were also at a significantly increased risk of GDM (RR: 1.72 (95% CI: 1.52 – 1.93)), pre-eclampsia (RR: 1.61 (95% CI: 1.33 – 1.94)), and gestational hypertension (RR: 1.66 (95% CI: 1.42 – 1.93)) in the second pregnancy when compared to women who maintained their BMI between pregnancies (- 1 unit ≤ BMI change < 1 unit). The risk of having a successful VBAC decreased (RR: 0.72 (95% CI: 0.58 – 0.88) for women who gained ≥ 3 units, compared to women who maintained their BMI (- 1 unit ≤ BMI change < 1 unit). GDM was also increased among those who increased their BMI by at least 2 units but not more than 3 units (RR: 1.40 (95% CI: 1.22 – 1.61)) and among those who gained at least 1 unit but no more than 2 BMI units (RR: 1.23 (95% CI: 1.08 – 1.40)). These findings have public health implications for the importance of weight management between pregnancies.

Table of Contents

List of Tables

CHAPTER 1
INTRODUCTION

Nearly 56% of reproductive aged women (20-39 years of age) are overweight or obese[1]. Obesity during pregnancy is associated with a high risk of maternal and newborn adverse outcomes. Less is known about how weight change between two consecutive pregnancies, hereafter known as interpregnancy BMI or weight change, impacts subsequent pregnancy complications and newborn outcomes. In 2012, 41.6% of 15-50 year old women in the US reported having two or more children[2]; thus, investigating the association between interpregnancy weight change and pregnancy complications is important. The best evidence for the impact of interpregnancy weight change on maternal health (pre-eclampsia, gestational hypertension, gestational diabetes mellitus (GDM), and cesarean delivery) comes from a study by Villamor and Cnattingius (2006)[3].

Using data from the Swedish Birth Register (n=151025 women), Villamor et al defined outcomes using the International Classifications of Diseases (ICD) ninth and tenth revisions[3]. They categorized the exposure into groups based on the participant's change in BMI units from the first to the second pregnancy (range: >1 BMI unit decrease to ≥ 3 unit increase)[3]. Using logistic regression models, they found significant associations in the odds of pre-eclampsia [odds ratio (OR): 1.78; 95% confidence interval (CI): 1.52 – 2.08)]; gestational hypertension [OR: 1.76; 95% CI: 1.39 – 2.23]; GDM [OR: 2.09; 95% CI: 1.68 – 2.61]; and cesarean section [OR: 1.32; 95% CI: 1.22 – 1.44] when

comparing women with an interpregnancy BMI gain of 3 or more units to women with a change of -1 to 0.9 units[3]. These main findings are in line with the overall findings of subsequent studies[4-12, 14, 15], which show that there is a positive association between an increase in intrepregnancy BMI and the risk of maternal adverse health outcomes.

Studies similar to the Villamor and Cnattingius[3] study have been conducted in the US. These studies utilized vital records data from Missouri[4-9] or Washington[10, 11] or had hospital-based cohort data[12]. Studies that used the vital statistics data examined the change in pre-pregnancy BMI between the first and second pregnancies as the exposure, which was categorized in different ways. One Missouri study, Mostello et al (2010)[7], used the following categories: those who decreased their BMI $\geq$ 2 units; those who increased their BMI $\geq$ 2 units; and those who maintained their BMI within $\pm$ 2 units. The other Missouri studies[4-6, 8, 9] utilized World Health Organization BMI categories[13] [underweight (BMI <18.5 kg/m^2); normal (BMI: 18.50 – 24.99); overweight (BMI: 25.00 – 29.99); obese (BMI $\geq$ 30.00)] classifying women based on their first and second pre-pregnancy BMI. For example, a woman who has a normal BMI at the start of her first pregnancy and was overweight at the start of her second pregnancy would be classified as "normal-overweight"[4-6, 8, 9]. All of the studies adjusted for the first prepregnancy BMI group in their models along with other potential confounders[4-5, 7-9]. One study[6] restricted their analysis to only include women whose first prepregnancy BMI was classified as overweight. The overall findings of the Missouri[4-9] cohort studies illustrate that there is a positive association with interpregnancy BMI increase and the risk of adverse maternal outcomes in the second pregnancy/delivery; the exclusion criteria and findings of these studies are reported in Tables 1.1 and 1.2.

Vital records data from Washington State[10, 11] have also been used to investigate the association between interpregnancy BMI change and adverse maternal outcomes. Paramsothy et al (2009)[10] investigated the association between interpregnancy weight change and cesarean section in the second pregnancy among women with GDM using data collected from 1992-2005 (n=2753). Unlike the previously described studies, they categorized their exposure as weight change in pounds: weight loss greater than 10 pounds (lbs); weight maintained (±10 lbs); weight gain of greater than 10 lbs and reported a significant association in the odds of having a cesarean delivery in the second pregnancy (OR: 1.70, 95% CI: 1.16 – 2.49) between women who gained more than 10 lbs and women with weight gain <10 lbs[10]. Another study utilizing data from Washington's vital records was done by Callegari et al (2014)[11]. They investigated the association between interpregnancy BMI change and vaginal birth after cesarean section (VBAC) utilizing data from 1992-2009 (n=8302)[11]. They categorized the exposure as follows: <1 BMI unit decrease or increase; ≥ 1 BMI unit decrease; ≥ 1 and < 2 units increase; ≥ 2 BMI units increase[11]. This study found that those with normal BMI before their first pregnancy had an 8% decrease in VBAC success with ≥ 1 and <2 BMI unit increase and a 12% decrease in success with ≥ 2 BMI unit increase compared with normal BMI women who maintained their weight[11]. The results of these studies[10, 11] further support the overall finding that an increase in interpregnancy weight is associated with an increased risk of adverse maternal outcomes in the second delivery, specifically GDM and VBAC.

All of the studies enumerated above[3-11] list the source of their data as a limitation. Vital records underreport the incidence of maternal complications compared to medical

records[27-30]. DiGiuseppe et al (2002)[27] utilized kappa statistics to investigate the agreement between vital records and medical records. For maternal risk factors and comorbidities, they report kappa statistics ranging from 0.085 – 0.545[27]. Additionally, for several complications of pregnancy and/or labor and delivery, they report kappa statistics ranging from 0.285 – 0.734[27]. Further, DiGiuseppe et al found high specificity (sp) for maternal risk factors, comorbidities, and pregnancy and/or labor and delivery complications (sp: 96.5 – 99.9%)[27]. In this instance, specificity is the probability that an individual did not report the outcome given that he or she did not have it. However, the same maternal risk factors, comorbidities, and complications resulted in lower sensitivities, which ranged from 8.6 – 65.4%[27]. Here, sensitivity is the probability that an individual reported the outcome given that he or she had it. Whether it is better to have a high sensitivity or specificity depends on the outcome, risk factor, or comorbidity of interest. DiGiuseppe et al conclude that utilizing vital records as opposed to medical records as a source for this type of data is 'suspect' at best[27].

To our knowledge, only one study in the US utilized a hospital-based cohort investigating the association between interpregnancy BMI change and GDM. Ehrlich et al (2011)[12] used data from Kaiser Permanente Hospital System in Northern California (n=22351) to examine this association. They found that, compared to women who were weight stable (± <1 BMI unit change), interpregnancy weight gain was significantly associated with a higher risk of GDM in the second pregnancy. A gain of 1.0 – 1.9 BMI units had odds of subsequent GDM 1.71 times (95% CI: 1.42 – 2.07); a gain of 2.0 – 2.9 BMI units had odds of subsequent GDM 2.46 times (95% CI: 2.00 – 3.02); a gain of 3.0 or more BMI units had the odds of subsequent GDM 3.40 times (95% CI: 2.81 – 4.12)[12].

Hospital-based cohort studies with larger sample sizes have been done in other countries, specifically Belgium[14] and Scotland[15]. The Belgian study investigated the association between interpregnancy BMI change and the risk of GDM, gestational hypertension, and caesarean section[14]. The Scottish study looked at the association between interpregnancy BMI change and the following maternal outcomes: pre-eclampsia, gestational hypertension, induced labor, elective caesarean, and emergency caesarean[15]. These studies, similar to Villamor and Cnattingius[3], categorized the exposure into groups based on the unit change in their BMI from the first to second pregnancy, which ranged from >1 BMI unit decrease to ≥ 3 units increase. The overall findings of these international studies[14,15] are in line with those seen with the Missouri [4-9] and Washington [10, 11] studies.

The majority of previous studies that investigated the association between interpregnancy weight change and adverse maternal outcomes in the US utilized vital records[4-11], which underreport maternal complications compared to medical records data[27-30]. In the US, hospital-based cohorts[12] that investigate this association are rare; thus, there is a gap in the literature that calls for a US hospital-based cohort with a large sample size. Analysis of the longitudinal, retrospective Consecutive Pregnancy Study dataset from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) addresses this gap. The NICHD Consecutive Pregnancy study collected data from 20 hospitals in Utah from 2002 – 2010. We examined the association between interpregnancy BMI change and the following adverse maternal outcomes in the second delivery: gestational hypertension; GDM; pre-eclampsia; non-repeat cesarean section; and VBAC. In line with the findings of previous literature, we hypothesized that

there is a positive association between interpregnancy BMI increase and the risk of adverse maternal outcomes.

Table 1.1: Details of Missouri vital records-based cohorts: cohort years, sample size, and exclusions[4-9]

Author (year)	Cohort years (sample size)	Study sample exclusion criteria
Getahun (2007)[4]	1989-1997 (n=113,789)	Those with only 1 pregnancy during study period; those that were not nulliparous at baseline; multiple births; stillbirths; missing data: maternal weight and height, births at <20 weeks gestation, cesarean; vaginal birth after cesarean (VBAC); repeated cesarean
Getahun (2007)[5]	1989-1997 (n=136,884)	Those with only 1 pregnancy during study period; those that were not nulliparous at baseline; multiple births; missing data: maternal height and weight; those with: chronic hypertension, chronic/gestational diabetes, pre-eclampsia in first pregnancy, pregnancies <20 weeks gestation
Hoff (2009)[6]	1995-2004 (n=1,035)	If their prepregnancy BMI was not classified overweight (BMI 25.0 – 29.9 kg/m^2) for the first pregnancy; those with only 1 pregnancy during study period; those that were not nulliparous at baseline; multiple births
Mostello (2010)[7]	1989-2005 (n=17,773)	Those with only 1 pregnancy during study period; those that were not nulliparous at baseline; multiple births; those whose first pregnancy was not complicated by pre-eclampsia
Whiteman (2011)[8]	1989-2005 (n=232,272)	Those with only 1 pregnancy during study period; those that were not nulliparous at baseline; births at <20 weeks gestation
Whiteman (2011)[9]	1989-2005 (n=100,828)	Those with only 1 pregnancy during study period; those that were not nulliparous at baseline; those that were classified as overweight for either pregnancy; births at <20 weeks gestation; those without vaginal birth for first pregnancy

Table 1.2: Details of Missouri vital records-based cohorts: outcomes and main findings[4-9]

Author (year)	Outcome(s) in second pregnancy	Main findings
Getahun (2007)[4]	Primary cesarean	Increase in BMI from underweight to overweight or obese within the first two pregnancies associated with increased risk of primary cesarean (odds ratio (OR) 1.20 to 3.04)) in second delivery
Getahun (2007)[5]	Pre-eclampsia incidence	Risk for pre-eclampsia increased when BMI category in first pregnancy was underweight and change to obese in second pregnancy (OR: 5.6 (95% CI: 1.7 18.2); normal to overweight (2.0 (1.7, 2.3); normal to obese (3.2 (2.5, 4.2); overweight to obese (3.7 (3.1, 4.3)
Hoff (2009)[6]	Pregnancy hypertension; emergency cesarean section	Upward BMI shift significantly associated with emergency cesarean section (p-value <0.02)
Mostello (2010)[7]	Recurrent pre-eclampsia	Increase in BMI significantly associated with higher risk of recurrent pre-eclampsia (risk ratio (RR): 1.29 (95% CI: 1.20, 1.38); decrease in BMI significantly associated with lower risk of recurrent pre-eclampsia (RR: 0.70 (0.60, 0.81))
Whiteman (2011)[8]	Development of diabetes (gestational or type II diabetes mellitus)	Mothers who moved from normal to obese BMI categories between pregnancies had increased risk (OR: 3.21 (2.76, 3.73)) of developing diabetes in the second pregnancy
Whiteman (2011)[9]	Primary cesarean (emergency and non-emergency)	Mothers who moved from normal to obese BMI categories between pregnancies had increased risk (OR: 1.41 (1.26, 1.57)) of cesarean delivery in the second pregnancy; mothers who maintained obese status between pregnancies also at increased risk (OR: 1.75 (1.65, 1.87) of cesarean delivery in the second pregnancy

CHAPTER 2
METHODS

2.1 STUDY POPULATION

The NICHD Consecutive Pregnancy Study enrolled a total of 51,086 women, regardless of their parity, with at least two pregnancies (range 2-6 pregnancies) who delivered between the years 2002 to 2010, which resulted in 114,679 pregnancies (live births or stillbirths ≥ 20 weeks' gestation). Data sources included electronic medical records (EMR) and ICD-9 codes collected from maternal and newborn discharge summaries and linked to each delivery. Extensive information on maternal demographic, reproductive and medical history, pregnancy complications, labor and delivery information, and neonatal outcomes were available. All study sites had approval for the study and waiver of informed consent from their individual institutional review boards.

2.2 DATA EXCLUSIONS

For the current study, the sample was restricted to each woman's first two singleton births (n=49,868) regardless of her parity upon enrollment in the study. Women with inconsistencies in their hypertensive status, such as being prescribed hypertensive medication or having hypertension as a labor indication without having hypertension (n=202); inconsistencies in their diabetes status, such as having an ICD-9 code for 'infant of a diabetic mother' with no diabetes recorded for the mother (n=23); with chronic diseases in their first pregnancy including diabetes mellitus, chronic hypertension, or superimposed pre-eclampsia (n = 920); with missing height or weight data in either pregnancy (n = 1546); with implausible BMI values, which was defined as

11 kg/m^2 > BMI > 70 kg/m^2 (n=1); and those with chronic hypertension, diabetes mellitus, or superimposed pre-eclampsia in their second pregnancy (n=655) were excluded resulting in 46,521 women for the current study (see figure 1). The demographics of those missing height or weight data differed slightly from those with data (supplementary table A.1). At the time of the second pregnancy, more of those missing data identified as Hispanic (27.72%); characterized themselves as single (13.91%); and smoked (4.22%), compared to those who were not missing data, who had rates of 10.09%, 7.93%, and 3.07%, respectively. Of those missing data, fewer had private insurance (61.06%) than those who were not missing data (74.16%). Those missing data had a higher incidence of gestational diabetes mellitus in the second pregnancy (5.89%) than those who were not missing data (3.54%). The incident rates of the other maternal second pregnancy outcomes did not differ substantially between the two groups (supplementary table A.1).

2.3 INTERPREGNANCY BMI CHANGE

The exposure, interpregnancy weight change, was calculated as the difference between the prepregnancy BMI of the first pregnancy and the prepregnancy BMI of the second pregnancy and was examined as both a continuous and a categorical variable as: difference in BMI <-1 units (i.e. loss of more than 1 BMI unit (kg/m^2)), -1 to less than 1 (reference group), 1 to less than 2, 2 to less than 3, and ≥ 3 BMI units (i.e. gain of 3 or more BMI units).

2.4 MATERNAL OUTCOMES

Maternal outcomes in the second pregnancy were ascertained from electronic medical records supplemented with ICD-9 codes and included: pre-eclampsia, gestational

hypertension, gestational diabetes, vaginal birth after cesarean delivery (VBAC), and non-repeat cesarean delivery. If the condition was coded in either source, then the woman was coded as having the diagnosis. During the study period, the definitions that were widely adopted in US clinical practice were utilized to identify the outcomes of interest. These definitions were as follows: pre-eclampsia and gestational hypertension defined as systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg occurring after 20 weeks' gestation among previously normotensive women with and without proteinuria and urinary excretion ≥ 0.3 grams of protein in 24-hour urine specimen, respectively[17, 18]. Mode of delivery (VBAC or non-repeat cesarean delivery (C-section)) was determined via the EMR. The denominator for the VBAC outcome was restricted to only include those who had a C-section in their first delivery (n=5132). Those with a C-section in the first delivery were excluded from the non-repeat cesarean delivery denominator (n=41389). Gestational diabetes was determined via diagnosis in the EMR and was supplemented with ICD-9 codes. ICD-9 codes for the examined maternal outcomes are listed in the supplementary table A.2.

2.5 STATISTICAL ANALYSIS

Potential confounders of the association between interpregnancy BMI change and the maternal outcomes are as follows: maternal race (categorized as: White; Hispanic; or Black/Asian/Pacific Islander/other); maternal age (measured at pregnancy 2); interpregnancy interval (measured as days between first delivery date and last menstrual period for second pregnancy); smoking and alcohol use during the second pregnancy (yes/no); pre-eclampsia, gestational hypertension, or gestational diabetes mellitus in the first pregnancy (yes/no); and first prepregnancy BMI. Because there is potentially more

variability in diagnosis between hospitals, the association was also adjusted for hospital site.

Poisson regression models with robust variance estimators were used to estimate the relative risk of the outcome while adjusting for these potential confounders[19]. Unadjusted and adjusted analyses were performed for each outcome, for which two Poisson regression models were built, treating interpregnancy BMI change as either categorical or continuous. Significance was evaluated at $\alpha = 0.05$.

Two sensitivity analyses were performed utilizing the same approach described above. The first sensitivity analysis restricted the sample to women who were nulliparous upon entry in the study (n=25429). Next, a sensitivity analysis was performed in which women who had any of the examined outcomes in their first pregnancy were excluded (gestational hypertension: n=1784; pre-eclampsia: n=1516; GDM: n=914). Of the women in this sample, 50 had both GDM and pre-eclampsia in their first pregnancy; 42 had both gestational hypertension and GDM in their first pregnancy. The final sample size was n=42399. Statistical analyses were conducted using software (SAS, version 9.4; SAS institute, Cary, NC).

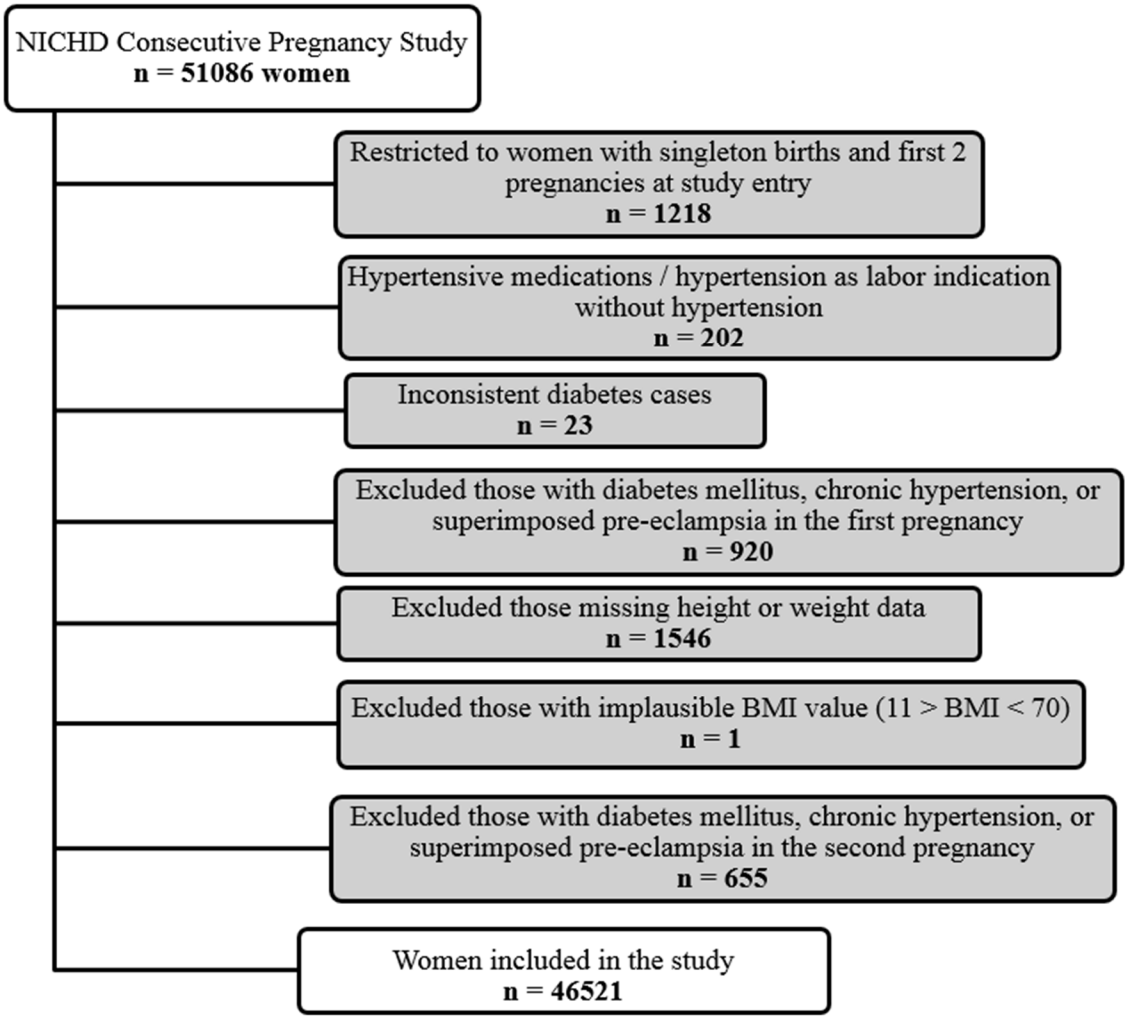

Figure 2.1: Study Sample Exclusions

CHAPTER 3
RESULTS

Study participants gained an average of 0.81 BMI units (median 0.46, interquartile range (IQR) -0.34 to 1.77) over an average interpregnancy interval of 634 days (median 561, IQR 373 to 814). At the first prepregnancy measurement, 20.69% of women were overweight ($25 \leq BMI < 30$) and 11.97% of women were obese ($BMI \geq 30$). While, at the second prepregnancy measurement 23.16% of women were overweight and 15.92% of women were obese. At the time of the second pregnancy, most study participants were married (90.42%); had private insurance (74.16%); identified as White (87.05%); had a vaginal birth in their second delivery (78.54%); and were nulliparous upon entry into the study (54.66%). The average age of the women at the second delivery was 28 years old (median 28, IQR 25 to 31). Women who identified as single had the highest mean change in BMI (1.50 BMI units (standard deviation (SD) = 3.02)), compared to women who identified as married or divorced/widowed. Hispanic women had the highest mean change in BMI (1.32 (SD: 2.73)), compared to women who identified as White, Black, Asian, Pacific Islander, or other. Women who had pregnancy complications in the second pregnancy including GDM, gestational hypertension, or preeclampsia gained on average around 1.4 to 1.5 (SD: 2.9) BMI units. The sample characteristics of the study participants are described in table 3.1.

Within the study population, the incidence rates of maternal outcomes in the second pregnancy were as follows: gestational hypertension: 2.31%; GDM: 3.54%; pre-

eclampsia: 1.70%; non-repeat C-section: 2.09%; VBAC: 16.02% (table 3.2). The greatest frequency of most of the outcomes was seen among those with the largest increase in interpregnancy BMI (≥ +3 units, n=6376). Within this group at the second delivery, 5.87% had GDM; 4.39% had gestational hypertension; 3.12% had pre-eclampsia; 1.87% had a non-repeat C-section; and 10.51% had a VBAC (table 3.2).

After adjusting for potential confounders, for every one unit increase in BMI between consecutive pregnancies, the risk of having GDM (relative risk (RR): 1.09 (95% CI: 1.07 – 1.11)), pre-eclampsia (RR: 1.06 (95% CI: 1.04 – 1.09)), and gestational hypertension in the second pregnancy increased (RR: 1.08 (95% CI: 1.06 – 1.10); while, the risk of having a successful VBAC decreased (RR: 0.95 (95% CI: 0.93 – 0.98)) (table 3.3). There was no significant association seen between interpregnancy BMI change and a non-repeat C-section. When interpregnancy BMI change was treated categorically, a similar trend was seen (table 3.4). A woman with an interpregnancy BMI gain of 3 or more units was at a higher risk of developing GDM (relative risk (RR): 1.72, 95% CI: 1.52 – 1.93), pre-eclampsia (RR: 1.61, 95% CI: 1.33 – 1.94), gestational hypertension (RR: 1.66, 95% CI:1.42 – 1.93), than those who maintained their interpregnancy BMI, after adjusting for potential confounders (table 3.4). A woman with an interpregnancy BMI gain of 3 or more units was less likely to have a successful VBAC (RR: 0.72 (95% CI: 0.58 – 0.88), than those who maintained their interpregnancy BMI, after adjusting for potential confounders (table 3.4). This group's risk of a non-repeat C-section did not differ from those who maintained their BMI between consecutive pregnancies after potential confounders were considered (table 3.4).

Compared to those who maintained their BMI between pregnancies (-1 ≤ BMI unit change < +1), those who increased their BMI by at least 2 units but not more than 3 units showed an increased risk of having GDM in the second pregnancy (RR: 1.40 (95% CI: 1.22 – 1.61)), after adjusting for potential confounders (table 3.4). This group did not differ in their risk of pre-eclampsia, gestational hypertension, non-repeat C-section, or VBAC, in comparison to those who maintained their BMI between pregnancies, after potential confounders were considered (table 3.4).

Compared to those who maintained their BMI between pregnancies, those who gained +1 ≤ BMI unit < 2 were at a higher risk of having GDM in the second pregnancy (RR: 1.23 (95% CI: 1.08 – 1.40)) and at a higher risk of having an unsuccessful VBAC (RR: 0.77 (95% CI: 0.64 – 0.94), after adjusting for potential confounders (table 3.4). This group's risk of pre-eclampsia, gestational hypertension, and non-repeat C-section did not differ from those who maintained their BMI between consecutive pregnancies, after potential confounders were considered (table 3.4).

Weight loss of more than one BMI unit between consecutive pregnancies was not significantly associated with an increased risk of GDM, pre-eclampsia, gestational hypertension, non-repeat cesarean section, or VBAC, after adjusting for potential confounders (table 3.4).

The results of the two sensitivity analyses did not differ from the findings of the full data. The findings for the nulliparous sensitivity analyses are reported for BMI change as continuous (table 3.5) and as categorical (table 3.6). Of the nulliparous sample, 739 (2.91%) had GDM; 599 (2.36%) had gestational hypertension; 2 (<0.01%) had a non-repeat C-section; 619 (14.01%) had a VBAC; and 465 (1.83%) had pre-eclampsia.

Similarly, the findings for excluding women who had any outcome in the first pregnancy (GDM, gestational hypertension, pre-eclampsia) are reported for BMI change as continuous (table 3.7) and as categorical (table 3.8). In this second sensitivity analysis, 812 (1.92%) had GDM; 587 (1.38%) had gestational hypertension; 828 (2.17%) had a non-repeat C-section; 741 (17.35%) had a VBAC; and 464 (1.09%) had pre-eclampsia.

Table 3.1: Sample Characteristics of NICHD Consecutive Pregnancy Study from 20 hospitals in Utah (n=46521)

Characteristic	Second Pregnancy	p-value*	Mean change in BMI (SD)
First pregnancy BMI category, n (%)		<0.0001	
Underweight (BMI < 18.5)	2738 (5.89)		0.95 (1.64)
Normal (18.5 ≤ BMI < 25)	28591 (61.46)		0.77 (1.94)
Overweight (25 ≤ BMI < 30)	9623 (20.69)		0.97 (2.73)
Obese (BMI ≥ 30)	5569 (11.97)		0.74 (3.56)
Marital status, n (%)		<0.0001	
Married	42063 (90.42)		0.75 (2.26)
Divorced/Widowed	767 (1.65)		0.98 (3.06)
Single	3742 (7.93)		1.50 (3.02)
Private insurance, n (%)	34498 (74.16)	<0.0001	0.69 (2.18)
Maternal race, n (%)		<0.0001	
White	40457 (87.05)		0.74 (2.29)
Hispanic	4691 (10.09)		1.32 (2.73)
Black/Asian/Pacific Islander/Other	1328 (2.86)		1.28 (2.72)
Lifestyle behaviors			
Smoking during pregnancy 2, n (%)	1427 (3.07)	<0.0001	1.07 (3.12)
Alcohol use during pregnancy 2, n (%)	696 (1.50)	<0.0001	1.03 (2.86)
Gestational diabetes mellitus, n (%)	1646 (3.54)	<0.0001	1.39 (2.85)
Gestational hypertension, n (%)	1073 (2.31)	<0.0001	1.54 (2.88)
Pre-eclampsia, n (%)	791 (1.70)	<0.0001	1.42 (2.92)
Delivery mode, n (%)		<0.0001	
Vaginal birth	36539 (78.54)		0.77 (2.26)
Vaginal birth after cesarean in first delivery	1685 (3.62)		0.69 (2.22)
Non-repeat cesarean in second delivery	1603 (3.45)		0.94 (2.64)
Repeat cesarean in second delivery	6693 (14.39)		1.07 (2.77)

*Chi-square test

Table 3.1 *continued*: Sample characteristics of NICHD Consecutive Pregnancy Study from 20 hospitals in Utah (n=46521)

Characteristic	Second Pregnancy	p-value*	Mean change in BMI (SD)
Maternal age, years, n (%)		<0.0001	
< 35	42268 (90.86)		0.83 (2.37)
≥ 35	4253 (9.14)		0.68 (2.23)
Maternal age, years, mean (SD)	27.97 (4.63)		
Parity		<0.0001	
1	25429 (54.66)		0.90 (2.43)
2	10624 (22.84)		0.75 (2.26)
3	6461 (13.89)		0.68 (2.26)
4	2507 (5.39)		0.71 (2.24)
5	925 (1.99)		0.67 (2.27)
6+	575 (1.24)		1.18 (1.89)
Interpregnancy interval		<0.0001	
0 – 5 months	2402 (5.16)		1.03 (2.37)
6 – 11 months	7536 (16.20)		0.73 (2.24)
12 – 17 months	11065 (23.78)		0.57 (2.14)
18 – 23 months	9630 (20.70)		0.64 (2.23)
24 – 59 months	15332 (32.96)		1.07 (2.54)
≥ 60 months	556 (1.20)		1.88 (3.36)
Interpregnancy interval, months, mean (SD)	21.15 (12.31)		

*Chi-square test

Table 3.2: Outcomes in second pregnancy by BMI change regardless of parity at baseline (N=46521), n (%)

BMI unit change	GDM n = 1646	Gestational hypertension n = 1073	Pre-eclampsia[c] n = 791	Non-repeat C-section[a] n = 863	VBAC[b] n = 822
BMI unit change < -1 (n=6560)	228 (3.48)	134 (2.04)	114 (1.74)	120 (2.07)	121 (16.09)
-1 ≤ BMI unit change < + 1 (n=22838)	609 (2.67)	408 (1.79)	304 (1.33)	437 (2.12)	426 (19.15)
+ 1 ≤ BMI unit change < + 2 (n=6737)	239 (3.55)	151 (2.24)	108 (1.60)	119 (1.99)	103 (13.79)
+2 ≤ BMI unit change < + 3 (n=4010)	196 (4.89)	100 (2.49)	66 (1.65)	86 (2.41)	71 (15.85)
BMI unit change ≥ + 3 (n=6376)	374 (5.87)	280 (4.39)	199 (3.12)	101 (1.87)	101 (10.51)
p-value[c]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

[a]Denominator excludes anyone with a c-section in the first pregnancy (n = 41389); [b]Denominator only includes those with c-section in first pregnancy (n=5132); [c]Chi-square test

Table 3.3: Relative risks (95% confidence intervals) of maternal outcomes by BMI difference (continuous) between consecutive pregnancies (n=46521)

Maternal Outcome in Second Pregnancy	BMI difference (continuous)
GDM	
Unadjusted	1.10 (1.08 – 1.12)**
Adjusted[a]	1.09 (1.07 – 1.11)**
Pre-eclampsia	
Unadjusted	1.10 (1.07 – 1.13)**
Adjusted[a]	1.06 (1.04 – 1.09)**
Gestational hypertension	
Unadjusted	1.12 (1.09 – 1.14)**
Adjusted[a]	1.08 (1.06 – 1.10)**
Non-repeat C-section	
Unadjusted	0.98 (0.95 – 1.00)*
Adjusted[a]	0.99 (0.96 – 1.02)
VBAC	
Unadjusted	0.95 (0.93 – 0.97)**
Adjusted[a]	0.95 (0.93 – 0.98)**

[a]Adjusted for: maternal race (referent level: white); maternal age; interpregnancy interval; smoking during 2nd pregnancy (referent level: yes); alcohol use during 2nd pregnancy (referent level: yes); Pre-eclampsia in 1st pregnancy (referent level: yes); gestational hypertension in 1st pregnancy (referent level: yes); GDM in 1st pregnancy (referent level: yes); pre-pregnancy 1 BMI; hospital site. *Marginally significant at $\alpha = 0.05$ level
**Significant at $\alpha = 0.05$ level

Table 3.4: Relative risks (95% confidence intervals) of maternal outcomes by BMI change (categorical) between consecutive pregnancies (n=46521) – Referent level: - 1 unit ≤ BMI change < 1 unit

Maternal Outcome in Second Pregnancy	BMI change < -1 unit	BMI change 1 to less than 2 units	BMI change 2 to less than 3	BMI change ≥ 3 units
GDM				
Unadjusted	1.30 (1.12 – 1.51)**	1.33 (1.15 – 1.54)**	1.83 (1.57 – 2.15)**	2.20 (1.94 – 2.49)**
Adjusted[a]	0.90 (0.79 – 1.02)	1.23 (1.08 – 1.40)**	1.40 (1.22 – 1.61)**	1.72 (1.52 – 1.93)**
Pre-eclampsia				
Unadjusted	1.31 (1.05 – 1.62)**	1.20 (0.97 – 1.50)	1.24 (0.95 – 1.50)	2.34 (1.97 – 2.80)**
Adjusted[a]	0.97 (0.78 – 1.20)	1.03 (0.83 – 1.28)	1.00 (0.77 – 1.30)	1.61 (1.33 – 1.94)**
Gestational hypertension				
Unadjusted	1.14 (0.94 – 1.39)	1.25 (1.04 – 1.51)**	1.40 (1.12 – 1.73)**	2.46 (2.12 – 2.85)**
Adjusted[a]	0.83 (0.69 – 1.01)	1.10 (0.91 – 1.31)	1.10 (0.89 – 1.36)	1.66 (1.42 – 1.93)**
Non-repeat C-section				
Unadjusted	0.97 (0.80 – 1.19)	0.94 (0.77 – 1.15)	1.14 (0.91 – 1.43)	0.88 (0.71 – 1.09)
Adjusted[a]	0.99 (0.81 – 1.22)	0.92 (0.75 – 1.13)	1.15 (0.92 – 1.45)	1.01 (0.81 – 1.25)
VBAC				
Unadjusted	0.84 (0.70 – 1.01)	0.72 (0.59 – 0.88)**	0.83 (0.66 – 1.04)	0.55 (0.45 – 0.67)**
Adjusted[a]	1.06 (0.88 – 1.27)	0.77 (0.64 – 0.94)**	0.98 (0.78 – 1.23)	0.72 (0.58 – 0.88)**

[a]Adjusted for: maternal race (referent level: white); maternal age; interpregnancy interval; smoking during 2nd pregnancy (referent level: yes); alcohol use during 2nd pregnancy (referent level: yes); Pre-eclampsia in 1st pregnancy (referent level: yes); gestational hypertension in 1st pregnancy (referent level: yes); GDM in 1st pregnancy (referent level: yes); pre-pregnancy 1 BMI; hospital site. *Marginally significant at $\alpha = 0.05$ level **Significant at $\alpha = 0.05$ level

Table 3.5: Relative risks (95% confidence intervals) of maternal outcomes by BMI difference (continuous) between consecutive pregnancies among nulliparous women at baseline (n=25429)

Maternal Outcome in Second Pregnancy	BMI difference (continuous)
GDM	
Unadjusted	1.12 (1.09 – 1.14)**
Adjusted[a]	1.11 (1.08 – 1.13)**
Pre-eclampsia	
Unadjusted	1.10 (1.06 – 1.13)**
Adjusted[a]	1.06 (1.03 – 1.09)**
Gestational hypertension	
Unadjusted	1.12 (1.09 – 1.15)**
Adjusted[a]	1.08 (1.05 – 1.10)**
Non-repeat C-section	
Unadjusted	-[b]
Adjusted[a]	-[b]
VBAC	
Unadjusted	0.95 (0.92 – 0.97)**
Adjusted[a]	0.95 (0.92 – 0.98)**

[a]Adjusted for: maternal race (referent level: white); maternal age; interpregnancy interval; smoking during 2nd pregnancy (referent level: yes); alcohol use during 2nd pregnancy (referent level: yes); Pre-eclampsia in 1st pregnancy (referent level: yes); gestational hypertension in 1st pregnancy (referent level: yes); pre-pregnancy 1 BMI; GDM in 1st pregnancy (referent level: yes); hospital site; [b]Models did not converge; outcome not frequent enough (prevalence = 2/21010); **Significant at $\alpha = 0.05$ level

Table 3.6: Relative risks (95% confidence intervals) of maternal outcomes by BMI change (categorical) between consecutive pregnancies of nulliparous women at baseline (n=25429) – Referent level: - 1 unit ≤ BMI change < 1 unit

Maternal Outcome in Second Pregnancy	BMI change < -1 unit	BMI change 1 to less than 2 units	BMI change 2 to less than 3	BMI change ≥ 3 units
GDM				
Unadjusted	1.06 (0.83 – 1.35)	1.33 (1.06 – 1.66)**	1.84 (1.45 – 2.33)**	2.24 (1.87 – 2.69)**
Adjusted[a]	0.87 (0.71 – 1.07)	1.28 (1.05 – 1.56)**	1.58 (1.27 – 1.96)**	1.87 (1.58 – 2.23)**
Pre-eclampsia				
Unadjusted	1.19 (0.89 – 1.59)	1.43 (1.08 – 1.87)**	1.19 (0.84 – 1.69)	2.22 (1.78 – 2.80)**
Adjusted[a]	0.93 (0.70 – 1.24)	1.15 (0.88 – 1.51)	0.99 (0.70 – 1.41)	1.52 (1.19 – 1.94)**
Gestational hypertension				
Unadjusted	0.96 (0.73 – 1.26)	1.27 (0.99 – 1.62)	1.37 (1.03 – 1.83)**	2.30 (1.89 – 2.80)**
Adjusted[a]	0.75 (0.58 – 0.98)	1.03 (0.81 – 1.32)	1.10 (0.83 – 1.46)	1.52 (1.24 – 1.87)**
Non-repeat C-section				
Unadjusted	-b	-b	-b	-b
Adjusted[a]	-b	-b	-b	-b
VBAC				
Unadjusted	0.92 (0.75 – 1.14)	0.74 (0.59 – 0.93)**	0.84 (0.64 – 1.10)	0.57 (0.45 – 0.71)**
Adjusted[a]	1.17 (0.95 – 1.44)	0.78 (0.62 – 0.98)**	1.00 (0.76 – 1.32)	0.72 (0.57 – 0.92)**

[a]Adjusted for: maternal race (referent level: white); maternal age; interpregnancy interval; smoking during 2nd pregnancy (referent level: yes); alcohol use during 2nd pregnancy (referent level: yes); Pre-eclampsia in 1st pregnancy (referent level: yes); gestational hypertension in 1st pregnancy (referent level: yes); GDM in 1st pregnancy (referent level: yes); pre-pregnancy 1 BMI; hospital site; [b]Models did not converge; outcome not frequent enough (prevalence = 3/21208); *Marginally significant at α = 0.05 level **Significant at α = 0.05 level

Table 3.7: Relative risks (95% confidence intervals) of maternal outcomes by BMI difference (continuous) between consecutive pregnancies – excluding those who had any outcome in the first pregnancy (n=42399)

Maternal Outcome in Second Pregnancy	BMI difference (continuous)
GDM	
Unadjusted	1.16 (1.13 – 1.18)**
Adjusted[a]	1.13 (1.11 – 1.16)**
Pre-eclampsia	
Unadjusted	1.11 (1.07 – 1.15)**
Adjusted[a]	1.08 (1.05 – 1.12)**
Gestational hypertension	
Unadjusted	1.14 (1.11 – 1.18)**
Adjusted[a]	1.12 (1.09 – 1.15)**
Non-repeat C-section	
Unadjusted	0.98 (0.95 – 1.01)
Adjusted[a]	0.99 (0.96 – 1.02)
VBAC	
Unadjusted	0.94 (0.92 – 0.97)**
Adjusted[a]	0.94 (0.91 – 0.97)**

[a]Adjusted for: maternal race (referent level: white); maternal age; interpregnancy interval; smoking during 2nd pregnancy (referent level: yes); alcohol use during 2nd pregnancy (referent level: yes); Pre-eclampsia in 1st pregnancy (referent level: yes); gestational hypertension in 1st pregnancy (referent level: yes); pre-pregnancy 1 BMI; GDM in 1st pregnancy (referent level: yes); hospital site. **Significant at $\alpha = 0.05$ level

Table 3.8: Relative risks (95% confidence intervals) of maternal outcomes by BMI change (categorical) between consecutive pregnancies – excluding those who had any outcome in the first pregnancy (n=42399) – Referent level: - 1 unit ≤ BMI change < 1 unit

Maternal Outcome in Second Pregnancy	BMI change < -1 unit	BMI change 1 to less than 2 units	BMI change 2 to less than 3	BMI change ≥ 3 units
GDM				
Unadjusted	1.09 (0.85 – 1.38)	1.62 (1.32 – 1.99)**	2.09 (1.66 – 2.62)**	2.94 (2.47 – 3.50)**
Adjusted[a]	0.83 (0.65 – 1.06)	1.43 (1.16 – 1.75)**	1.75 (1.39 – 2.19)**	2.27 (1.88 – 2.73)**
Pre-eclampsia				
Unadjusted	1.13 (0.85 – 1.50)	1.11 (0.84 – 1.48)	1.04 (0.72 – 1.49)	2.24 (1.78 – 2.82)**
Adjusted[a]	0.84 (0.63 – 1.13)	0.98 (0.74 – 1.31)	0.87 (0.60 – 1.26)	1.65 (1.28 – 2.13)**
Gestational hypertension				
Unadjusted	1.07 (0.81 – 1.40)	1.35 (1.05 – 1.72)**	1.20 (0.87 – 1.65)	2.90 (2.38 – 3.53)**
Adjusted[a]	0.78 (0.59 – 1.02)	1.24 (0.97 – 1.59)	1.03 (0.75 – 1.42)	2.23 (1.81 – 2.75)**
Non-repeat C-section				
Unadjusted	1.00 (0.82 – 1.23)	0.94 (0.76 – 1.15)	1.13 (0.89 – 1.43)	0.90 (0.72 – 1.12)
Adjusted[a]	1.01 (0.82 – 1.25)	0.91 (0.74 – 1.12)	1.12 (0.89 – 1.42)	1.00 (0.80 – 1.25)
VBAC				
Unadjusted	0.88 (0.73 – 1.06)	0.73 (0.59 – 0.90)**	0.85 (0.66 – 1.08)	0.53 (0.43 – 0.67)**
Adjusted[a]	1.10 (0.91 – 1.33)	0.79 (0.64 – 0.97)**	0.97 (0.76 – 1.23)	0.68 (0.54 – 0.85)**

[a]Adjusted for: maternal race (referent level: white); maternal age; interpregnancy interval; smoking during 2nd pregnancy (referent level: yes); alcohol use during 2nd pregnancy (referent level: yes); Pre-eclampsia in 1st pregnancy (referent level: yes); gestational hypertension in 1st pregnancy (referent level: yes); GDM in 1st pregnancy (referent level: yes); pre-pregnancy 1 BMI; hospital site. *Marginally significant at α = 0.05 level **Significant at α = 0.05 level

CHAPTER 4
DISCUSSION

We found that there was a significant association between a one unit increase in BMI between consecutive pregnancies and increased risk of GDM, gestational hypertension, pre-eclampsia, and an unsuccessful VBAC in the second pregnancy when potential confounders were taken into consideration. No association was found between interpregnancy BMI change and non-repeat C-section. The highest magnitude of risk of these adverse maternal outcomes was seen when comparing the group with the largest increase in interpregnancy BMI (≥ +3 units), which for this study was representative of 13.79% of participants, with those who maintained their interpregnancy BMI (-1 unit ≤ BMI change < 1 unit), which was representative of 49.38% of participants. Overall, the results of the current study were in line with findings of previous studies[3-12, 14, 15]; however, it must be noted that all of the previous studies except for one[12] utilized vital records data, which tend to underreport maternal complications[27-30] compared to medical records.

4.1 GESTATIONAL DIABETES MELLITUS (GDM)

We found that any increase in BMI between consecutive pregnancies was significantly associated with an elevated risk of GDM, compared with those who maintained their BMI. We found that a BMI increase of ≥ 3 units had a risk 1.72 (95% CI: 1.52 – 1.93) times that of those who maintained their BMI. When comparing those same groups,

Villamor and Cnattingius found an odds ratio of GDM in the second pregnancy of 2.09 (95% CI: 1.68 – 2.61)[3]. Although both Whiteman et al[8] and Ehrlich et al[12] categorized their exposures differently, they found significant associations between an increase in BMI and an increase of GDM risk in the second pregnancy. Bogaerts et al[14] found that this association was only significant in those who had a BMI < 25 at the first prepregnancy measurement. Unlike the findings of the current study, both Whiteman et al[8] and Ehrlich et al[12] found that as BMI decreased between consecutive pregnancies, the odds of GDM in the second pregnancy decreased. However, Ehrlich et al[12] only found this amongst women who were categorized as overweight or obese in their first pregnancy. Also, because Whiteman et al[8] categorized their exposure differently, it may be difficult to compare their results to the current study.

4.2 PRE-ECLAMPSIA

We found that an increase in BMI between consecutive pregnancies was associated with an increased risk of pre-eclampsia in the second pregnancy. A BMI increase of ≥ 3 units (compared to interpregnancy BMI maintenance) was associated with a RR of 1.61 (95% CI: 1.33 – 1.94) of pre-eclampsia. Villamor and Cnattingius[3] and Wallace et al[15] categorized the exposure the same way we did and found that if a woman increases her BMI ≥ 3 units between consecutive pregnancies, her odds of pre-eclampsia in the second pregnancy increases. Although Getahun et al[5] categorized their exposure differently than our current study, they found a similar positive significant association. Mostello et al[7] only looked at recurrent pre-eclampsia in the second pregnancy. Similar to our results, they found that as BMI increases, the odds of pre-eclampsia in the second pregnancy increases. However, they also found that as BMI decreases, the odds of pre-eclampsia

decreases. As they only included those with pre-eclampsia in their first pregnancy, it may not be appropriate to compare the results of Mostello et al[7] to our results.

4.3 GESTATIONAL HYPERTENSION

We found that a BMI increase of ≥ 3 units between consecutive pregnancies had an elevated risk of gestational hypertension in the second pregnancy 1.66 times that of women who maintained their weight (95% CI: 1.42 – 1.93). Both Villamor and Cnattingius[3] and Wallace et al[15] found a similar positive, significant association when comparing women whose BMI increased ≥ 3 units between consecutive pregnancies compared to those who maintained their weight. Bogaerts et al[14] found a positive, significant association when comparing the same groups above at a higher magnitude (OR: 3.76 (95% CI: 2.16 – 6.57), but this was only seen in women whose first prepregnancy BMI was < 25 kg/m^2. Hoff et al[9] did not find any association between interpregnancy BMI change and the risk of gestational hypertension in the second pregnancy; however, they only included women who were overweight at their first prepregnancy measurement.

4.4 NON-REPEAT CESAREAN DELIVERY

We found no association between interpregnancy BMI change and risk of non-repeat C-section. Several previous studies explored this same association but had mixed results. Villamor and Cnattigius[3] found that those with a BMI increase of ≥ 3 units (compared to interpregnancy BMI maintenance) had odds of 1.32 (95% CI: 1.22 - 1.44) of a C-section in their second delivery. Villamor and Cnattingius[3] did not exclude women with a C-section in their first delivery from the denominator of their analysis. Although Getahun et al[4] and Whiteman et al[9] categorized their exposure differently than Villamor and

Cnattingius[3] did, they found the same trend that as BMI increased so did odds of a non-repeat C-section in the second delivery. Both Hoff et al[6] and Bogaerts et al[14] found that the association between increase in BMI and risk of C-section in the second pregnancy was only significant if women were categorized as overweight or obese in their first pregnancy. Although Paramsothy et al[10] only included women with GDM in their first pregnancy, they also found that as BMI increases so does risk of C-section in the second delivery. Wallace et al[15] did not find an association between an increase in BMI and the risk of neither elective nor emergency C-section in the second delivery; however, Wallace et al[15] did not look at the outcome as a 'non-repeat' C-section as we did in the current study.

4.5 VAGINAL BIRTH AFTER CESAREAN DELIVERY (VBAC)

We found that a BMI increase of ≥ 3 units between consecutive pregnancies had a decreased rate of VBAC success (RR: 0.72 (95% CI: 0.58 – 0.88)). Only one of the previous studies explored this association and had similar results to ours[11]. Callegari et al[11] found that those who increased their BMI ≥ 1 unit or < 2 units had an 8% decrease in VBAC success (95% CI: 2-13%). Similarly, they found that those who increased their BMI ≥ 2 units had a 12% decrease in VBAC success (95% CI: 7-17%)[11]. Their analysis only included women who were nulliparous at their first pregnancy[11].

4.6 FURTHER DISCUSSION

The incidence rates of the outcomes measured in the current study were less than the national estimates[18, 21]. The discrepancy between these incident rates can be explained by the overall health status of the study population (Utah based) being better than the national population[24].

Significant associations were found between interpregnancy BMI increase of 3 or more units and GDM, gestational hypertension, pre-eclampsia, and unsuccessful VBAC, when compared to those who maintained their interpregnancy BMI. To put this comparison into perspective, the Centers for Disease Control and Prevention reports that the average height of US women who are 20 years old and over is 162.1 cm[20]. For a woman of average height, a BMI unit change of 3 units is equivalent to gaining approximately 17.38 pounds between consecutive pregnancies.

The biological mechanisms to explain the association between interpregnancy BMI gains and the adverse maternal outcomes of interest are speculative at best. Ros et al (1998)[25] suggest that BMI impacts lipid metabolism, which in turn elevates the level of free fatty acids. As this level increases, insulin resistance increases via tumor necrosis factor alpha. This resulting insulin resistance is counteracted by hyperinsulinemia, which causes vasoconstriction. This vasoconstriction eventually leads to hypertension, which could be transient, i.e. gestational, or can become chronic. Ros et al (1998)[25] also report that tumor necrosis factor alpha has been found to be at higher levels in pre-eclamptic women, which leads to endothelial dysfunction. The resulting insulin resistance mentioned above could also result in GDM, which is the manifestation of underlying beta cell dysfunction[16]. Again, these associations are hypothetical, but these adverse outcomes and obesity share several characteristics, such as inflammatory biomarkers, oxidative stress, and dyslipidemia[26]. Future research into the physiological biomarkers of these factors is needed[26].

The main strength of the current study was the combination of both EMRs and ICD-9 codes as data sources, which allowed us to gather extensive demographic,

diagnostic, and history information about study participants and many different outcomes. Further, as previously described, the majority of the previous studies that investigated the association between interpregnancy BMI change and adverse maternal outcomes utilized vital records data for analysis, which tend to underreport maternal complications[27-30]. Another strength of the current study was that the study population is homogeneous reducing the potential for residual confounding of the association of interest. The large sample size and retrospective US-based cohort design are further strengths of the current study. Unlike the Missouri cohort studies[4-9] and Callegari et al[11], we included women regardless of their parity. The results of the first sensitivity analysis, which only included nulliparous women, showed that there is no change in the magnitude and direction of the association between these two groups based on parity. Unlike several of the previous studies, the current study utilized Poisson regression with robust variance estimators allowing us to estimate relative risk, instead of odds ratios, as was done in previous studies[3-6, 8-12, 14, 15].

One limitation of the current study was the lack of information on diet, physical activity, and prenatal care of the study participants. Similarly, we lacked information about family history of hypertension and diabetes mellitus, as well as paternity, which may impact a woman's risk of an adverse outcome in her second pregnancy. Change in paternity has been associated with elevated odds of pre-eclampsia[23], but since the majority of the women in the current study were married, i.e. in stable relationships, at the time of the second pregnancy (90.42%), we do not expect this to impact our risk estimates. The prevalence of married women in the current study is higher than the national estimate of 41.5%[24]. The current study population was also predominantly white

(87.05%); thus, the generalizability of our findings is limited. The homogeneity of the population also limited our ability to analyze whether race was an effect modifier of the association of interest. Another limitation of the current study was that weight was self-reported. However, because the exposure of interest was a difference in weight measurement between two consecutive pregnancies, this should not over or underestimate the exposure[31-33].

In conclusion, this retrospective, US-based cohort study filled a gap in the literature and provided evidence that there was a significant association between interpregnancy BMI gain and the risk of adverse maternal outcomes: gestational hypertension, pre-eclampsia, gestational diabetes mellitus, and unsuccessful VBAC, when comparing those with the highest BMI change ($\geq +3$ units) and those who maintained their BMI between pregnancies (-1 unit $\leq$ BMI $< +1$ unit). These findings are in line with previous studies and have public health implications for the importance of weight management between pregnancies.

REFERENCES

1. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA. 2012 Feb; 307(5):491-497.

2. Monte LM, Ellis RE. Fertility of Women in the United States: 2012. Final Report. US Department of Commerce, Economics and Statistics Administration, US Census Bureau; 2014 July. Report No.: P20-575.

3. Villamor E, Cnattingius S. Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. Lancet. 2006 Sep 30;368(9542):1164-70.

4. Getahun D, Kaminsky LM, Elsasser DA, Kirby RS, Ananth CV, Vintzileos AM. Changes in prepregnancy body mass index between pregnancies and risk of primary cesarean delivery. Am J Obstet Gynecol. 2007 Oct;197(4):376.e1-7.

5. Getahun D, Ananth CV, Oyelese Y, Chavez MR, Kirby RS, Smulian JC. Primary preeclampsia in the second pregnancy: effects of changes in prepregnancy body mass index between pregnancies. Obstet Gynecol. 2007 Dec;110(6): 1319-25.

6. Hoff GL, Cai J, Okah FA, Dew PC. Pre-pregnancy overweight status between successive pregnancies and pregnancy outcomes. J Womens Health (Larchmt). 2009 Sep;18(9);1413-7.

7. Mostello D, Jen Chang J, Allen J, Luehr L, Shyken J, Leet T. Recurrent preeclampsia: the effect of weight change between pregnancies. Obstet Gynecol. 2010 Sep; 116(3):667-72.

8. Whiteman VE, Aliyu MH, August EM, McIntosh C, Duan J, Alio AP, Salihu HM. Changes in prepregnancy body mass index between pregnancies and risk of gestational and type 2 diabetes. Arch Gynecol Obstet. 2011 Jul;284(1):235-40.

9. Whiteman VE, McIntosh C, Rao K, Mbah AK, Salihu HM. Interpregnancy BMI change and risk of primary caesarean delivery. J Obstet Gynaecol. 2011 Oct;31(7):589-93.

10. Paramsothy P, Lin YS, Kernic MA, Foster-Schubert KE. Interpregnancy weight gain and cesarean delivery risk in women with a history of gestational diabetes. Obstet Gynecol. 2009 Apr; 113(4):817-823.

11. Callegari LS, Sterling LA, Zelek ST, Hawes SE, Reed SD. Interpregnancy body mass index change and success of term vaginal birth after cesarean delivery. Am J Obstet Gynecol. 2014 Apr;210(4):330.e1-7.

12. Ehrlich SF, Hedderson MM, Feng J, Davenport ER, Gunderson EP, Ferrara A. Change in body mass index between pregnancies and the risk of gestational diabetes in a second pregnancy. Obstet Gynecol. 2011 Jun;117(6):1323-30.

13. World Health Organization. Global Database on Body Mass Index (Table 1: The International Classification of adult underweight, overweight and obesity according to BMI). Accessed 30 December 2014. Available from: [URL: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html].

14. Bogaerts A, Van den Bergh BR, Ameye L, Witters I, Martens E, Timmerman D, Devlieger R. Interpregnancy weight change and risk for adverse perinatal outcome. Obstet Gynecol. 2013 Nov;122(5):999-1009.

15. Wallace JM, Bhattacharya S, Campbell DM, Horgan GW. Inter-pregnancy weight change impacts placental weight and is associated with the risk of adverse pregnancy outcomes in the second pregnancy. BMC Pregnancy Childbirth. 2014 Jan 22;14:40.

16. Boghossian NS, Yeung E, Albert PS, Mendola P, Laughon SK, Hinkle SN, Zhang C. Changes in diabetes status between pregnancies and impact on subsequent newborn outcomes. Am J Obstet Gynecol. 2014 May: 210(5): 431.e1-14.

17. Boghossian NS, Albert PS, Mendola P, Grantz KL, Yeung E. Delivery blood pressure and other first pregnancy risk factors in relation to hypertensive disorders in second pregnancies. Am J Hypertens. 2015 Feb 11: pii: hpv001.

18. Seely EW, Ecker J. Chronic hypertension in pregnancy. Circulation 2014; 129:1254 1261.

19. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidem. 2004; 159: 702-706.

20. Fryar CD, Gu Q, Ogden CL. Anthropometric reference data for children and adults: United State, 2007 – 2010. National Center for Health Statistics. Vital Health Stat 11 (252). 2012.

21. Martin JA, Hamilton BE, Ventura SJ, et al. Births: Final Data for 2009. National vital statistics reports; vol 60 no 1. Hyattsville, MD: National Center for Health Statistics. 2011.

22. Bandoli G, Lindsay S, Johnson DL, Kao K, Luo Y, Chambers CD. Change in paternity and select perinatal outcomes: causal or confounded? J Obstet Gynaecol. 2012 Oct;32(7):657-62.

23. Copen CE, Daniels K, Vespa J, Mosher WD. First marriages in the United States: Data from the 2006-2010 National Survey of Family Growth. National health statistics reports; no 49. Hyattsville, MD: National Center for Health Statistics. 2012.

24. Utah. America's Health Rankings 2014. United Health Foundation. Accessed 11 June 2015. Available from: [URL: http://cdnfiles.americashealthrankings.org/SiteFiles/StateSummaries/Utah-Health-Summary-2014.pdf].

25. Ros HS, Cnattignius S, Lipworth L. Comparison of risk factors for preeclampsia and gestational hypertension in a population-based cohort study. Am J Epidemiol. 1998; 147(11):1062-70.

26. Boghossian NS, Yeung E, Mendola P, Hinkle SN, Laughon SK, Zhang C, Albert PS. Risk factors differ between recurrent and incident preeclampsia: a hospital-based cohort study. Ann Epidemiol. 2014 Dec;24(12): 871-7e3.

27. DiGiuseppe DL, Aron DC, Random L, Harper DL, Rosenthal GE. Reliability of birth certificate data: a multi-hospital comparison to medical records information. Matern Child Health J. 2002 Sep;6(3):169-79.

28. Horon IL. Underreporting of maternal deaths on death certificates and the magnitude of the problem of maternal mortality. Am J Pub Health. 2005 Mar;95(3):478-82.

29. Dietz P, Bombard J, Mulready-Ward C, Gauthier J, Sackoff J, Brozicevic P, Gambatese M, Nyland-Funke M, England L, Harrison L, Farr S. Validation of selected items on the 2003 U.S. standard certificate of live birth: New York City and Vermont. Public Health Rep. 2015 Jan-Feb;130(1):60-70.

30. Roohan PJ, Josberger RE, Acar J, Dabir P, Feder HM, Gagliano PJ. Validation of birth certificate data in New York State. J Community Health. 2003 Oct;28(5):335-46.

31. Oken E, Taveras EM, Popoola FA, Rich-Edwards JW, Gillman MW. Television, walking, and diet: associations with postpartum weight retention. Am J Prev Med 2007;32:305-11.

32. Pedersen P, Baker JL, Henriksen TB, Lissner L, Heitmann BL, Sorensen TI, Nohr EA. Influence of psychosocial factors on postpartum weight retention. Obesity (Silver Spring) 2011;19:636-46.

33. Boghossian NS, Yeung EH, Lipsky LM, Poon AK, Albert PS. Dietary patterns in association with postpartum weight retention. Am J Clin Nutr, 2913 Jun;97(6):1338-45.

APPENDIX A: SUPPLEMENTARY TABLES

Table A.1: Comparison of the demographics of those missing BMI data and those not missing BMI data

Characteristic of the second pregnancy	Missing BMI (n = 1546)	Not missing BMI (n = 46521)	p-value*
Marital status, n (%)			<0.0001
Married	1303 (84.28)	42063 (90.42)	
Divorced/Widowed	27 (1.75)	767 (1.65)	
Single	215 (13.91)	3742 (7.93)	
Private insurance, n (%)	944 (61.06)	34498 (74.16)	<0.0001
Maternal race, n (%)			<0.0001
White	1038 (67.23)	40457 (87.05)	
Hispanic	428 (27.72)	4691 (10.09)	
Black/Asian/Pacific Islander/Other	1370 (5.05)	1328 (2.86)	
Lifestyle behaviors			
Smoking during pregnancy 2, n (%)	65 (4.22)	1427 (3.07)	<0.0001
Alcohol use during pregnancy 2, n (%)	30 (1.95)	696 (1.50)	0.1568
Gestational diabetes mellitus, n (%)	91 (5.89)	1646 (3.54)	<0.0001
Gestational hypertension, n (%)	37 (2.39)	1073 (2.31)	0.0673
Pre-eclampsia, n (%)	21 (1.36)	791 (1.70)	0.8434
Delivery mode, n (%)			0.0046
Vaginal birth	1195 (77.30)	36539 (78.54)	
Vaginal birth after cesarean in first delivery	69 (4.46)	1685 (3.62)	
Non-repeat cesarean in second delivery	53 (3.43)	1603 (3.45)	
Repeat cesarean in second delivery	229 (14.81)	6693 (14.39)	
Maternal age, years, n (%)			<0.0001
< 35	1365 (88.29)	42268 (90.86)	
≥ 35	181 (11.71)	4253 (9.14)	
Maternal age, years, mean (SD)	27.90 (4.50)	27.97 (4.63)	

*Chi-square test

Table A.1 *continued*: Comparison of the demographics of those missing BMI data and those not missing BMI data

Characteristic of the second pregnancy	Missing BMI (n = 1546)	Not missing BMI (n = 46521)	p-value*
Parity			0.0005
1	772 (49.94)	25429 (54.66)	
2	359 (23.22)	10624 (22.84)	
3	250 (16.17)	6461 (13.89)	
4	102 (6.60)	2507 (5.39)	
5	35 (2.26)	925 (1.99)	
6+	27 (1.81)	575 (1.24)	
Interpregnancy interval			<0.0001
0 – 5 months	137 (8.86)	2402 (5.16)	
6 – 11 months	297 (19.21)	7536 (16.20)	
12 – 17 months	359 (23.22)	11065 (23.78)	
18 – 23 months	250 (16.17)	9630 (20.70)	
24 – 59 months	489 (31.63)	15332 (32.96)	
≥ 60 months	14 (0.91)	556 (1.20)	

*Chi-square test

Table A.2: ICD-9 codes for maternal outcomes

Outcome	ICD-9 code	Definition
Pre-eclampsia	642.4	Mild or unspecified pre-eclampsia
	642.5	Severe pre-eclampsia
Gestational hypertension	642.3	Transient hypertension of pregnancy
Gestational diabetes	648.8	Abnormal glucose tolerance of mother complicating pregnancy, childbirth, or the puerperium
Chronic hypertension	401	Essential hypertension
	401.0	Malignant essential hypertension
	401.1	Benign essential hypertension
	401.9	Unspecified essential hypertension
	402	Hypertensive heart disease
	402.0	Malignant hypertensive heart disease
	402.1	Benign hypertensive heart disease
	402.9	Unspecified hypertensive heart disease
	403	Hypertensive chronic kidney disease
	403.0	Malignant hypertensive renal disease
	403.1	Benign hypertensive renal disease
	403.9	Unspecified renal disease
	404	Hypertensive heart and chronic kidney disease
	404.0	Malignant hypertensive heart and renal disease
	404.1	Benign hypertensive heart and renal disease
	404.9	Unspecified hypertensive heart and renal disease
	405	Secondary hypertension
	405.0	Malignant secondary hypertension
	405.1	Benign secondary hypertension
	405.9	Unspecified secondary hypertension
	642	Hypertension complicating pregnancy and childbirth and the puerperium
	642.0	Benign essential hypertension
	642.1	Hypertension secondary to renal disease
	642.2	Other pre-existing hypertension